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Intensity-dependent effects of exercise therapy on walking performance and aerobic fitness in symptomatic patients with lower-extremity peripheral artery disease: A systematic review and meta-analysis

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Abstract

We investigated how nonpain-based exercise therapy intensity (light-to-moderate or vigorous) affects improvements in walking performance and cardiorespiratory fitness of patients with symptomatic lower-extremity peripheral artery disease (PAD). We searched the Embase, MEDLINE, Cochrane, Web of Science, and Google Scholar databases up to April 2021 and included randomized controlled trials reporting training therapies targeting exercise intensity (heart rate, oxygen consumption, or perceived exertion). The main outcomes were walking performance (pain-free [PFWD] and maximal [MWD] walking distance) and cardiorespiratory fitness ($\dot{V}O_{2peak}$). Secondary subanalyses examined the training modality (walking or other modalities) and the approach (high-intensity interval or moderate-intensity training). A total of 1132 patients were included. Light-to-moderate was superior to vigorous exercise intensity in improving MWD (223 m [95% CI 174 to 271], $p < 0.00001$; 153 m [95% CI 113 to 193], $p < 0.00001$; respectively) and PFWD (130 m [95% CI 87 to 173], $p < 0.00001$; 83 m [95% CI 61 to 104], $p < 0.00001$; respectively). When training modalities were considered, walking at a vigorous intensity (272 m [95% CI 207 to 337], $p < 0.00001$) showed the largest improvement in MWD compared to other exercise modalities. A larger increase in $\dot{V}O_{2peak}$ was observed following vigorous (3.0 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ [95% CI 2.4 to 3.6], $p < 0.00001$) compared to light-to-moderate (1.1 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ [95% CI 0.4 to 1.7], $p = 0.001$) exercise intensity. These results indicate that vigorous was less effective than light-to-moderate intensity in improving walking performance, whereas it was more effective in improving $\dot{V}O_{2peak}$. When the training modalities were considered, walking at a vigorous intensity showed the greatest improvement in MWD. **(PROSPERO Registration No.: CRD42020199469)**

Keywords

exercise therapy, high-intensity interval training, intermittent claudication, vascular rehabilitation, peripheral artery disease (PAD)

Introduction

Lower-extremity peripheral artery disease (PAD) affects more than 200 million people worldwide.[1,2] PAD is characterized by atherosclerotic lumen narrowing or occlusion of the lower limb arteries, leading to an imbalance between oxygen supply and demand downstream, especially in activated muscle during exertion.[1,2] The hallmark symptom of PAD is typical intermittent claudication, defined as reproducible exertion-induced cramping or pain in the lower extremities, which is rapidly relieved with rest.[1–4] However, a fairly large proportion of patients present with atypical claudication and experience exertional pain not meeting all of the Rose Claudication Questionnaire criteria.[5]

Patients with symptomatic PAD avoid exertion[6,7] and tend to have muscle weakness, and altered gait and lower limb biomechanics.[8–15] This results in impaired walking

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performance,[4,16] accelerated functional decline,[17–19] and a diminished quality of life.[20,21]

Supervised exercise training (SET) is considered among first-line therapies for patients with symptomatic PAD, combined with general cardiovascular risk management, lifestyle adaptation, and pharmacological treatment.[1,2,4,16] The clinical benefits of SET for patients with PAD are well established, with improved walking capacity and an improved quality of life as the primary outcomes.[4,16,22–27]

Although without clear consistency,[16] the guidelines give recommendations in terms of claudication pain severity, SET volume, duration, and frequency.[1,4,28–31] However, no or little guidance is offered as far as training intensity is concer ned.[1,4,28–31] Most of the previous studies on SET, in the context of PAD, did not distinguish between symptom intensity and common training intensity measures such as % of maximal heart rate (%HR_{max}), % of HR reserve (%HRR), % of peak oxygen uptake (%$\dot{V}O_{2peak}$), % of $\dot{V}O_2$ reserve (%$\dot{V}O_2R$), or the rate of perceived exertion (RPE).[4,16,22–27,32]

A meta-analysis by Parmenter et al.[24] showed that vigorous exercise training improved cardiorespiratory fitness ($\dot{V}O_{2peak}$) more than light-to-moderate exercise therapy intensity in patients with PAD, but the changes in walking performance in these patients were not investigated.[24] High-intensity interval training (HIIT) may be better than moderate-intensity training (MIT) in improving cardiorespiratory fitness and functional capacity in patients with cardiovascular and metabolic diseases,[33–37] but, in patients with symptomatic PAD, the effects of such modalities on walking ability and cardiorespiratory fitness remain to be determined.

Therefore, we performed a meta-analysis investigating the role of exercise therapy intensity in improving walking performance and cardiorespiratory fitness in symptomatic patients with PAD. First, we investigated which exercise therapy intensity (light-to-moderate or vigorous) was better for improving walking performance (maximal [MWD], pain-free [PFWD] walking distance), and cardiorespiratory fitness. Second, we investigated the effects of different specific training approaches (HIIT vs MIT) on walking performance and cardiorespiratory fitness. Third, we investigated the effects of different training modalities (walking vs other forms of exercise) associated with different exercise therapy intensities on walking performance and cardiorespiratory fitness.

Methods

This review was registered with The International Prospective Register of Systematic Reviews (PROSPERO) on August 20, 2020 (Registration No. CRD42020199469) and it follows the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.[38]

Search strategy

Five electronic databases (Embase, MEDLINE Ovid SP, Cochrane Central Register of Controlled Trials Wiley, Web of Science (all databases), and Google Scholar) were searched by a specialist librarian (CJ) from the earliest record available until June 2020. Searches were rerun in the bibliographic databases in April 2021, but no new relevant studies were identified. Search terms were adapted to the particulars of the databases. The different search strategies are presented in the online supplementary material (Suppl 1). After excluding duplicates with EndNote X9 and uploading the search results into Rayyan,[39] two authors (MF and SL) independently screened all titles and abstracts for possible inclusion, and, subsequently, full texts of any potentially eligible articles were screened. Any disagreement was settled by consensus with a third author (BK). In addition, recent systematic analyses and the reference lists of the qualifying articles were checked to find any research missed by the database queries.

Inclusion criteria

Studies were included if they were randomized controlled trials (RCTs) investigating cardiorespiratory exercise training programs longer than 4 weeks in patients with symptomatic PAD (Fontaine II/Rutherford stages 1–3). The control group had to be provided with usual medical care, with or without exercise advice. To be included, studies had to clearly describe the exercise training modality and the intensity prescribed on the basis of a targeted exercise intensity according to common measures as defined by the American College of Sports Medicine (ACSM)[32] (i.e., %HR_{max}, %HRR, %$\dot{V}O_{2peak}$, %$\dot{V}O_2R$,, or RPE). In addition, for those studies prescribing exercise training based on % of maximal workload obtained during a maximal treadmill test (%W_{peak}), the classification of Hansen et al.[40] was used.

Vigorous exercise intensity was defined with the following cutoffs[32,40]: %$\dot{V}O_2R$ or %HRR: 60–89%; %HR_{max}: 77–95%; %$\dot{V}O_{2max}$: 64–90%; RPE: 14–17; %W_{peak}: 70–99%. Moderate exercise intensity was defined with the following cutoffs[32,40]: %$\dot{V}O_2R$ or %HRR: 40–59%; %HR_{max}: 64–76%; %$\dot{V}O_{2max}$: 46–63%; RPE: 12–13; %W_{peak}: 50–70%. Light exercise intensity was defined as below the moderate cutoff points.[32,40]

A second classification was made for HIIT, moderate intensity interval training (MIIT), and MIT. HIIT was defined as an interval approach conducted with the following criteria[37]: %HR_{peak} $\geqslant$ 85%, % maximal exercise capacity, $\dot{V}O_{2peak}$ $\geqslant$ 80%, or RPE $\geqslant$ 15. MIIT was defined as an interval approach with an exercise intensity lower than the HIIT cutoffs. MIT was defined as a noninterval approach based on claudication pain severity yielding an exercise intensity lower than the HIIT cutoffs.

A third classification was made for different training modalities (walking vs other forms of exercise) associated with different exercise therapy intensities. Notably, the walking modality includes treadmill walking and overground walking with or without poles.

The included studies had to report one or more of the following outcomes before and after the training interventions: MWD and/or time, PFWD and/or time, assessed with treadmill protocols (incremental or constant-load) or shuttle tests; and/or cardiorespiratory fitness ($\dot{V}O_{2peak}$). Finally, there was no exclusion based on aerobic exercise training modality and duration; however, studies reporting interventions other than aerobic training (such as resistance training or electro-acupuncture) were excluded.

Data extraction

The data were collected by two authors (MF and SL). The following information was extracted for each study: authors, year of publication, participant characteristics (age, sex, and diagnosis), SET parameters (number of participants, duration of the program, sessions per week, duration of the training sessions, claudication pain severity, exercise therapy intensity, and mode of training), parameters of the walking capacity test (type of protocol, grade, and speed), and the results of the pre- and postintervention for MWD, PFWD, and $\dot{V}O_{2peak}$. If any of this information or other data necessary for statistical analysis were missing, the study authors were contacted.

