Resistance training as a treatment for older persons with peripheral artery disease: A systematic review and meta- analysis

Parmenter: Resistance training for peripheral artery disease.

Parmenter, BJ[1] PhD. Mavros, Y[2] PhD. Ritti-Dias, RM[3] PhD. King, S[4] PhD. and Fiatarone Singh MA[2, 5] MD.

[1] Department of Exercise, Physiology, School of Medical Sciences, Faculty of Medicine, UNSW Sydney, NSW, Australia

[2] Physical Activity, Lifestyle, Ageing and Wellbeing Faculty Research Group, Faculty of Health Sciences, University of Sydney, NSW, Australia

[3] Rehabilitation Sciences Post-graduate Program, Universidade Nove de Julho, São Paulo, SP, Brazil

[4] Sport, Health and Exercise Sciences, University of Hull, Hull, United Kingdom.

[5] Sydney Medical School, USYD, NSW, Australia; Hebrew SeniorLife and Jean Mayer USDA Human Nutrition Center on Aging at Tufts University, Boston, MA, USA

Address for Correspondence to: Dr Belinda Parmenter

Department of Exercise Physiology

School of Medical Science

University of NSW

Sydney, NSW, Australia, 2052

Telephone: +61 2 9385 8313

Email: b.parmenter@unsw.edu.au

This article has been accepted for publication in British Journal of Sports Medicine. The definitive copyedited, typeset version Parmenter, B. J., Mavros, Y., Ritti Dias, R., King, S., & Fiatarone Singh, M. (2019). Resistance training as a treatment for older persons with peripheral artery disease: A systematic review and meta-analysis. British journal of sports medicine, 1-11. https://doi.org/10.1136/ bjsports-2018-100205 is available online at : http://bjsm.bmj.com

Abstract

Objective: Resistance training (RT) improves walking ability in persons with peripheral artery disease. We conducted a meta-analysis of randomised controlled trials (RCTs) investigating the effect of RT on peripheral artery disease (as measured by walking ability).

Design: We included RCTs that investigated the effect of RT on treadmill and/or 6-minute walk (6-MWT) distances. RT intensity was assessed according to ACSM guidelines by 1RM or Rating of Perceived Exertion (RPE). Standardised mean (SMD) and mean differences (MD) were calculated using a random effects inverse variance model. Heterogeneity and bias were assessed using Revman 5.3. Meta-regression and meta-anova were performed as moderator analyses.

Data Sources: Databases (Medline, Embase, Web of Science, Cinahl, Google Scholar) were searched until July 2018.

Results: Fifteen trials isolated RT; 7 trials compared RT to aerobic exercise. We analysed 826 patients (n=363 completing RT), mean age 67.1±3.8 years. Training ranged from low-high intensity; 2-7 times per week for 17±7weeks, with a mix of upper, lower or whole body training. Overall RT significantly improved constant load treadmill claudication onset (COD)(SMD 0.66[0.40, 0.93], p<0.00001) and total walking distance (WD)(SMD 0.51[0.23, 0.79], p=0.0003), progressive treadmill COD(SMD 0.56[0.00, 1.13], p=0.05) and total WD(SMD 0.45[0.08, 0.82], p=0.02) and 6-MWT COD(MD 82.23m[40.91, 123.54], p<0.0001). Intensity played a role in improvements, with high intensity training yielding the greatest improvement (p=0.02).

Conclusions: RT clinically improved treadmill and flat ground walking ability in persons with PAD. Higher intensity training was associated with better outcomes. Our study makes a case for clinicians to include high intensity lower body RT in treatment of peripheral artery disease.

PROSPERO Systematic Review Registration #: CRD42017081184

Summary Points: What is already known?

- Interval walking is the current gold standard treatment for PAD.
- Resistance training can improve walking ability in persons with peripheral artery disease; there has been no previous synthesis of the literature.

What are the new findings?

- Resistance training improves both flat ground and graded treadmill walking ability in persons with peripheral artery disease, by a clinically meaningful extent.
- Better results were related to higher intensity training.

Introduction

Peripheral artery disease (PAD) is an atherosclerotic disease affecting the arteries of the periphery, most commonly the aorta and iliac arteries, and the arteries of the lower limbs and it affects over 200 million people worldwide(1). Although some people may be asymptomatic, others may present with intermittent claudication symptoms. Claudication, a fatigue, cramp, discomfort or pain in the lower limb, is a symptom of reduced muscle blood supply(2). Peripheral artery disease eventually denervates lower limb muscle fibres(3), which causes muscle weakness,(4, 5) atrophy(6, 7) and altered lower limb biomechanics(8-10). This limits walking ability and impairs quality of life in this population.

Current treatment guidelines for peripheral artery disease (PAD) recommend interval walking as the first line therapy, along with other modes of aerobic exercise and resistance training (RT) as an adjunct treatment for the condition(2, 11). In addition, some guidelines omit the mode of exercise and only provide prescriptive elements of supervision, frequency, duration and length of program(12). Whilst intermittent walking is an effective exercise prescription for people who can complete it, people with severe intermittent claudication may struggle to take part due to chronic diseases and conditions that limit the ability to walk or be physically active (e.g. chronic obstructive pulmonary disease, obesity, arthritis, amputation or cerebrovascular disease with stroke(13)). Furthermore, people with intermittent claudication have intense pain with walking(14, 15). Some people have low confidence in their walking ability, and believe the pain induced by it can be harmful(14, 16). These factors might lead to increased sedentary behaviour(17), accelerated functional decline(18), reduced aerobic capacity or cardiorespiratory fitness and reduced muscle strength and endurance (19-22), all impairing walking ability further and ultimately reducing quality of life(23).

RT does not typically cause claudication pain(24-28), and improves cardiovascular disease risk factors(29-35) and aerobic capacity and attenuates functional decline, yet is typically recommended only as an adjunct to aerobic exercise for the treatment of PAD(2, 36). Therefore, we conducted a systematic review and meta-analysis on randomised controlled trials (RCTs) using RT as an intervention for persons with PAD, with walking ability as an outcome. We aimed to identify whether or not RT is effective at improving walking ability in this population by analysing the effect of RT compared to usual care or aerobic exercise training on six minute walk (6-MWT) distance and treadmill walking. Primary outcomes included claudication onset distance (COD) and total walking distance (WD) for all walking tests. We also aimed to identify whether there are any moderators associated with changes in walking ability. For the purpose of this review, RT included any structured body weight, machine and/or free weight-based RT where muscles contracted against some form of external resistance or immovable object/surface.