In the preparation of the statistical analysis, the following data transformations were performed. In the study conducted by Chehuen et al.,[41] training was performed at the HR corresponding to the onset of claudication pain. Since only the absolute HR was reported in this study,[41] we calculated the relative exercise intensity (%HR_{max}) using the theoretical HR_{max} formula: 211 – (0.64*age).[42] For studies proposing a wide range of exercise intensities during SET, we calculated the average to include it in a single category (e.g., if a study set the walking intensity at grades between 50% and 80% of the maximal HR, we considered it an intensity of 65%).[41,43–55] For RCTs comparing multiple groups (e.g., walking, cycling, and control), only those reporting exercise intensity were taken into consideration. In cases of the inclusion of multiple study groups within the same study, each single group was compared to an evenly divided control group according to the Cochrane guidelines.[56] When walking performance was reported over time, it was transformed to walking distance in meters.

For the meta-analysis, individual group sample size, mean difference (MD), SD, or 95% CI of the change scores were extracted from each study. The included studies reported changes from baseline score or postintervention scores, and sometimes the SD of one or the other was missing. Consequently, to avoid imputation, we decided, in line with the Cochrane guidelines,[56] to combine these values in the meta-analysis (change and postintervention scores). Since studies recording change scores generally have smaller SDs and, as a result, higher weights, these two different scores were then separated in the analysis. Where postintervention score studies presented a clinical difference between the control group and the intervention group at baseline, the variance was measured on the basis of the SD of the MD, in line with the Cochrane guidelines.[56] This was done because the postintervention score comparison method assumes that random allocation of participants creates intervention groups matched at baseline for age and disease severity. In the latter case, the MD was calculated for the outcome measures by subtracting the baseline from the postintervention values, and the SD was calculated depending on the situation.

Whenever statistical analyses comparing the changes were presented (e.g., CI, standard errors, *t*-values, *p*-values, *F*-values), calculations were possible simply by entering the data into the Cochrane calculator; otherwise, the technique for imputing missing SDs for changes from baseline described in the Cochrane guidelines was used.[56] When studies reported the median and standard error range or IQR, the estimated mean and SD were calculated using Wan et al.'s formulas.[57]

Assessment of the risk of bias

Studies included in the analysis were independently assessed by two reviewers (MF and SL) using the checklist described in the *Cochrane Handbook for Systematic Reviews of Interventions* to determine their methodological quality.[58] This tool contains seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Each category was assessed as having a low, unclear, or high risk of bias, and this allowed for rapid identification of the internal validity.

Statistical analysis

Rayyan software was used to prepare the data from the included studies.[39] Review Manager software (RevMan, version 5.4)[59] was used for statistical analysis. Continuous data are reported as the mean ± SD, and $p \leqslant 0.05$ was considered significant. The data were pooled using a random-effects model considering heterogeneity, and effect sizes for continuous variables were calculated. An overall forest plot was constructed, including all studies for each outcome. Statistical heterogeneity was tested using the *Q*-test and I^2 statistics, and was considered significant at $p < 0.01$. Heterogeneity was considered minimal if the I^2 was between 0 and 30%, moderate if between 30% and 50%, substantial if between 50% and 90%, and considerable if > 90%. Publication bias was analyzed using a funnel plot derived in RevMan when > 10 studies were available.[59] Sensitivity analysis for the individual study effects was conducted by removing each study one at a time to assess whether the absence of a particular study significantly changed the results.

Results

Included trials and patient characteristics

The search identified 3463 studies. Of these, 3262 were removed after screening the titles and abstracts. Of the remaining 201 articles, 181 did not meet the inclusion criteria (Suppl 2). One study[60] was excluded since it did not include the walking performance protocol assessment. A total of 19 studies were included in the quantitative analysis[41,43–55,61–65] (Suppl 2 and 3).

The total number of included patients was 1132 allocated to 26 intervention groups (exercise therapy: $n = 719$; control: $n = 413$). The control group usually received standard care, and was in some studies, informed on the benefits of an active lifestyle (Suppl 3). There were some exceptions: one study compared exercise with vitamin E supplementation,[44] and two studies performed stretching classes[41,62] with the control group. The average age of the patients was 65.7 ± 2.6 years, and the average ankle–brachial index (ABI) was 0.67 ± 0.06 (not all of the studies specified how the ABI was measured, leading to a mix of lowest resting values, most symptomatic limb values, and

mean values between both legs). The sex of the patients was unsystematically reported; on average, in studies reporting sex, 74 ± 15% were men.

Training protocols varied widely among the studies and included different modes of exercise (treadmill walking, overground walking, pole striding, aquatic walking, cycling, arm- and leg-ergometer, plantar-flexion ergometer). Session frequency, duration, and program length varied among the studies, with a mean of 2.6 ± 0.7 sessions per week, 43 ± 14 min of training per session, and 12.7 ± 5.8 weeks of program duration (Suppl 3).

Most studies specified supervision during exercise training sessions, except for Cucato et al.,[62] where it was not explicit but could be assumed; for Brenner et al.,[61] in which participants were instructed to train at home by measuring their HR and monitoring their exercise intensity; and for Sandercock et al.,[49] in which the participants performed a home-based intervention and were instructed to undertake three weekly 30-min walking sessions at an RPE of 12–14. The majority of studies assessed walking performance with treadmill protocols (incremental or inclined constant-load); Zwierska et al.[55] and Walker et al.[53] used the shuttle walk test.

Effects of the interventions

Vigorous vs light-to-moderate exercise intensity

Maximal walking distance. Data on MWD were available from 24 intervention groups with a total sample size of 1044 participants with PAD (Figure 1 and Suppl 4). Exercise therapy improved MWD by 178 m (95% CI 142 to 214; $p < 0.00001$) compared to the control. Heterogeneity among the studies was substantial ($I^2 = 65\%$, $p < 0.00001$). A larger increase in MWD was observed following light-to-moderate (223 m; 95% CI 174 to 271; $p < 0.00001$, $I^2 = 22\%$) compared to vigorous (153 m; 95% CI 113 to 193; $p < 0.00001$, $I^2 = 62\%$) exercise therapy intensity (Figure 1).

Pain-free walking distance. Data on PFWD were available from 19 study groups with a total sample size of 895 participants (Figure 2 and Suppl 5). An overall improvement of 103 m was observed (95% CI 81 to 125; $p < 0.00001$) compared to the controls (Figure 2). There was moderate heterogeneity with a random-effects model ($I^2 = 37\%$, $p = 0.05$). PFWD improved more with a light-to-moderate (130 m; 95% CI 87 to 173; $p < 0.00001$, $I^2 = 59\%$) compared to a vigorous (83 m; 95% CI 61 to 104; $p < 0.00001$, $I^2 = 0\%$) exercise therapy intensity (Figure 2).

Cardiorespiratory fitness ($\dot{V}O_{2peak}$). Data for the $\dot{V}O_{2peak}$ were available from 15 intervention groups with a total sample size of 665 participants (Figure 3). The mean baseline value was 15.7 ± 2.8 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$. An overall improvement of 2.1 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ (95% CI 1.3 to 2.8; $p < 0.00001$) was observed compared to the control group. There was substantial heterogeneity ($I^2 = 68\%$, $p < 0.0001$) in the random-effects model. A larger increase in $\dot{V}O_{2peak}$ was observed following a vigorous (3.0 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$; 95% CI 2.4 to 3.6; $p < 0.00001$, $I^2 = 29\%$) compared to a light-to-moderate (1.1 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$; 95% CI 0.4 to 1.7; $p = 0.001$, $I^2 = 0\%$) exercise therapy intensity (Figure 3).