Methods

This review was registered with PROSPERO on the 8th December 2017 CRD42017081184 Five electronic databases (Ovid Medline/PubMed, Scopus/Web of Science, PEDro, EMBASE and Cochrane Library) were searched from earliest record until July 2018. Search terms used include (peripheral vascular or claudica* or peripheral arter*) AND (exer* or resist* or weightlifting or strength or musc* exercise or circuit or endurance) AND (random* or control*). One study author (BP) ran the search and uploaded the search results into one Endnote database. After excluding duplicates one author (BP) reviewed all titles and abstracts for possible inclusion. Any full papers that were retrieved for evaluation were then screened by two authors for inclusion (BP and YM). Any disputes were settled by a third author

(MFS). The reference lists of eligible papers were reviewed to identify other relevant studies and recent related systematic reviews were consulted to identify any additional studies that may have been missed.

Studies were included if they were a randomised controlled trial on any persons with diagnosed PAD who took part in a RT intervention for ≥4 weeks, with walking ability measured via treadmill protocols and/or the six minute walk test (6-MWT) distance as an outcome. For the purpose of this review, muscular fitness was defined according to the American College of Sports Medicine (ACSM) where it is used as a collective term for muscular strength, power and endurance(37). Muscular fitness can be improved by a strength exercise training program, where a movement is performed that causes the muscles to contract against an external resistance with the expectation of increases in strength, tone, mass and/or endurance(38). Equipment used can include free weights, machines with stacked weights, pneumatic resistance, resistance bands, springs or body weight. To be included in this review RT must have included multi-joint or compound exercises (e.g., chest press, shoulder press, pull downs, rows, leg press, squats, deadlifts), or single joint exercises targeting major muscle groups (e.g., bicep curls, triceps extensions, quadriceps extensions, leg curls, calf raises). Studies that included exercises targeting the core muscles (e.g., planks, bridges) were also included. Training programs could be circuit type in nature, where clear exercise:rest intervals were defined, or a more traditional form of RT where reps and sets were completed without specified set time and recovery between sets was 2-3 minutes. To be labelled progressive, the resistance exercise must have been progressive by design, in that the absolute workload prescribed increased over time(38). The workload increase may have been achieved by greater forces used, number of exercises, volumes (sets/reps), frequencies of training, or relative intensities of the loads or maximal effort prescribed.

As there is a dose-response association between the volume of exercise and some outcomes(38), RT volume was defined using sets x repetitions x number of days per week(37). Intensity was also defined according to ACSM(39) where:

- ≥85% of 1 repetition maximum (1RM) or Rate of Perceived Exertion(40) (RPE) ≥18 is very high, near maximal or maximal;
- 70-84% of 1 RM or RPE 14-17 is high;
- 50-69% of 1 RM or RPE 12-13 is moderate;
- 30-49% 1RM or RPE 9-11 is light;
- <30% 1RM or RPE<9 is very light.

To be included studies must have compared the intervention to the current unsupervised walking guidelines (usual medical care), or a supervised aerobic exercise training program. Outcomes to be assessed included COD, defined as the moment in which claudication pain starts, and total WD, defined as the maximal walking distance obtained from a constant load and/or graded treadmill test and/or 6-MWT. A secondary outcome of muscle strength was assessed for trials that included this measure. Trials were excluded if they combined a RT intervention with an aerobic exercise intervention and the effects of RT could not be isolated; or if they were completed on animals, or not published in English in a peer-reviewed journal or thesis. Trials were also excluded if asymptomatic patients were grouped with symptomatic patients with PAD and the symptomatic patients were unable to be isolated. Data was extracted by one author (BP) on to pre-piloted data forms. Authors were contacted for missing data.

<u>Risk of Bias</u>

Risk of bias of the included studies was assessed using the Cochrane Collaboration's tool for assessing risk of bias. Eight domains of potential bias were assessed (Supplementary Table 1): including sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessors; complete outcome data; free of selective outcome reporting, baseline similarity and ITT data analyses. Scores were summed across all 8 domains to give a total score of risk bias for each study, with a possible range of 1–8. Studies with a higher score were deemed to be of higher quality, and therefore lower risk of bias. However, rather than focusing on just the scores, the quality of each study was assessed by whether or not points were given for individual quality criterion. With randomisation already being a necessary criterion, studies that have points allocated for randomised sequence generation, allocation concealment, blinding of participants, blinding of outcome assessors, and intention to treat analysis and were free of any other bias were deemed higher quality and therefore lower risk of bias.

<u>Data Extraction</u>

Walking distances analysed were the mean difference (MD) between pre- and post-group data which was calculated by subtracting baseline from post values for both the control and intervention groups. Data required was the individual group sample size, mean change and standard deviation (SD) or 95% confidence interval of the change score and/or within group p-value. When the confidence interval or SD was not available actual p-values for pre/post intervention change were used. If only the level of significance was available, we used default p-values where $p<0.05$ becomes $p=0.049$, $p<0.001$ becomes $p=0.0099$ and p=not significant becomes $p=0.051$. Values were taken from baseline measures, and then at the time-point closest to the end of the intervention period. For studies that contributed multiple comparisons (e.g., one control group and two interventions groups(41)), the control group data were evenly divided into two smaller groups.