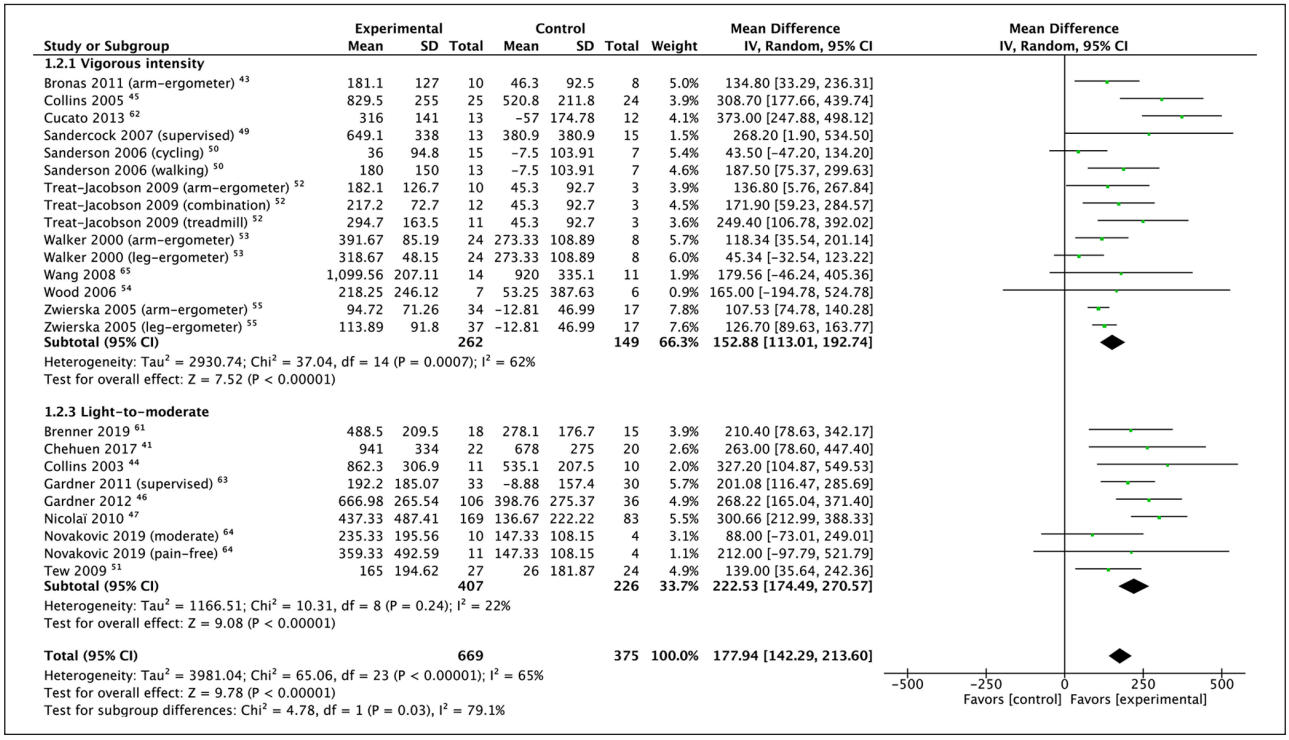

Figure 1. Maximal walking distance (m) following vigorous and light-to-moderate exercise intensity.
IV, inverse variance; SD, standard deviation of change.

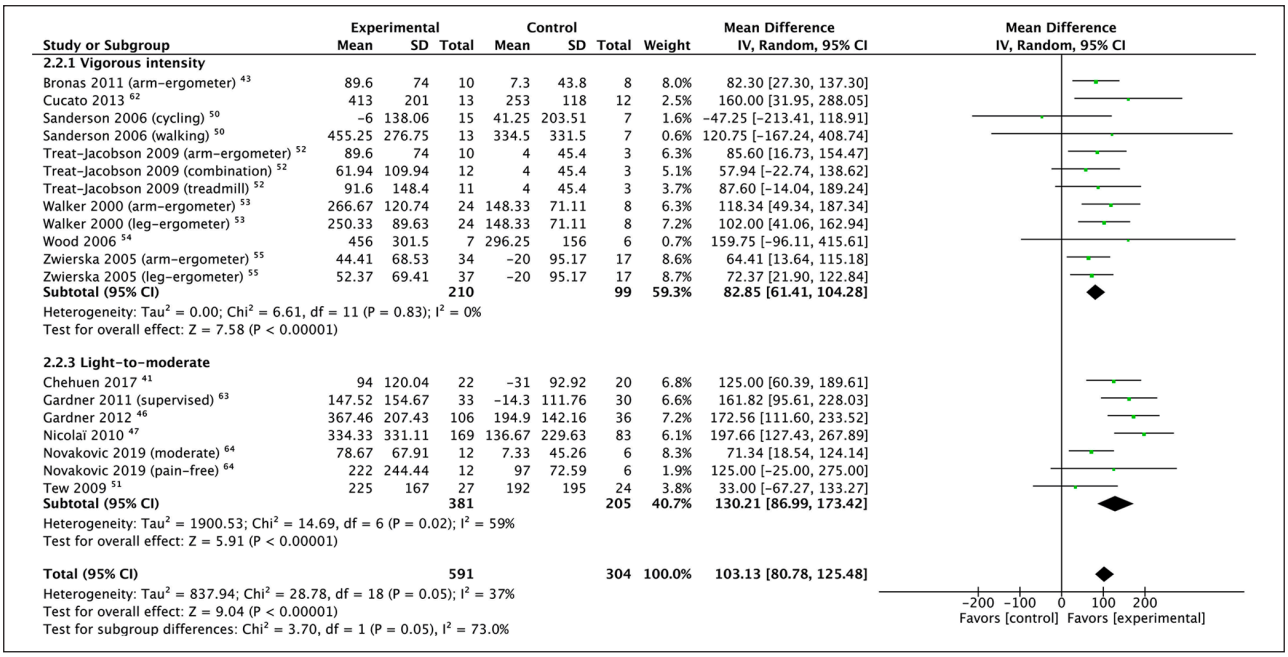

Figure 2. Pain-free walking distance (m) following vigorous and light-to-moderate exercise intensity.
IV, inverse variance; SD: standard deviation of change.

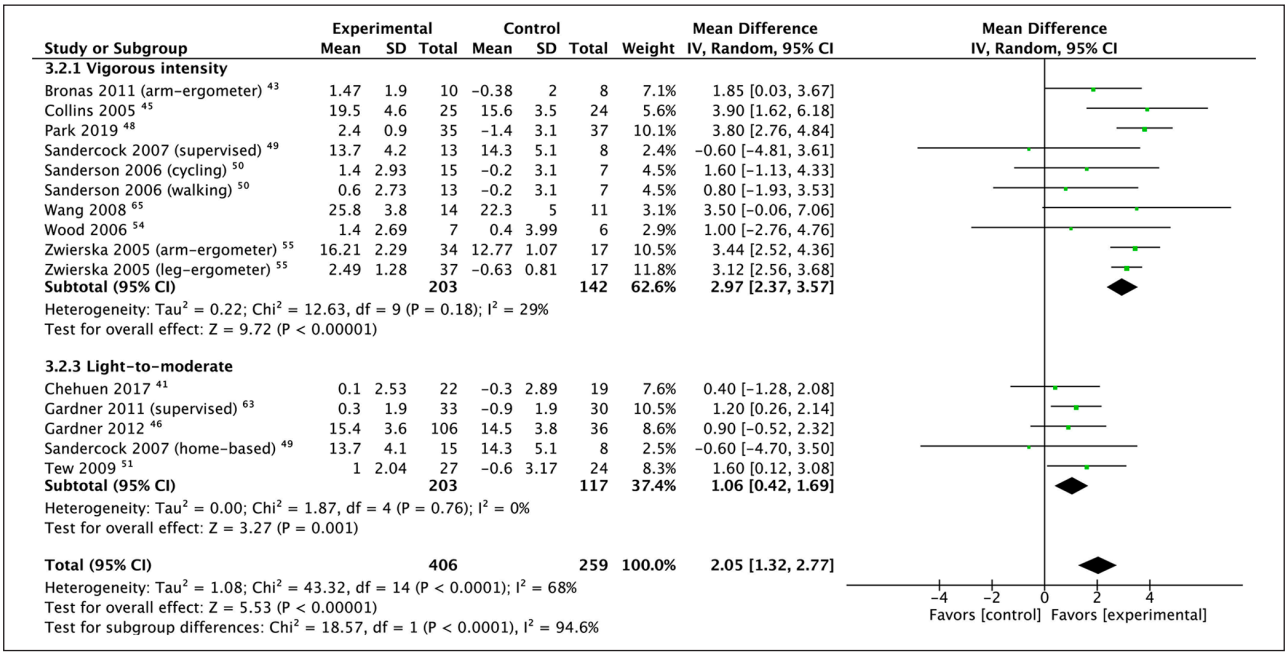

Figure 3. Cardiorespiratory fitness ($\dot{V}O_{2peak}$, mL $O_2 \cdot kg^{-1} \cdot min^{-1}$) following vigorous and light-to-moderate exercise intensity.
IV, inverse variance; SD, standard deviation of change.

High- vs moderate-intensity interval training (HIIT vs MIIT) vs moderate-intensity training (MIT)

Maximal walking distance. Data on MWD were available from 23 intervention groups with a total sample size of 1016 participants (Suppl 6). An overall improvement of 177 m (95% CI 141 to 213; $p < 0.00001$) was observed compared to the control. There was substantial heterogeneity in the random-effects model ($I^2 = 66\%$, $p < 0.00001$). A larger increase in MWD was observed following MIT (235 m; 95% CI 188 to 281; $p < 0.00001$, $I^2 = 9\%$) compared to HIIT (149 m; 95% CI 88 to 210; $p = 0.00001$, $I^2 = 76\%$) and MIIT (159 m; 95% CI 106 to 212; $p < 0.00001$, $I^2 = 48\%$).