Data Synthesis

A narrative synthesis regarding participant characteristics and study interventions was completed. Aggregate data were used in the analyses. Mean difference (MD) and 95% Confidence Interval (CI) was calculated for the 6-MWT measures (reported in meters) and to account for any differences in testing protocols, SMD and 95% CI was calculated for the treadmill WD using the Cochrane RevMan calculator(42) in Revman version 5.3 (Nordic Cochrane Centre, Denmark). MD was unable to be calculated for constant and progressive load treadmill protocols due to the difference in protocols used across trials (i.e., some constant load protocols ran at different speeds and/or grades to other constant load protocols, and vice versa for progressive grade protocols). If enough data were provided then a quantitative synthesis was completed on each of the outcomes using an inverse variance, random effects analysis. Both statistical and clinical meaningfulness of outcomes were characterized. Statistical significance of SMDs was inferred if the CIs did not cross zero. Clinical meaningfulness of the MDs were interpreted such that a 50 m improvement in 6-MWT distance was considered to be the lower threshold of a clinically important difference in this cohort(43), as this improvement is associated with a reduction in cardiovascular mortality.

Moderator Analysis

The significance of any heterogeneity identified was examined using the Cochran's Q (χ^2) test with $p<0.05$ indicating significant heterogeneity. Interpretation of heterogeneity was based on Cochrane recommendations(41) using Higgins I^2, with scores ranging from 0 to

100%. A cut-off of 40% was used to proceed to moderator analysis if 3 or more studies were present to help identify sources of heterogeneity in the overall meta-analysis. Moderators assessed included age, ankle brachial index, frequency, intensity, RT method, number and area of exercises, total repetitions, program length, progression and study quality. Univariate meta-regression analyses were used to assess the influence of continuous variables such as frequency, length of intervention, duration of session on walking ability. Meta-anova was completed on categorical variables such as intensity or location of training. Meta-regression/anova analyses were completed with a random intercept, fixed slopes model using "Wilson's SPSS macro(44)" and SPSS Statistics for Windows, Version 24.0 (IBM Corp, Armonk, New York, USA). For studies where both a graded treadmill protocol and constant grade protocol and below knee and above knee strength were completed and reported, effect sizes and study weighting were averaged, so both outcomes were represented in the meta regression analysis. If inconsistency remained, it was decided that the random effects model used accounted for any other differences between studies.

Reporting Bias

If, as according to Cochrane more than 10 studies were included in an outcome analysis, funnel plot symmetry was used to detect reporting bias(41). Funnel plots are provided in supplementary file.

Results

Included studies

Overall, 18 studies met the inclusion criteria for this analysis(22, 24-28, 45-56). Fourteen studies compared RT to a control group of usual medical care. Seven studies compared RT to an aerobic exercise group(22, 24, 25, 27, 47, 48, 55), 3 of these also had a control group(24, 25, 27). Seventeen studies published or provided enough data to be included in the quantitative analysis, Figure 1. Study quality and risk of bias is outlined in Supplementary Table 1. On average, study quality was moderate, with most trials failing to blind outcome assessors in the trials potentially leading to a detection bias, where there could be a difference between groups in how outcomes are determined.

Participant Characteristics

In total 826 participants were studied, with 363 completing a RT intervention. Mean age was 67.1±3.8 years, range 61 to 74, and on average 68% of participants studied were male. Mean ankle brachial index was 0.66±0.23, range 0.54 to 0.75. Cardiovascular risk factors such as body mass index, waist circumference and blood pressure were poorly reported across studies.

Intervention Characteristics

Characteristics of the RT interventions are outlined in Table 1. Program length varied from 6 to 24 weeks, (18±7 weeks). Average training frequency was 3 times per week. Six trials trained participants twice a week(22, 47, 49, 50, 54, 55), one trial four times a week(45) and one trial daily(53). Intensity ranged from light (30% 1RM)(26) to high at 80% 1RM(26, 57) and the number of different exercises performed ranged from 1 to 14 (7±4 exercises), while the number of sets for each type of exercises ranged from 1 to 3, when reported, with the most common number being 3. The number of repetitions per set when reported ranged from

6 to 15 (10±5 reps). Exercises involved the use of arms, legs and trunk in six studies(22, 26, 28, 48-50), the upper limb only in one study(27) and the lower limb in the remainder of studies(24, 25, 45-47, 51-56). One study focussed only on the calf muscles, using plantarflexion as the chosen exercise(56). Nine trials reported using a circuit training protocol(45, 46, 49-54, 56), while the remaining studies(22, 24-28, 47, 48, 55) had participants complete 1-3 sets of 3 to 14 reps of dynamic exercise, with 2-3 minute rests intervals between sets. Duration of exercise sessions ranged from 20 through to 60 minutes. Ten trials(22, 24-28, 47, 48, 53, 55) reported that the RT was progressed weekly during the exercise sessions; in the remaining trials progression was not reported. Out of the 18 trials, 8(22, 24-28, 48, 55) reported that RT did not produce claudication pain, 8 trials(26, 46, 47, 51-53) reported mild pain and 2 trials(49, 50) reported moderate pain.

The Effect of RT vs. Control/Usual Care Condition

Claudication Onset Distance (COD)

In the eight studies(26, 46, 49, 50, 52-54, 56) measuring this outcome RT lead to a significant improvement in COD on a constant grade treadmill protocol; SMD 0.64 [0.38, 0.90]; P<0.00001, with zero heterogeneity I^2=0%; p=0.57, Figure 2a.

In the five studies(24-28, 46) measuring this outcome (across 6 interventions), RT lead to a significant improvement in COD on a progressive grade treadmill protocol; SMD 0.81 [0.09, 1.52]; p=0.03, however, heterogeneity was substantial at I^2=61%; p=0.02, Figure 2b. When only machine-based training studies (free weights excluded) were analysed, heterogeneity was reduced; I^2=42%; p=0.14; however the pooled effect was no longer significant SMD 0.53[-0.07, 1.13]; p=0.08.

In the three studies(26-28, 46) that measured it, (across 4 interventions), RT lead to a clinically meaningful improvement in COD during the 6-minute walk; MD 82.23m [40.91, 123.54]; $p<0.0001$, with zero heterogeneity $I^2=0\%$; $p=0.46$, Figure 2c.

Total Walking Distance (WD)

Nine studies completed a constant grade treadmill protocol(26, 45, 46, 49, 50, 52-54, 56) (across 10 interventions). In the studies that measured it, RT lead to a significant improvement in WD in this protocol; SMD 0.48 [0.18, 0.78]; $p=0.002$, with minimal heterogeneity $I^2=33\%$; $p=0.14$, Figure 3a.