Pain-free walking distance. Data on PFWD were available from 19 intervention groups with a total sample size of 895 participants (Suppl 7). An overall improvement of 103 m (95% CI 81 to 125; $p < 0.00001$) was observed compared

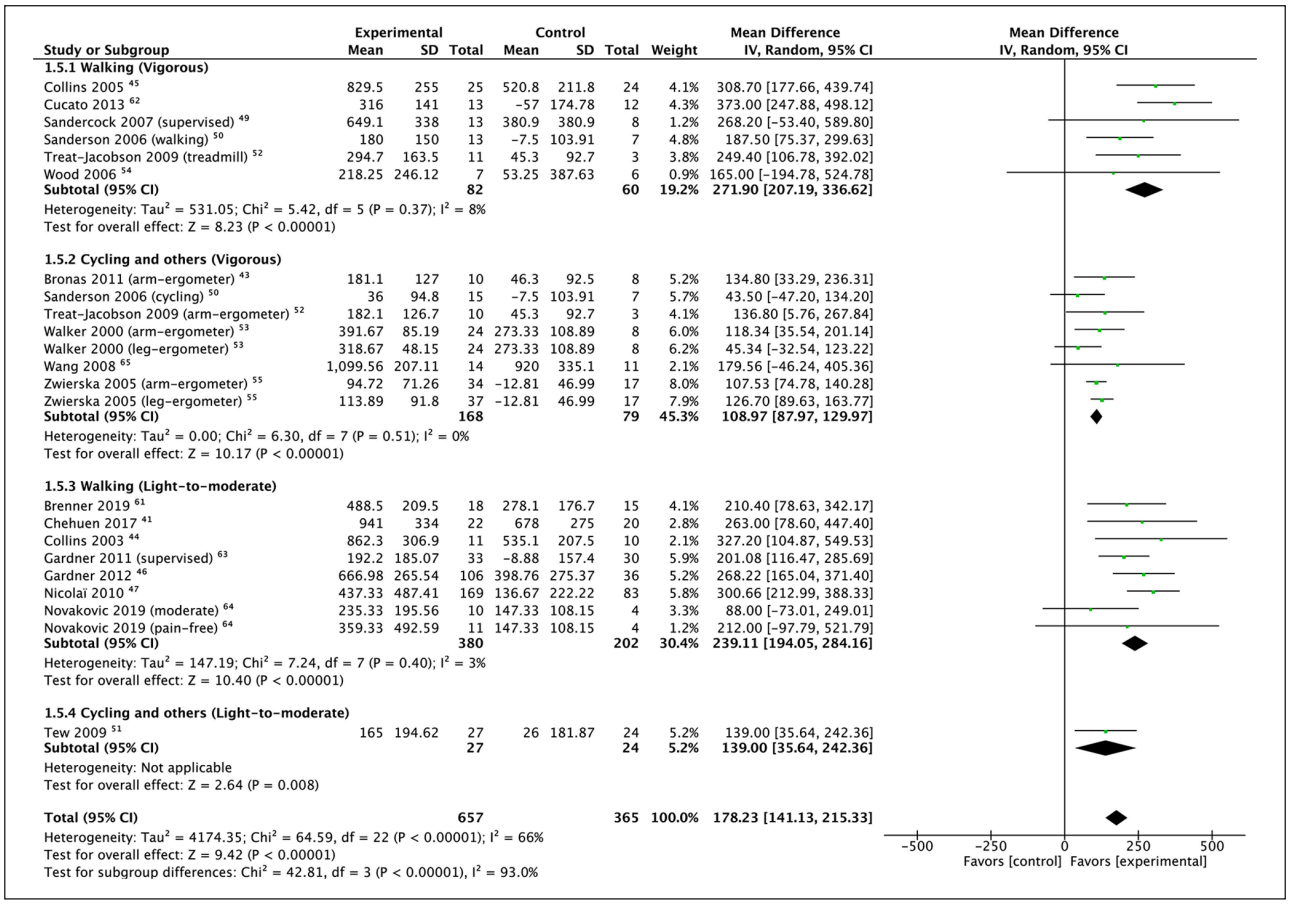

Figure 4. Maximal walking distance (m) following vigorous and light-to-moderate exercise intensity in different training modalities (walking vs others).
IV, inverse variance; SD, standard deviation of change.

to the control. There was moderate heterogeneity (I^2 = 37%, p = 0.05). A larger increase in PFWD was observed following MIT (138 m; 95% CI 92 to 185; $p < 0.00001$, I^2 = 57%) compared to HIIT (72 m; 95% CI 39 to 105; $p < 0.0001$, I^2 = 0%) and MIIT (92 m; 95% CI 67 to 118; $p < 0.00001$, I^2 = 0%).

Cardiorespiratory fitness ($\dot{V}O_{2peak}$). Data for $\dot{V}O_{2peak}$ were available from 13 intervention groups with a total sample size of 600 participants (Suppl 8). An overall improvement of 2.0 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ (95% CI 1.3 to 2.7; $p < 0.00001$) was observed compared to the control. There was substantial heterogeneity in the random-effects model (I^2 = 65%, p = 0.0007). A larger increase in $\dot{V}O_{2peak}$ was observed following HIIT (2.9 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$; 95% CI 2.2 to 3.6; $p < 0.00001$, I^2 = 28%) compared to MIT (1.2 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$; 95% CI 0.5 to 1.9; p = 0.0006, I^2 = 0%) and MIIT (1.9 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$; 95% CI 0.8 to 3.1; p = 0.001, I^2 = 42%).

Training modalities and exercise intensities (walking vs other forms of training)

Maximal walking distance. Data on MWD were available from 23 intervention groups with a total sample size of 1022 participants (Figure 4). A larger increase in MWD was observed following walking training at vigorous (272 m; 95% CI 207 to 337; $p < 0.00001$, I^2 = 8%) compared to light-to-moderate (239 m; 95% CI 194 to 284; $p < 0.00001$, I^2 = 3%) exercise therapy intensity. A single study group[51] was available for cycling and other training modalities performed at a moderate intensity. There was substantial heterogeneity (I^2 = 66%, $p < 0.00001$) in the random-effects model.

Pain-free walking distance. Data on PFWD were available from 14 intervention groups with a total sample size of 771 participants (Suppl 9). A larger increase in PFWD was observed following walking training at light-to-moderate (142 m; 95% CI 100 to 183; $p < 0.00001$, I^2 = 54%) compared to vigorous (97 m; 95% CI 3 to 192; p = 0.04, I^2 = 0%) exercise training. Only two study groups[52,54] were available for walking performed at a vigorous intensity. A single study group[51] was included for cycling and other training modalities performed at a moderate intensity. There was substantial heterogeneity (I^2 = 51%, p = 0.01) in the random-effects model.

Cardiorespiratory fitness ($\dot{V}O_{2peak}$). Data for $\dot{V}O_{2peak}$ were available from 15 intervention groups with a total sample size of 665 participants (Suppl 10). An overall improvement of 2.1 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ (95% CI 1.3 to 2.8; $p <$ 0.00001, I^2 = 68%) was observed compared to

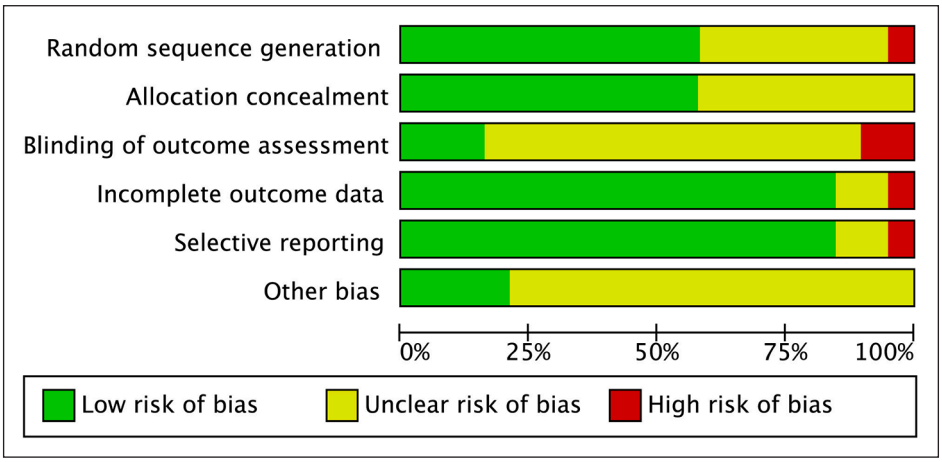

Figure 5. Review of authors' judgements about each risk of bias item presented as percentages across all included studies.

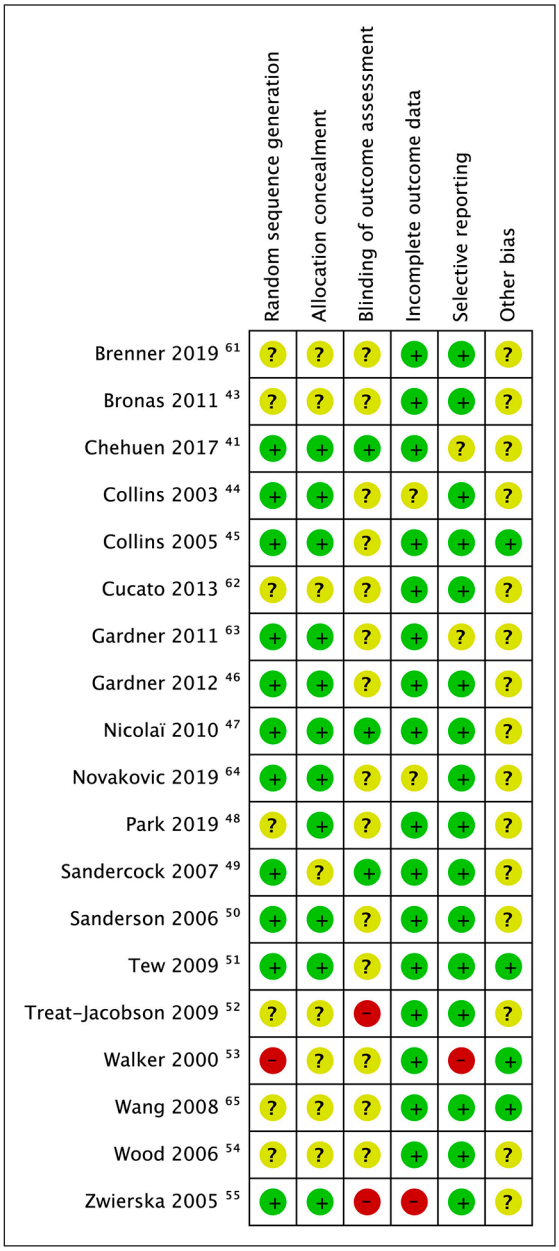

Figure 6. Review of authors' judgements about each risk of bias item for each included study.
+: indicates low risk of bias; -: indicates high risk of bias; ?: indicates unclear risk of bias.

the control. A larger increase in $\dot{V}O_{2peak}$ was observed following cycling and other training modalities with vigorous training (3.1 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$; 95% CI 2.7 to 3.6; $p < 0.00001$, $I^2 = 0\%$). The greatest benefits from light-to-moderate intensity were seen for cycling and other training modalities (1.6 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$; 95% CI 0.1 to 3.1; $p = 0.03$), but only a single study reported on these interventions.[51]

Risk of bias

A summary of bias present within each included study is presented in Figures 5 and 6. Overall, the risk of bias of the included trials was modest, with the major limitations being the blinding of the outcome assessment and some concerns about the concealment of randomization and random sequence generation. Blinding of the participants was removed from the analysis of quality, as the nature of the exercise interventions does not allow for blinding. Three trials[41,47,49] were judged to have a low risk of blinding of outcome assessment because the study personnel who administered the treadmill tests were blinded to the previous outcomes and the participants' group assignment.

Discussion

The results of our analyses show that (1) few studies clearly report exercise therapy intensity in symptomatic patients with PAD using conventional % heart rate, % peak oxygen uptake, or the rate of perceived exertion cut-offs; (2) for the 19 included studies doing so, light-to-moderate was superior to vigorous exercise intensity in improving PFWD and MWD; (3) when training modalities were considered, walking at vigorous intensity showed the greatest improvement in MWD, while walking at light-to-moderate intensity showed the greatest improvement in PFWD; (4) vigorous was superior to light-to-moderate exercise intensity in improving cardiorespiratory fitness; and (5) when training modalities were considered, cycling and other nonwalking forms of training performed at vigorous intensity elicited the greatest improvements in $\dot{V}O_{2peak}$.

Over the past 50 years, many studies have reported the beneficial effects of SET on walking performance in patients with symptomatic PAD. A recent meta-analysis showed that SET (including different exercise modalities) improves PFWD (82 m; 95% CI 72 to 92) and MWD (120 m; 95% CI 51 to 190) in patients with symptomatic PAD.[22] Another meta-analysis by Fakhry et al.[66] showed slightly better improvements (PFWD: 128 m [95% CI 92 to 165]; MWD: 180 m [95% CI 130 to 238]) following supervised walking exercise. Treadmill or overground (track) walking, common training modalities in patients with claudication, have been investigated the most.[4,16,22,24,67] The majority of trials used claudication pain severity to provide guidance during the training sessions.[1,4,16,28–31,67] Patients are usually instructed to walk at a speed that induces the onset of claudication pain within 3–5 min and moderate-to-severe claudication pain within 8–10 min.[4,16,67] Then, the patients are instructed to rest for 2–5 min (until pain resolution) before resuming walking.[4,16,67] This cycle is repeated over 30–60 min, depending on the patient's exercise and pain tolerance.

Whether training therapy should be performed at pain-free, mild, or moderate-to-severe claudication in patients with symptomatic PAD remains a matter of debate.[4,16,67] Although many studies have suggested that exercise therapy should be performed at moderate-to-severe claudication pain to produce better results,[22,27,66] others have reported that improvements in walking performance may be obtained with less severe claudication pain during exertion.[26] McDermott et al.[68] recently showed in patients with PAD that 12-month home-based unsupervised exercise therapy performed at moderate-to-severe ischemic leg symptoms (the high-intensity pain walking group) was more effective than exercise therapy performed without ischemic leg symptoms (the low-intensity pain walking group) for improving their 6-minute walking distance, even though the high-intensity pain walking group walked 50% less. Claudication pain severity during exercise interventions may thus be a key factor for walking improvement in patients with PAD. However, lower completion and adherence rates in 'high-pain' exercise therapy programs have been observed, suggesting the need for alternative training modalities in this population.[69]

Today's guidelines give recommendations in terms of claudication pain severity, SET volume, duration, and frequency, but little or no guidance is offered as far as training intensity is concerned.[1,4,28–31] The novelty of the present meta-analysis is that improvements in walking capacity and cardiorespiratory fitness following exercise therapy were assessed as a function of the generally recognized relative therapy intensity cutoffs (based on the heart rate, peak oxygen uptake or the rate of perceived exertion) and different protocols of exercise intervention in patients with symptomatic PAD. Using our selection criteria, only 19 studies could be included in our meta-analysis, suggesting that the investigation of exercise intensity (which was not only based on claudication pain severity) is understudied during exercise therapy in patients with PAD.

Compared to previous meta-analyses, our findings on walking performance yielded similar results, somewhat higher than some[22,24] and lower than others.[27,70] The first major result of the present meta-analysis was that the degree of improvement in walking performance varied according to the training exercise intensity. Our quantitative meta-analysis revealed that vigorous was less effective than light-to-moderate exercise training intensity in improving walking performance. The difference between vigorous and light-to-moderate exercise training was ~70 m for MWD and ~47 m for PFWD in favor of light-to-moderate intensity. Furthermore, similar results were observed when the training protocol was considered, and the difference between HIIT and MIT was ~86 m for MWD and ~66 m for PFWD in favor of MIT. The second major result of the present meta-analysis was that when the mode of training was considered, walking (including other forms such as pole striding) at vigorous intensity was better for improving MWD compared to cycling and other nonwalking forms of training. The difference was ~163 m for MWD in favor of walking training. Our results also showed (although with few studies included) that greater improvements in PFWD were observed following walking at light-to-moderate intensity compared to cycling and other nonwalking forms of training. The difference was ~109 m for PFWD in favor of walking training.

These results contrast with those of Gardner et al.,[71] who reported that walking exercise intensity (40% vs 80% of maximal workload) was not related to PFWD and MWD improvement in patients with PAD. Our results are in line with those of Slørdahl et al.[72] comparing the effects of different walking exercise training intensities (60% vs 80% of the $\dot{V}O_{2peak}$) in patients with symptomatic PAD. The results of that study[72] showed a better outcome for treadmill time-to-exhaustion following HIIT compared to low-intensity exercise training, even if the work economy improved similarly in both groups following exercise therapy.

It is now well accepted that nonwalking training modalities (such as arm ergometer, resistance training, cycling) are effective for improving walking performance in patients with PAD.[25,26,73] Although others have reported no clear difference between training modalities for improving walking performance,[73] our results indicate that walking training elicits a greater improvement in walking performance (PFWD and MWD) compared to other forms of training. In addition, our results show that both low-to-moderate and vigorous walking exercise intensity resulted in greater improvement in walking performance compared to other forms of training performed at the same exercise intensity. Alternative exercise modalities are also beneficial but to a lesser extent. Although not yet completely elucidated,[4,16,67] a possible explanation may reside in the importance of the presence of ischemic leg pain during exertion for inducing greater walking adaptations. Nonwalking training alternatives may induce lower or no ischemic leg pain compared to walking among patients with PAD. On the other hand, in the included studies in the present meta-analysis, most of the walking training programs were performed under pain (from mild to maximal) conditions (Suppl 3). These findings suggest that walking at any exercise intensity (low-to-moderate or vigorous), which elicits claudication leg pain during exertion, should be considered the primary exercise modality for improving walking abilities in patients with PAD. This is