Five studies(24-28) used a progressive grade treadmill protocol. In these studies, RT lead to a significant improvement in total WD; SMD 0.46 [0.09, 0.82]; $p=0.01$, with zero heterogeneity $I^2=0\%$; $p=0.66$, Figure 3b.

In the four studies that measured 6-minute walk (across five interventions)(25-28) RT did not significantly improve WD; MD 25.56m [-3.12, 54.24], $p=0.08$; and there was minimal heterogeneity across studies $I^2=34\%$; $p=0.19$, Figure 3c.

The Effect of Resistance Training compared to Walking Training

Five studies(22, 24, 25, 48, 55) compared RT to supervised treadmill walking training. There were only 2 studies(47, 55) that reported claudication onset during the 6-MWT; therefore, these data were unable to be combined and analysed. For 6-MWT distance, 4 studies reported enough data to be included in the analysis. Treadmill walking training was significantly better than RT, however this difference was not clinically meaningful; MD -16.04m [-27.48, -4.60], p=0.006; I^2=0%, p=0.68; Figure 4a.

Five studies reported enough data to analyse progressive treadmill COD. Treadmill walking training was significantly better than RT; SMD -0.47 [-0.85, -0.08], p=0.02; Figure 4b. Notably, heterogeneity was moderate and significant at I^2=59%, p=0.04. However, when high intensity studies alone were analysed, the difference between walking distances for treadmill COD was no longer significant and heterogeneity reduced substantially: progressive treadmill COD; SMD -0.30 [-0.68, 0.07], p=0.11; I^2=13%, p=0.32; Figure 4c.

Five studies reported enough data to analyse progressive treadmill total WD. Treadmill walking training was not significantly better than RT; SMD -0.38 [-0.80, 0.04], p=0.07; Figure 4d). However, heterogeneity was again moderate at I^2=66%, p=0.02. When moderate-to-high intensity studies only were analysed, there was still no significant difference between treadmill training and RT, but heterogeneity was eliminated; SMD -0.27 [-0.60, 0.06], p=0.10; I^2=0%, p=0.60; Figure 4e. As there were only 3 studies, this result warrants further exploration.

Moderator Analysis for Identifying Optimal Exercise Prescriptive Elements

The Effect of Intensity of RT

Random effects meta-anova results indicate that higher intensity RT leads to greater improvements in total WD (ß=0.53; p=0.03; low intensity (n=5) mean effect size (ES)=-0.21 [-0.74, 0.29]; moderate intensity (n=6) ES=0.46 [-0.25, 0.67]; and high intensity (n=2) ES=0.66 [0.24, 1.07]; with between group p=0.02).

<u>The Effect of Muscle Groups Trained</u>

Random effects meta-anova results indicate that lower body RT leads to a greater improvement in total WD (lower body mean ES=0.67; whole body mean ES=0.39. However, the between group difference was not significant p=0.09).

No statistically significant relationships with any other prescriptive elements or participant characteristics were identified.

<u>Muscle Strength Testing</u>

Although ten studies(24-28, 47, 48, 55, 57) reported muscle strength as an outcome, only four(24-26, 28) reported enough information to be included in the analysis. All four studies used a version of repetition maximum (RM) testing. Two studies(25, 26) completed a 1RM with no adverse events, one study(24) completed a 5RM on the calf muscles only and the last study completed a 10RM. Overall RT improved muscle strength with a small ES; SMD 0.43 [0.16, 0.70]; p=0.002, with zero heterogeneity; I^2=0%, p=0.65; Figure 5. Strength improved more robustly in the upper leg/above knee muscles of the claudicants, where a moderate ES was noted; SMD 0.71 [0.29, 1.13], p=0.0009; and results were similar across trials; I^2=0%, p=0.70.

Risk of Publication Bias

The number of trials reaching 10 only occurred in two outcomes; constant grade treadmill total WD and change in overall muscle strength. Funnel plots for each of the analyses are presented in Figure 1 and Figure 2 of the Supplementary material. Funnel plots are symmetrical and do not indicate publication bias for either outcome.

Discussion

Patients with PAD have reduced leg strength and function(22, 26). This study has shown that RT improves leg strength and both flat ground and graded walking distances in persons with PAD. Furthermore, supervised RT programs can also improve each of the individual risk factors for cardiovascular disease in older healthy adults(58), Trials of RT in persons with PAD therefore warrant further research to identify whether different prescriptions (i.e. adjusting frequency and intensity) may be more effective in individual patients with PAD with varied cardiovascular risk profiles.

Effects of RT on walking capacity

This analysis has shown that RT alone improves walking ability for persons with PAD. The mechanisms underlying these effects have been explored in few studies. RT increases muscle mass(28) and muscle strength(22, 26), measures that are already reduced in patients with PAD(21). This meta-analysis included studies showing a strong association between the changes in strength levels and the changes in walking capacity after RT(22, 26), suggesting that strength gains leads to lowers muscle fibre recruitment during walking, thereby reducing the energy cost of walking. However, as only 4 studies included in this analysis reported strength testing results, it was difficult to explore this relationship.

Walking exercise has been recommended as the primary mode of exercise for patients with PAD. Therefore, the comparison of walking exercise against RT is useful to understand the effects of RT compared to this gold-standard mode of exercise for PAD patients. This meta-analysis indicated superior effects of walking exercises compared to RT. However, when sub-group analyses were conducted, high intensity RT produced similar increases in walking capacity assessed during a maximal graded treadmill test compared to walking training. Although we could not compare the effects of RT against walking training during the 6-MWT because there were too few studies, the similar effects of high intensity RT compared to walking training assessed during graded treadmill tests, suggest that high intensity RT may be a feasible alternative therapy to walking for patients with PAD. This could help improve adherence of exercise programs, given that patients have reported RT as being less painful than walking training(22).