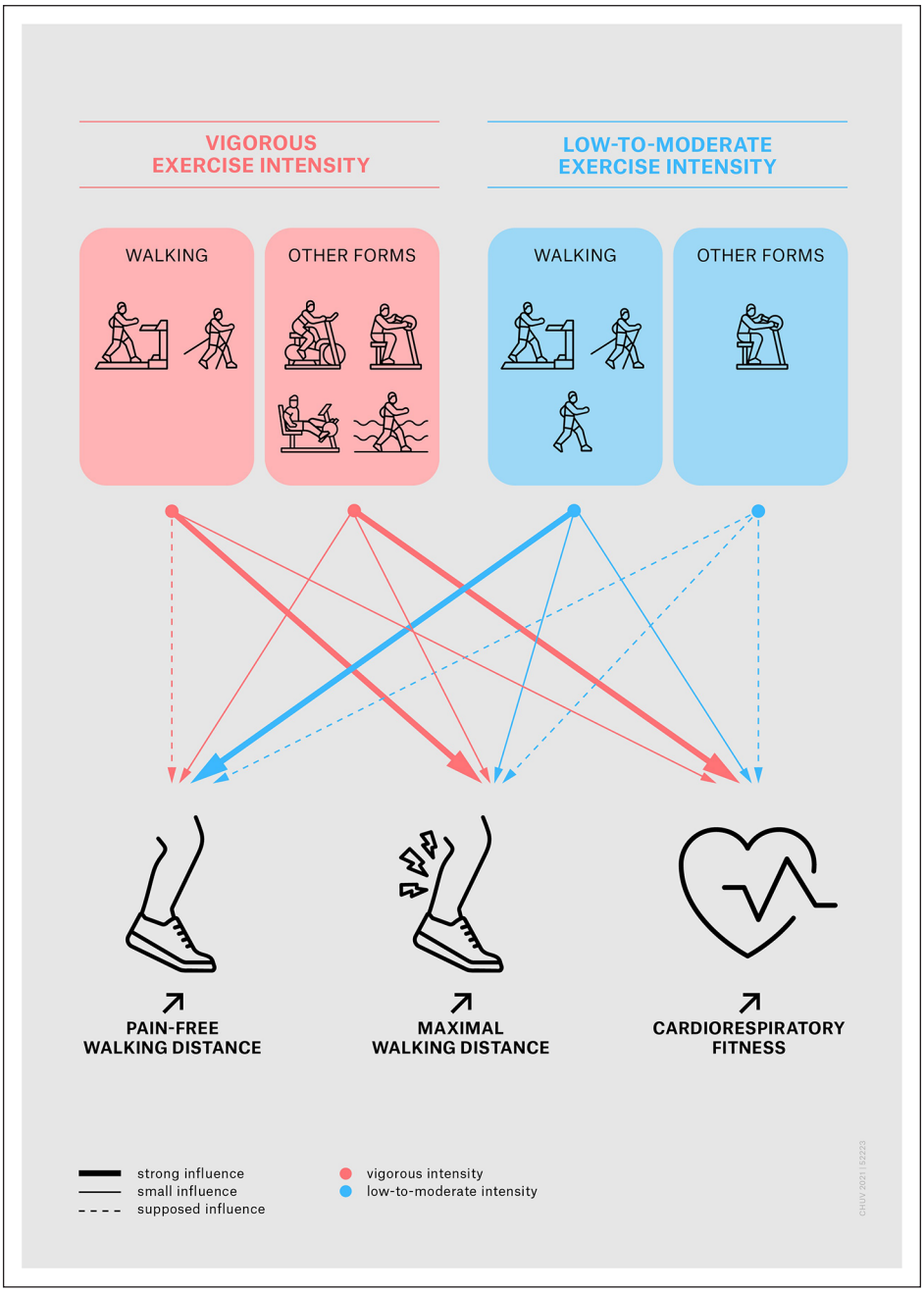

Figure 7. Summary findings of the meta-analysis. This figure shows how nonpain-based exercise therapy intensity (light-to-moderate or vigorous) affects improvements in walking performance (pain-free and maximal walking distance) and cardiorespiratory fitness of patients with symptomatic lower-extremity PAD. The thickness of the arrows illustrates the strength of the effect, based on the results of the quantitative meta-analysis as reported in Figure 4, Suppl 9, and Suppl 10. The exercise therapy intensity and modality that improved each outcome to a greatest extent was reported as 'strong influence'. The others were reported as 'small influence' or 'supposed influence'. The latter was used when the quantitative meta-analysis was based on two or fewer studies. Overall, our results suggest that both exercise therapy intensity and modality should be considered for a personalized approach, depending on the patient's current limitations and functional capacity and, in general, the goals of exercise therapy in patients with PAD.
PAD, peripheral artery disease.

consistent with current international guidelines that recommend walking training in the management of intermittent claudication.[1,4,16,28–31,67] Other nonwalking training modalities should be proposed as an effective alternative in patients who are unable to perform walking sessions.[1,4,16,28–31,67]

Cardiorespiratory fitness, quantified as $\dot{V}O_{2max}$ or MET_{max} (i.e., maximal metabolic rate over that at rest) is a major predictor of all-cause mortality.[74,75] We found that vigorous-type exercise therapy was superior to moderate exercise therapy in increasing cardiorespiratory fitness. There is growing evidence that HIIT may be better than MIT in improving cardiorespiratory fitness, including patients with cardiovascular and metabolic diseases.[33–37,76,77] In patients with symptomatic PAD, the differing effects of HIIT and MIT need to be more fully investigated. A meta-analysis by Parmenter et al.[24] showed an overall greater improvement in $\dot{V}O_{2peak}$ following vigorous compared to low-to-moderate exercise intensity. A systematic review

conducted by Pymer et al.[78] showed the potential role of HIIT in improving cardiorespiratory fitness in patients with PAD. The results of our meta-analysis agree with these findings.[24,78] We found a difference of ~1.9 mL O_2·kg^{-1}·min^{-1} in favor of vigorous intensity training. In symptomatic patients with PAD, functional performance (i.e., walking) and its impact on their quality of life are of prime importance. Participants who followed a vigorous exercise training program and improved their $\dot{V}O_{2peak}$ more increased their walking performance less compared to those who trained at light-to-moderate exercise intensity. Although inconsistent with previous results,[43] this observation supports the hypothesis that in this population, claudication pain, rather than cardiorespiratory fitness, is likely to be the main walking performance limiting factor. It is interesting to note that when the mode of training was considered, cycling and other forms of training performed at vigorous intensity elicited the greatest improvements in $\dot{V}O_{2peak}$. During exertion, cycling and other forms of training might elicit lower claudication pain (or no pain) compared to walking (Suppl 3); it is therefore possible that a higher exercise intensity would be reached during these training modalities. This may lead to greater improvements in cardiorespiratory fitness in this population.

Taken together, both training modality and exercise intensity should be considered for a personalized approach depending on a patient's current limitations and functional capacity and the goals of exercise therapy. This highlights that different outcomes (walking performance and cardiorespiratory fitness) can be improved with specific training approaches (intensity and modality) in patients with symptomatic PAD. Figure 7 summarizes and highlights the main findings of our meta-analysis.

Perspectives

The results of our meta-analysis suggest that both training modality and exercise intensity (based on % peak heart rate, % peak oxygen uptake, or the rate of perceived exertion) should be considered when looking for the best results in patients with symptomatic PAD. Both functional and cardiorespiratory capacities are desirable outcomes but they need different exercise therapy programs (Figure 7). Current guidelines suggest using claudication pain severity to provide guidance during training sessions in patients with PAD.[1,4,16,28–31,67] However, in most studies, no clear distinction is made between exercise intensity and claudication pain severity concerning the monitoring of exercise therapy.[16] Indeed, an increase in claudication pain severity during a walking bout does not necessarily imply an increase in exercise intensity.[79] For example, after an initial increase, the heart rate does not necessarily increase much further during a walking bout, whereas claudication pain severity can. This suggests that an increase in claudication pain severity with time is more related to an increase in exercise duration than exercise intensity.[79]

Future investigations in this field should assess how and by how much each exercise intensity and modality is incorporated into a training program to obtain the best results. In addition, other outcomes, such as physical function (6-minute walking test[80] or Short Performance Physical Battery score[81]) and self-perceived quality of life and walking abilities,[82,83] should also be assessed. Presently, only one study is investigating the safety and feasibility of a novel, pragmatic, high-intensity interval training program in patients with intermittent claudication.[84,85]

The approach of prescribing exercise therapy intensity in patients with PAD should align with that of other cardiovascular and metabolic diseases.[86,87] Exercise therapy should be monitored concerning exercise intensity and the severity of claudication pain; this latter parameter is useful in adjusting the training according to the ability and condition of the patient. Because of claudication pain, prescribing a specific exercise intensity (especially vigorous) may be unfeasible in some symptomatic patients with PAD. However, from a clinical standpoint, such an approach would allow us to better understand which type of training the patient can carry out and would allow for systematic and replicable development by others.

Limitations

Some methodological limitations need to be addressed. First, we accepted any mode of cardiorespiratory training, and we pooled different walking capacities in the same analysis. This approach led to moderate-to-high among-study heterogeneity. Including different walking test protocols (incremental or constant-load inclined treadmill or shuttle walk test) for assessing walking performance may have affected the outcomes since previous studies reported that the reliabilities of walking performance depend on the testing protocols used for patients with PAD.[88,89] Second, the classification system used to determine the exercise intensity based on the RPE may have affected the results. Indeed, it is still debated which cutoff is more appropriate to distinguish low-to-moderate from vigorous exercise training. Some have defined low-to-moderate exercise intensity with an RPE $\leqslant$ 13,[32] others $\leqslant$ 14,[90] or $\leqslant$ 15.[37] In the present meta-analysis, we decided to use the widely used ACSM guidelines,[32] which provide concomitant exercise intensity cutoffs for different parameters, such as heart rate, oxygen consumption, and perceived exertion. Third, in the few studies where it was necessary to impute the SD, the correlation coefficient proposed by the Cochrane guidelines was used.[41,50,54,61,64] Only a single study[63] provided the complete required data (baseline, post and change scores, with associated SDs).

Conclusions

Current guidelines suggest using claudication pain severity to provide guidance during training sessions in patients with PAD. Our meta-analysis and systematic review are the first to investigate walking capacity and cardiorespiratory fitness as a function of relative therapy intensity based on heart rate, oxygen uptake or RPE and different protocols of exercise intervention in patients with symptomatic PAD. Our results revealed that vigorous exercise was less effective than light-to-moderate exercise intensity in improving MWD and PFWD but it provided more benefits for cardiorespiratory fitness. When exercise modalities were

considered (walking vs other forms of exercise), walking at a vigorous intensity showed the greatest improvement in MWD, whereas light-to-moderate intensity walking training achieved better results for PFWD. These results (1) suggest that both exercise therapy intensity and modality should be considered for a personalized approach depending on the patient's current limitations and functional capacity and the goals of exercise therapy, and (2) call for study of the individual roles of each exercise intensity and modality on walking performance and cardiorespiratory fitness in patients with symptomatic PAD. More precision in prescribing therapy intensity is required for future guidance, distinguishing between claudication pain severity and exercise therapy intensity in patients with symptomatic PAD.

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Supplementary material

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References

1. Aboyans V, Ricco JB, Bartelink MEL, et al. 2017 ESC Guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the European Stroke Organization (ESO)The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). *Eur Heart J* 2018; 39: 763–816.
2. Frank U, Nikol S, Belch J. 5 Conservative treatment for PAD – Risk factor management. *Vasa* 2019; 48(suppl 102): 1–12.
3. Kullo IJ, Rooke TW. Peripheral artery disease. *N Engl J Med* 2016; 374: 861–871.
4. Treat-Jacobson D, McDermott MM, Bronas UG, et al. Optimal exercise programs for patients with peripheral artery disease: A scientific statement from the American Heart Association. *Circulation* 2019; 139: e10–e33.
5. Hirsch AT, Criqui MH, Treat-Jacobson D, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. *JAMA* 2001; 286: 1317–1324.
6. Bartelink ML, Stoffers HE, Biesheuvel CJ, et al. Walking exercise in patients with intermittent claudication. Experience in routine clinical practice. *Br J Gen Pract* 2004; 54: 196–200.
7. McDermott MM, Liu K, O'Brien E, et al. Measuring physical activity in peripheral arterial disease: A comparison of two physical activity questionnaires with an accelerometer. *Angiology* 2000; 51: 91–100.
8. Camara LC, Ritti-Dias RM, Meneses AL, et al. Isokinetic strength and endurance in proximal and distal muscles in patients with peripheral artery disease. *Ann Vasc Surg* 2012; 26: 1114–1119.
9. Gommans LNM, Smid AT, Scheltinga MRM, et al. Prolonged stance phase during walking in intermittent claudication. *J Vasc Surg* 2017; 66: 515–522.
10. Koutakis P, Johanning JM, Haynatzki GR, et al. Abnormal joint powers before and after the onset of claudication symptoms. *J Vasc Surg* 2010; 52: 340–347.
11. Lanzi S, Boichat J, Calanca L, et al. Gait changes after supervised exercise training in patients with symptomatic lower extremity peripheral artery disease. *Vasc Med* 2021; 26: 259–266.
12. Myers SA, Huben NB, Yentes JM, et al. Spatiotemporal changes posttreatment in peripheral arterial disease. *Rehabil Res Pract* 2015; 2015: 124023.
13. Pipinos II, Judge AR, Selsby JT, et al. The myopathy of peripheral arterial occlusive disease: Part 1. Functional and histomorphological changes and evidence for mitochondrial dysfunction. *Vasc Endovascular Surg* 2007; 41: 481–489.
14. Pipinos II, Judge AR, Selsby JT, et al. The myopathy of peripheral arterial occlusive disease: Part 2. Oxidative stress, neuropathy, and shift in muscle fiber type. *Vasc Endovascular Surg* 2008; 42: 101–112.
15. Schieber MN, Hasenkamp RM, Pipinos II, et al. Muscle strength and control characteristics are altered by peripheral artery disease. *J Vasc Surg* 2017; 66: 178–186.e112.
16. Harwood A, Pymer S, Ingle L, et al. Exercise training for intermittent claudication: A narrative review and summary of guidelines for practitioners. *BMJ Open Sport Exerc Med* 2020; 6: e000897.
17. McDermott MM, Ferrucci L, Liu K, et al. Leg symptom categories and rates of mobility decline in peripheral arterial disease. *J Am Geriatr Soc* 2010; 58: 1256–1262.
18. McDermott MM, Liu K, Greenland P, et al. Functional decline in peripheral arterial disease: Associations with the ankle brachial index and leg symptoms. *JAMA* 2004; 292: 453–461.
19. McDermott MM, Liu K, Ferrucci L, et al. Greater sedentary hours and slower walking speed outside the home predict faster declines in functioning and adverse calf muscle changes in peripheral arterial disease. *J Am Coll Cardiol* 2011; 57: 2356–2364.
20. Regensteiner JG, Hiatt WR, Coll JR, et al. The impact of peripheral arterial disease on health-related quality of life in the Peripheral Arterial Disease Awareness, Risk, and Treatment: New Resources for Survival (PARTNERS) Program. *Vasc Med* 2008; 13: 15–24.
21. Liles DR, Kallen MA, Petersen LA, et al. Quality of life and peripheral arterial disease. *J Surg Res* 2006; 136: 294–301.
22. Lane R, Harwood A, Watson L, et al. Exercise for intermittent claudication. *Cochrane Database Syst Rev* 2017; 12: CD000990.
23. Parmenter BJ, Dieberg G, Phipps G, et al. Exercise training for health-related quality of life in peripheral artery disease:

A systematic review and meta-analysis. *Vasc Med* 2015; 20: 30–40.
24. Parmenter BJ, Dieberg G, Smart NA. Exercise training for management of peripheral arterial disease: A systematic review and meta-analysis. *Sports Med* 2015; 45: 231–244.
25. Parmenter BJ, Mavros Y, Ritti Dias R, et al. Resistance training as a treatment for older persons with peripheral artery disease: A systematic review and meta-analysis. *Br J Sports Med* 2020; 54: 452–461.
26. Parmenter BJ, Raymond J, Dinnen P, et al. A systematic review of randomized controlled trials: Walking versus alternative exercise prescription as treatment for intermittent claudication. *Atherosclerosis* 2011; 218: 1–12.
27. Gardner AW, Poehlman ET. Exercise rehabilitation programs for the treatment of claudication pain. A meta-analysis. *JAMA* 1995; 274: 975–980.
28. NICE. *Peripheral arterial disease: Diagnosis and management clinical guideline [CG147]*. London: National Institute for Health and Care Excellence, 2012.
29. Au TB, Golledge J, Walker PJ, et al. Peripheral arterial disease – diagnosis and management in general practice. *Aust Fam Physician* 2013; 42: 397–400.
30. Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: Executive Summary: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2017; 135: e686–e725.
31. Norgren L, Hiatt WR, Dormandy JA, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *J Vasc Surg* 2007; 45 Suppl S: S5–67.
32. Garber CE, Blissmer B, Deschenes MR, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: Guidance for prescribing exercise. *Med Sci Sports Exerc* 2011; 43: 1334–1359.
33. Costa EC, Hay JL, Kehler DS, et al. Effects of high-intensity interval training versus moderate-intensity continuous training on blood pressure in adults with pre- to established hypertension: A systematic review and meta-analysis of randomized trials. *Sports Med* 2018; 48: 2127–2142.
34. Giallauria F, Smart NA, Cittadini A, et al. Exercise training modalities in chronic heart failure: Does high intensity aerobic interval training make the difference? *Monaldi Arch Chest Dis* 2016; 86: 754.
35. Karlsen T, Aamot IL, Haykowsky M, et al. High intensity interval training for maximizing health outcomes. *Prog Cardiovasc Dis* 2017; 60: 67–77.
36. Viana AA, Fernandes B, Alvarez C, et al. Prescribing high-intensity interval exercise by RPE in individuals with type 2 diabetes: Metabolic and hemodynamic responses. *Appl Physiol Nutr Metab* 2019; 44: 348–356.
37. Wewege MA, Ahn D, Yu J, et al. High-intensity interval training for patients with cardiovascular disease—is it safe? A systematic review. *J Am Heart Assoc* 2018; 7: e009305.
38. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* 2021; 372: n71.
39. Ouzzani M, Hammady H, Fedorowicz Z, et al. Rayyan—A web and mobile app for systematic reviews. *Syst Rev* 2016; 5: 210.
40. Hansen D, Bonne K, Alders T, et al. Exercise training intensity determination in cardiovascular rehabilitation: Should the guidelines be reconsidered? *Eur J Prev Cardiol* 2019; 26: 1921–1928.
41. Chehuen M, Cucato GG, Carvalho CRF, et al. Walking training at the heart rate of pain threshold improves cardiovascular function and autonomic regulation in intermittent claudication: A randomized controlled trial. *J Sci Med Sport* 2017; 20: 886–892.
42. Nes BM, Janszky I, Wisloff U, et al. Age-predicted maximal heart rate in healthy subjects: The HUNT fitness study. *Scand J Med Sci Sports* 2013; 23: 697–704.
43. Bronas UG, Treat-Jacobson D, Leon AS. Comparison of the effect of upper body-ergometry aerobic training vs treadmill training on central cardiorespiratory improvement and walking distance in patients with claudication. *J Vasc Surg* 2011; 53: 1557–1564.
44. Collins EG, Edwin Langbein W, Orebaugh C, et al. PoleStriding exercise and vitamin E for management of peripheral vascular disease. *Med Sci Sports Exerc* 2003; 35: 384–393.
45. Collins EG, Langbein WE, Orebaugh C, et al. Cardiovascular training effect associated with polestriding exercise in patients with peripheral arterial disease. *J Cardiovasc Nurs* 2005; 20: 177–185.
46. Gardner AW, Montgomery PS, Parker DE. Optimal exercise program length for patients with claudication. *J Vasc Surg* 2012; 55: 1346–1354.
47. Nicolaï SP, Teijink JA, Prins MH, et al. Multicenter randomized clinical trial of supervised exercise therapy with or without feedback versus walking advice for intermittent claudication. *J Vasc Surg* 2010; 52: 348–355.
48. Park SY, Kwak YS, Pekas EJ. Impacts of aquatic walking on arterial stiffness, exercise tolerance, and physical function in patients with peripheral artery disease: A randomized clinical trial. *J Appl Physiol (1985)* 2019; 127: 940–949.
49. Sandercock GR, Hodges LD, Das SK, et al. The impact of short term supervised and home-based walking programmes on heart rate variability in patients with peripheral arterial disease. *J Sports Sci Med* 2007; 6: 471–476.
50. Sanderson B, Askew C, Stewart I, et al. Short-term effects of cycle and treadmill training on exercise tolerance in peripheral arterial disease. *J Vasc Surg* 2006; 44: 119–127.
51. Tew G, Nawaz S, Zwierska I, et al. Limb-specific and cross-transfer effects of arm-crank exercise training in patients with symptomatic peripheral arterial disease. *Clin Sci (Lond)* 2009; 117: 405–413.
52. Treat-Jacobson D, Bronas UG, Leon AS. Efficacy of arm-ergometry versus treadmill exercise training to improve walking distance in patients with claudication. *Vasc Med* 2009; 14: 203–213.
53. Walker RD, Nawaz S, Wilkinson CH, et al. Influence of upper- and lower-limb exercise training on cardiovascular function and walking distances in patients with intermittent claudication. *J Vasc Surg* 2000; 31: 662–669.
54. Wood RE, Sanderson BE, Askew CD, et al. Effect of training on the response of plasma vascular endothelial growth factor to exercise in patients with peripheral arterial disease. *Clin Sci (Lond)* 2006; 111: 401–409.
55. Zwierska I, Walker RD, Choksy SA, et al. Upper- vs lower-limb aerobic exercise rehabilitation in patients with symptomatic peripheral arterial disease: A randomized controlled trial. *J Vasc Surg* 2005; 42: 1122–1130.
56. Cumpston M, Li T, Page MJ, et al. Updated guidance for trusted systematic reviews: A new edition of the Cochrane Handbook for Systematic Reviews of Interventions. *Cochrane Database Syst Rev* 2019; 10: ED000142.