<u>Elements of the most effective RT interventions and recommendations for future research</u>

When we examined which elements of interventions were associated with large, significant improvements in walking ability, high intensity RT of the lower body was the most effective element. Exercises focussing on the lower body: calf muscles, quadriceps, hamstrings and gluteals were included in the interventions with the larger effects. Further comparisons of RT intensity would be better verified with direct comparisons [i.e. moderate 60% 1RM versus high intensity (80% 1RM] within trials. Only one study has done this to date(26), results of which showed the ineffectiveness of low intensity (30% 1RM) training against the efficacy of high intensity (80% 1RM). Other elements of exercise prescription such as frequency of training sessions, length of program, and whether whole body exercises are more beneficial than lower limb only, remain unclear and need to be tested explicitly.

Limitations

Though poorly reported, some studies showed that the changes in walking distance were associated with changes in above knee leg strength(22, 26). The lack of strength testing of participants and/or lack of reporting testing results in the included trials is a major limitation of this literature. Future trials should ensure baseline strength measures are completed prior to commencement of strength training in order to ensure appropriate overload and progression is consistently applied to the training muscles. Furthermore, trials should report both the baseline and follow up strength test results for individual muscle groups, along with changes in walking distances so the relationship between leg strength and walking distance can be explored further in future meta-analyses.

As cardiovascular risk is increased in this cohort, future trials should also report the effect of the exercise training on cardiovascular risk factors such as body mass index, waist circumference, arterial stiffness, inflammation, and blood pressure. Research should also include more women and culturally and linguistically diverse cohorts. Outcomes should including measures of quality of life and physical function such as balance, chair stand, gait speed and stair climb power, in order to identify RT prescriptions that are most efficacious at improving performance of activities of daily living. Finally, studies need to report and investigate more prescriptive elements of strength training including the number of exercises, intensity and frequency of exercise training, and conduct longer follow up testing in an effort to identify how long the effects of RT are maintained.

Disclosures

The authors disclose no conflicts of interest for this research.

References

1. Benjamin E, Blaha M, Chiuve S, et al. Heart disease and stroke statistics—2017 update: a report from the American Heart Association Circulation. 2017.

2. Gerhard-Herman M, Gornik H, Barrett C, et al. AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease. Circulation. 2016;135(12):e726-e79.

3. McDermott M, Guralnik J, Albay M, et al. Impairments of muscles and nerves associated with peripheral arterial disease and their relationship with lower extremity functioning: the InCHIANTI Study. J Am Ger Soc. 2004;52(3):405-10.

4. Parmenter B, Raymond J, Dinnen P, et al. Preliminary evidence that low ankle brachial index is associated with reduced bilateral hip extensor strength and functional mobility in peripheral arterial disease. J Vasc Surg. 2013;57(4):963-73.

5. McDermott M, Criqui M, Greenland P, et al. Leg strength in peripheral arterial disease: associations with disease severity and lower-extremity performance. J Vasc Surg. 2004;39(3):523-30.

6. Garg P, Liu K, Ferrucci L, et al. Lower extremity nerve function, calf skeletal muscle characteristics, and functional performance in peripheral arterial disease. J Amer Ger Soc. 2011;59:1855-63.

7. King S, Vanicek N, O'Brien T. Dynamic muscle quality of the plantar flexors is impaired in claudicant patients with peripheral arterial disease and associated with poorer walking endurance. J Vasc Surg. 2015;62(3):689-97.

8. Myers S, Johanning J, Stergiou N, et al. Gait variability is altered in patients with peripheral arterial disease. J Vasc Surg. 2009;49(4):924-31 e1.

9. King S, Vanicek N, O'Brien T. Sagittal plane joint kinetics during stair ascent in patients with peripheral arterial disease and intermittent claudication. Gait & Posture. 2017;55:81-6.

10. King S, Vanicek N, O'Brien T. Joint moment strategies during stair descent in patients with peripheral arterial disease and intermittent claudication. Gait Posture. 2018;62:359-65.

11. Society for Vascular Surgery Lower Extremity Guidelines Writing Group, Conte M, Pomposelli F, et al. Society for Vascular Surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities: Management of asymptomatic disease and claudication. J Vasc Surg. 2015;61(3 Supplement):2S-41S.

12. Anderson J, Halperin J, Albert N, et al. Management of patients with peripheral artery disease (compilation of 2005 and 2011 ACCF/AHA guideline recommendations): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;127(13):1425-43.

13. Dörenkamp S, Mesters I, de Bie R, et al. Patient Characteristics and Comorbidities Influence Walking Distances in Symptomatic Peripheral Arterial Disease: A Large One-Year Physiotherapy Cohort Study. PLoS One. 2016;11(1):e0146828.

14. Cunningham M, Swanson V, Holdsworth R. Using a psychological model to investigate the relationship between illness beliefs and walking behaviour ofpatients with intermittent claudication. Br J Surg. 2010;97(Supp 1):6.

15. Katzel L, Sorkin J, Powell C, et al. Comorbidities and exercise capacity in older patients with intermittent claudication. Vasc Med. 2001;6(3):157-62.

16. Barbosa J, Farah B, Chehuen M, et al. Barriers to physical activity in patients with intermittent claudication. Int J Behav Med. 2015;22(1):70-5.

17. Garg P, Tian L, Criqui M, et al. Physical activity during daily life and mortality in patients with peripheral arterial disease. Circulation. 2006;114:242-8.

18. Oka R, Szuba A, Giacomini J, et al. Predictors of physical function in patients with peripherial arterial disease and claudication. Prog Cardiovasc Nurs. 2004;19(3):89-94.
19. Parmenter B, Raymond J, Dinnen P, et al. Preliminary evidence that low ankle-brachial index is associated with reduced bilateral hip extensor strength and functional mobility in peripheral arterial disease. J Vasc Surg. 2013;57(4):963-73.
20. Parmenter B, Dieberg G, Smart N. Exercise training for management of peripheral arterial disease: a systematic review and meta-analysis. Sports Med. 2015;45(2):231-44.
21. McDermott M, Liu K, Tian L, et al. Calf muscle characteristics, strength measures, and mortality in peripheral arterial disease: a longitudinal study. J Am Coll Cardiol. 2012;59(13):1159-67.
22. Ritti-Dias R, Wolosker N, Forjaz C, et al. Strength training increases walking tolerance in intermittent claudication patients: Randomized trial. J Vasc Surg. 2010;51(1):89-95.
23. Parmenter B, 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(1):30-40.
24. Hiatt W, Wolfel E, Meier R, et al. Superiority of treadmill walking exercise versus strength training for patients with peripheral arterial disease. Implications for the mechanism of the training response. Circulation. 1994;90(4):1866.
25. McDermott M, Ades P, Guralnik J, et al. Treadmill exercise and resistance training in patients with peripheral arterial disease with and without intermittent claudication: A randomized controlled trial. JAMA - Journal of the American Medical Association. 2009;301(2):165-74.
26. Parmenter B, Raymond J, Dinnen P, et al. High-intensity progressive resistance training improves flat-ground walking in older adults with symptomatic peripheral arterial disease. Journal of the American Geriatrics Society. 2013;61(11):1964-70.
27. Parr B, Noakes T, Derman E. Peripheral arterial disease and intermittent claudication: Efficacy of short-term upper body strength training, dynamic exercise training, and advice to exercise at home. South African Medical Journal. 2009;99(11):800-4.
28. McGuigan M, Bronks R, Newton R, et al. Resistance training in patients with peripheral arterial disease: effects on myosin isoforms, fiber type distribution, and capillary supply to skeletal muscle. J Gerontol A Biol Sci Med Sci. 2001;56(7):B302-10.
29. Halbert J, Silagy C, Finucane P, et al. Exercise training and blood lipids in hyperlipidemic and normolipidemic adults: a meta-analysis of randomized, controlled trials. European journal of clinical nutrition. 1999;53(7):514-22.
30. Hordern MD, Dunstan DW, Prins JB, et al. Exercise prescription for patients with type 2 diabetes and pre-diabetes: A position statement from Exercise and Sport Science Australia. Journal of Science and Medicine in Sport. 2012;15(1):25-31.
31. MacDonald H, Johnson B, Huedo-Medina T, et al. Dynamic Resistance Training as Stand-Alone Antihypertensive Lifestyle Therapy: A Meta-Analysis. Journal of the American Heart Association. 2016;5(10).
32. Whelton S, Chin A, Xin X, et al. Effect of aerobic exercise on blood pressure: a meta-analysis of randomized, controlled trials. Annals of internal medicine. 2002;136(7):493-503.
33. Yang Z, Scott C, Mao C, et al. Resistance exercise versus aerobic exercise for type 2 diabetes: a systematic review and meta-analysis. Sports Med. 2014;44(4):487-99.
34. Gomes APF CM, Soares AHG, Cucato GG, Lima AHRA, Cavalcante BR, Sobral-Filho DC, Ritti-Dias RM. Effects of Resistance Training on Cardiovascular Function in Patients With Peripheral Artery Disease: A Randomized Controlled Trial. J Strength Cond Res. 2018;32(4):1072-80.

35. Grizzo Cucato G, de Moraes Forjaz C, Kanegusuku H, et al. Effects of walking and strength training on resting and exercise cardiovascular responses in patients with intermittent claudication. VASA. 2011;40(5):390-7.
36. Askew C, Parmenter B, Leicht A, et al. Exercise & Sports Science Australia (ESSA) position statement on exercise prescription for patients with peripheral arterial disease and intermittent claudication. J Sc Med Spp. 2014;17:623-29.
37. American College of Sports Medicine AS, Baruith M, Baynard T, Beck D and et al. . ACSM Guidelines for Exercise Testing and Prescription. . Tenth ed. Philadelphia PWKH, editor2018.
38. Garber C, Blissmer B, Deschenes M, et al. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: Guidance for prescribing exercise. Med Sci Sp Ex. 2011;43:1334-59.
39. American College of Sports Medicine, Agiovlasitis S, Baruith M, et al. ACSM Guidelines for Exercise Testing and Prescription. Tenth ed. Riebe D, editor. Philadelphia, PA.: Wolters Kluwer Health; 2018.
40. Borg G. Perceived exertion: a note on "history" and methods. . Med Sci Sports. 1973;5:90-3.
41. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions. West Sussex, England.: John Wiley & Sons Ltd; 2008.
42. Drahota A, Beller E. Cochrane RevMan Calculator [Available from: https://training.cochrane.org/resource/revman-calculator.
43. Rasekaba T, Lee A, Naughton M, et al. The six-minute walk test: a useful metric for the cardiopulmonary patient. Intern Med J. 2009;39(8):495-501.
44. Wilson D. Meta-analysis macros for SAS, SPSS and Stata. 2005 [Available from: http://mason.gmu.edu/_dwilsonb/ma.
45. Cheetham D, Burgess L, Ellis M, et al. Does supervised exercise offer adjuvant benefit over exercise advice alone for the treatment of intermittent claudication? A randomised trial. Eur J Vasc Endovasc Surg. 2004;27:17-23.
46. Dahllöf AG, Björntorp P, Holm J, et al. Metabolic Activity of Skeletal Muscle in Patients with Peripheral Arterial Insufficiency: Effect of Physical Training. European Journal of Clinical Investigation. 1974;4(1):9-15.
47. Delaney C, Miller M, Chataway T, et al. A randomised controlled trial of supervised exercise regimens and their impact on walking performance, skeletal muscle mass and Calpain activity in patients with intermittent claudication. European Journal of Vascular and Endovascular Surgery. 2014;47(3):304-10.
48. Gardner A, Parker D, Montgomery P, et al. Step-monitored home exercise improves ambulation, vascular function, and inflammation in symptomatic patients with peripheral artery disease: A randomized controlled trial. Journal of the American Heart Association. 2014;3(5).
49. Hobbs S, Marshall T, Fegan C, et al. The constitutive procoagulant and hypofibrinolytic state in patients with intermittent claudication due to infrainguinal disease significantly improves with percutaneous transluminal balloon angioplasty. J Vasc Surg. 2006;43:40-6.
50. Hobbs S, Marshall T, Fegan C, et al. The effect of supervised exercise and cilostazol on coagulation and fibrinolysis in intermittent claudication: a randomized controlled trial. J Vasc Surg. 2007;45:65-70.
51. Holm J, Dahllof AG, Bjorntorp P, et al. Enzyme studies in muscles of patients with intermittent claudication. Effect of training. Scandinavian Journal of Clinical and Laboratory Investigation. 1973;31(SUP.128):201-5.