57. Wan X, Wang W, Liu J, et al. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014; 14: 135.
58. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; 343: d5928.
59. Drahota A, Beller E. Cochrane Training. RevMan calculator, https://training.cochrane.org/resource/revman-calculator (2020, accessed 13 May 2021).
60. Ahmed H, Helmy Z, Abdeen H, et al. Efficacy of high intensity interval training on endothelial function in diabetics with peripheral arterial insufficiency. *Biosi Res* 2019; 16: 629–638.
61. Brenner IKM, Brown CA, Hains SJM, et al. Low-intensity exercise training increases heart rate variability in patients with peripheral artery disease. *Biol Res Nurs* 2020; 22: 24–33.
62. Cucato GG, Chehuen Mda R, Costa LA, et al. Exercise prescription using the heart of claudication pain onset in patients with intermittent claudication. *Clinics (Sao Paulo)* 2013; 68: 974–978.
63. Gardner AW, Parker DE, Montgomery PS, et al. Efficacy of quantified home-based exercise and supervised exercise in patients with intermittent claudication: A randomized controlled trial. *Circulation* 2011; 123: 491–498.
64. Novakovic M, Krevel B, Rajkovic U, et al. Moderate-pain versus pain-free exercise, walking capacity, and cardiovascular health in patients with peripheral artery disease. *J Vasc Surg* 2019; 70: 148–156.
65. Wang E, Hoff J, Loe H, et al. Plantar flexion: An effective training for peripheral arterial disease. *Eur J Appl Physiol* 2008; 104: 749–756.
66. Fakhry F, van de Luijtgaarden KM, Bax L, et al. Supervised walking therapy in patients with intermittent claudication. *J Vasc Surg* 2012; 56: 1132–1142.
67. Treat-Jacobson D, McDermott MM, Beckman JA, et al. Implementation of supervised exercise therapy for patients with symptomatic peripheral artery disease: A science advisory from the American Heart Association. *Circulation* 2019; 140: e700–e710.
68. McDermott MM, Spring B, Tian L, et al. Effect of low-intensity vs high-intensity home-based walking exercise on walk distance in patients with peripheral artery disease: The LITE Randomized Clinical Trial. *JAMA* 2021; 325: 1266–1276.
69. Lin E, Nguyen CH, Thomas SG. Completion and adherence rates to exercise interventions in intermittent claudication: Traditional exercise versus alternative exercise – a systematic review. *Eur J Prev Cardiol* 2019; 26: 1625–1633.
70. Lyu X, Li S, Peng S, et al. Intensive walking exercise for lower extremity peripheral arterial disease: A systematic review and meta-analysis. *J Diabetes* 2016; 8: 363–377.
71. Gardner AW, Montgomery PS, Flinn WR, et al. The effect of exercise intensity on the response to exercise rehabilitation in patients with intermittent claudication. *J Vasc Surg* 2005; 42: 702–709.
72. Slørdahl SA, Wang E, Hoff J, et al. Effective training for patients with intermittent claudication. *Scand Cardiovasc J* 2005; 39: 244–249.
73. Jansen SC, Abaraogu UO, Lauret GJ, et al. Modes of exercise training for intermittent claudication. *Cochrane Database Syst Rev* 2020; 8: CD009638.
74. Kokkinos P, Myers J, Kokkinos JP, et al. Exercise capacity and mortality in black and white men. *Circulation* 2008; 117: 614–622.
75. Leeper NJ, Myers J, Zhou M, et al. Exercise capacity is the strongest predictor of mortality in patients with peripheral arterial disease. *J Vasc Surg* 2013; 57: 728–733.
76. Hannan AL, Hing W, Simas V, et al. High-intensity interval training versus moderate-intensity continuous training within cardiac rehabilitation: A systematic review and meta-analysis. *Open Access J Sports Med* 2018; 9: 1–17.
77. Weston KS, Wisloff U, Coombes JS. High-intensity interval training in patients with lifestyle-induced cardiometabolic disease: A systematic review and meta-analysis. *Br J Sports Med* 2014; 48: 1227–1234.
78. Pymer S, Palmer J, Harwood AE, et al. A systematic review of high-intensity interval training as an exercise intervention for intermittent claudication. *J Vasc Surg* 2019; 70: 2076–2087.
79. Gardner AW, Afaq A. Management of lower extremity peripheral arterial disease. *J Cardiopulm Rehabil Prev* 2008; 28: 349–357.
80. McDermott MM, Guralnik JM, Criqui MH, et al. Six-minute walk is a better outcome measure than treadmill walking tests in therapeutic trials of patients with peripheral artery disease. *Circulation* 2014; 130: 61–68.
81. Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery assessing lower extremity function: Association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol* 1994; 49: M85–94.
82. Coyne KS, Margolis MK, Gilchrist KA, et al. Evaluating effects of method of administration on Walking Impairment Questionnaire. *J Vasc Surg* 2003; 38: 296–304.
83. Ware JE Jr, Sherbourne CD. The MOS 36-item Short-Form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992; 30: 473–483.
84. Pymer S, Harwood A, Ibeggazene S, et al. High INtensity Interval Training In pATiEnts with intermittent claudication (INITIATE): Protocol for a multicentre, proof-of-concept, prospective interventional study. *BMJ Open* 2020; 10: e038825.
85. Pymer S, Ibeggazene S, Palmer J, et al. Considering the feasibility, tolerability, and safety of high-intensity interval training as a novel treatment for patients with intermittent claudication. *J Cardiopulm Rehabil Prev* 2021; 41: 188–193.
86. Colberg SR, Sigal RJ, Yardley JE, et al. Physical activity/exercise and diabetes: A position statement of the American Diabetes Association. *Diabetes Care* 2016; 39: 2065–2079.
87. Mezzani A, Hamm LF, Jones AM, et al. Aerobic exercise intensity assessment and prescription in cardiac rehabilitation: A joint position statement of the European Association for Cardiovascular Prevention and Rehabilitation, the American Association of Cardiovascular and Pulmonary Rehabilitation and the Canadian Association of Cardiac Rehabilitation. *Eur J Prev Cardiol* 2013; 20: 442–467.
88. Hiatt WR, Rogers RK, Brass EP. The treadmill is a better functional test than the 6-minute walk test in therapeutic trials of patients with peripheral artery disease. *Circulation* 2014; 130: 69–78.
89. Nicolaï SP, Viechtbauer W, Kruidenier LM, et al. Reliability of treadmill testing in peripheral arterial disease: A meta-regression analysis. *J Vasc Surg* 2009; 50: 322–329.
90. Centers for Disease Control and Prevention, Division of Nutrition, Physical Activity, and Obesity. Perceived exertion (Borg Rating of Perceived Exertion Scale), https://www.cdc.gov/physicalactivity/basics/measuring/exertion.htm (2020, accessed 13 May 2021).