52. Lundgren F, Dahloff A, Lundholm K, et al. Intermittent Claudication: Surgical Reconstruction or Physical Training. Ann Surg. 1989;209(3):346-55.

53. Mannarino E, Pasqualini L, Innocente S, et al. Physical Training and Antiplatelet Treatment in Stage II Peripheral Arterial Occlusive Disease: Alone or Combined? . Angiology. 1991;42(7):513-21.

54. Stewart A, Smith F, Baird R, et al. Local versus systemic mechanisms underlying supervised exercise training for intermittent claudication. Vasc Endovasc Surg. 2008;42(4):314-20.

55. Szymczak M, Oszkinis G, Majchrzycki M. The Impact of Walking Exercises and Resistance Training upon the Walking Distance in Patients with Chronic Lower Limb Ischaemia. Biomed Research International. 2016:8.

56. Tebbutt N, Robinson L, Todhunter J, et al. A plantar flexion device exercise programme for patients with peripheral arterial disease: A randomised prospective feasibility study. Physiotherapy. 2011;97(3):244-9.

57. Albaghdadi M, Wang Z, Gao Y, et al. High-Density Lipoprotein Subfractions and Cholesterol Efflux Capacity Are Not Affected by Supervised Exercise but Are Associated with Baseline Interleukin-6 in Patients with Peripheral Artery Disease. Front Cardiovasc Med. 2017;4:10.

58. Ratamess N, Alvar B, Evetoch T, et al. Progression Models in Resistance Training for Healthy Adults: ACSM Position Stand. Med Sci Sp Ex. 2009;41(3):687-708.

Figure Legend

Figure 1: PRISMA Flow chart for study identification. N= number; RT= Resistance training; RCT= Randomised controlled trial; PAD= Peripheral artery disease.

Figure 2: Claudication Onset Distance for (A) Constant grade treadmill protocol; (B) Progressive grade treadmill protocol; and (C) 6-minute walk. SD= Standard deviation, CI= Confidence interval, RT= Resistance training, INR= Intensity not reported, Mod=Moderate.

Figure 3: Total Walking Distance for (A) Constant grade treadmill protocol; (B) Progressive grade treadmill protocol; and (C) 6-minute walk. SD= Standard deviation, CI= Confidence interval, RT= Resistance training, INR= Intensity not reported, Mod=Moderate.

Figure 4: (A) 6-MWT distance for RT vs Trd training trials; (B) Progressive treadmill COD RT vs Trd training; (C) Progressive treadmill COD Mod-High Intensity RT vs Trd training; (D) Progressive treadmill total WD RT vs Trd training; (E) Progressive treadmill total WD Mod-High Intensity RT vs Trd training. SD= Standard deviation, CI= Confidence interval, RT= Resistance training, Mod=Moderate, RT= Resistance training; Trd= Treadmill; COD= Claudication onset distance; WD= Walking distance.

Figure 5: Change in muscle strength across studies measuring 2.1.1 Below knee muscle strength; 2.1.2 Above knee muscle strength; and 2.1.3 Whole body muscle strength. SD= Standard deviation, CI= Confidence interval, RT= Resistance training, INR= Intensity not reported, Mod=Moderate.

Table 1 Intervention Characteristics

							Strength Training Intervention Characteristics							
Author	Group (n)	Sample size (n)	Sex (% male)	Age (yrs)	ABI	RT method and Type of Resistance	Freq (per week)	Session length (mins)	Intensity*	N of ex	Area of ex	N of sets or ex:rest ratio	N of reps/set	Prog length (wks)
Strength training versus usual care control														
Cheetham 2004	ST Con	29 30	73	67	0.69	Dynamic Circuit BW	4	28	Self-paced	7	LB	2:2 mins		24
Dahloff 1974	ST Con	10 8	72	61	NR	Dynamic Circuit BW	3	30	NR	NR	LB	NR	NR	24
Hobbs 2006	ST Con	7 7	71	72	0.70	Dynamic circuit BW	2	60	Mod	11	WB	3:2 mins		12
Hobbs 2007	ST Con	9 9	72	67	0.75	Dynamic circuit BW	2	60	Mod	11	WB	3:2 mins		12
Holm 1973	ST Con	6 6	NR	63	NR	Dynamic circuit BW	3	30	NR	NR	LB	NR	NR	24
Lundgren 1989	ST Con	25 25	NR	64	0.57	Dynamic circuit BW	3	30	NR	NR	LB	NR	NR	24
Mannarino 1991	ST Con	10 10	67	63	0.67	Dynamic circuit BW	7	60	NR	6	LB	NR	NR	24
Stewart 2008	ST Con	30 30	70	68	0.67	Dynamic circuit BW	2	40	NR	5	LB	NR	NR	12
Tebbut 2010	ST Con	18 24	67	69	0.69	Dynamic Plantar-flexion M	1	20	Light–mod	1	Calf	2:2 mins		12
Hiatt 1994	ST Con	9 10	100	67	0.56	Dynamic FW	3	NR	Mod	5	LB	3	6	12
McDermott 2009	ST Con	52 40	48	70	0.61	Dynamic M	3	NR	Mod	5	LB	3	8	24

McGuigan 2010	ST	11	46	70	0.64	Dynamic M/FW/BW	3	NR	Mod-High	8	WB	3	8	24
	Con	9												
Parmenter 2013	ST 1	7	64	73	0.54		3	60	Light	7	WB	3	8	24
	ST 2	7				Dynamic M			High					
	Con	7												
Parr 2009	ST	9	68	62	NR	Dynamic M/FW	3	NR	Mod	14	UB	1	15	6
	Con	8												
Strength training versus other exercise														
Delaney 2014	ST	17	77	69	0.72	Dynamic M	2	60	Light	6	LB	3	8 to 12	12
	Alt Ex	18	67	73	0.71	Trd walk		60	Self-paced			Max pain:rest		
Gardner 2014	ST	60	60	65	0.74	Dynamic M	3	NR	Light	9	WB	1	15	12
	Alt Ex	60	52	67	0.68	Home walk		20 ↑ - 45	Self-paced			Mild-Mod pain:rest		
	Alt Ex	60	48	65	0.68	Trd walk		15 ↑ - 40	40% ^{peak}					
Hiatt 1994	ST	See above												
	Alt Ex	10	100	67	0.55	Trd walk	3	60	Self-paced			Mod pain:rest		12
McDermott 2009	ST	See above												
	Alt Ex	51	47	72	0.60	Trd walk	3	15 ↑ - 40	Mod			Mod-max pain:rest		24
Ritti-Dias 2010	ST	15	60	66	0.63	Dynamic M	2	60	Mod	8	WB	3	10	12
	Alt Ex	15	73	65	0.66	Trd walk						2:2 mins mild pain		
Szymczak 2016	ST	26	NR	NR	0.67	Dynamic M	2	50	Light-mod	6	LB	3	15	12
	Alt Ex	24				Trd walk			Self-paced			Mild pain		

N= number; ST= strength training; Ex= exercise; Freq= frequency; Mins= minutes; Con= control; RT= resistance training; RM= repetition maximum; LB= lower body; UB= upper body; WB= whole body; BW= body weight; M= machine based training; FW= free weights; NR= not reported; Mod= moderate; Vig= vigorous; Alt Ex= Alternate exercise; Vol*= volume (sets x repetitions x days); Prog= progression;

* According to American College of Sports Medicine;

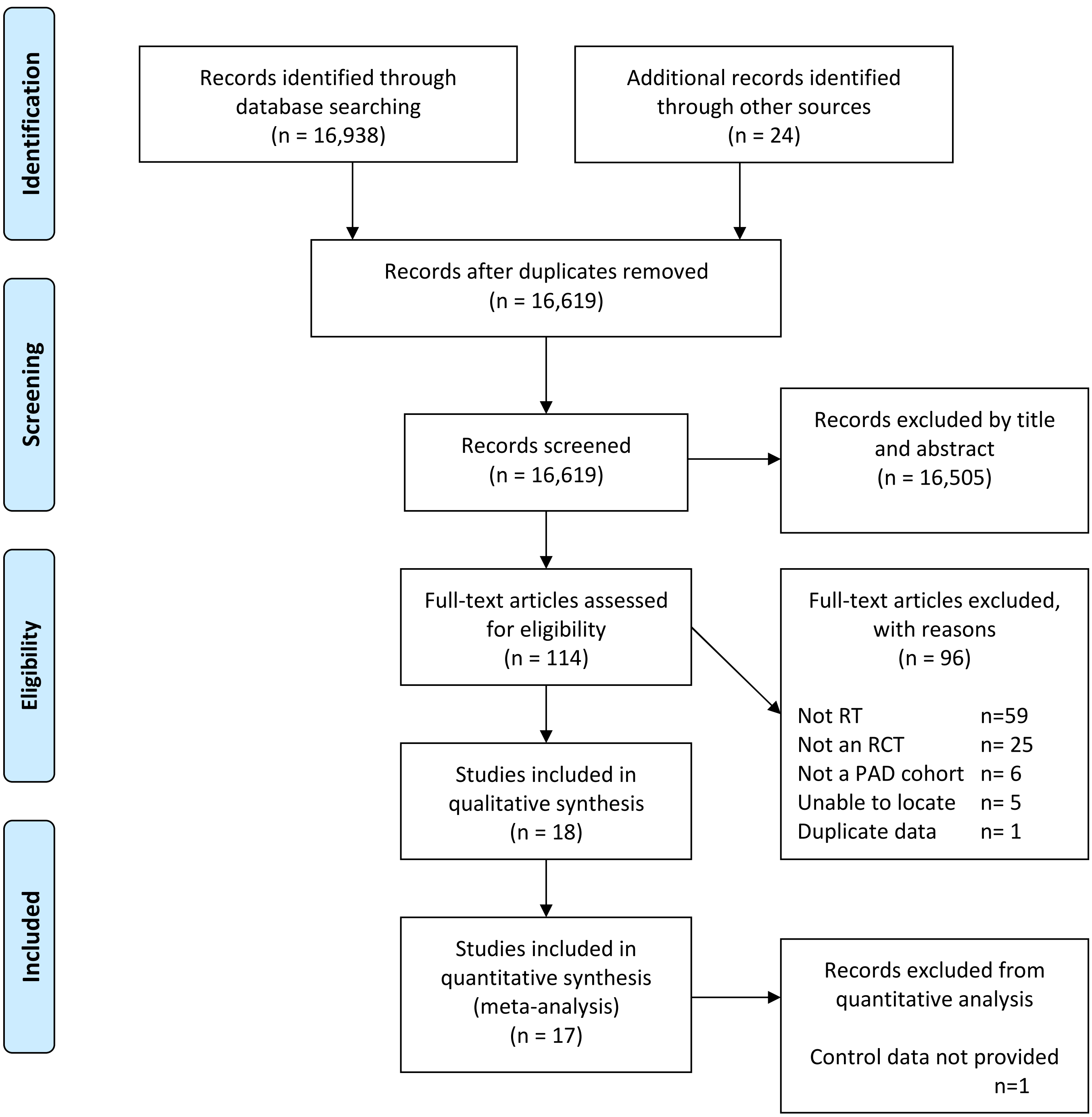
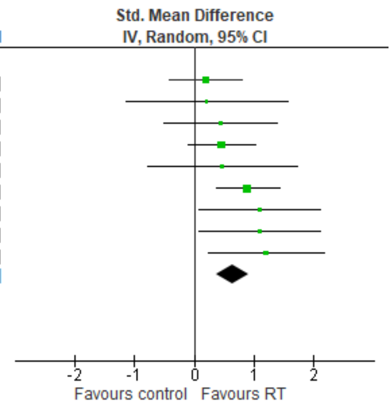

Identification
Screening
Eligibility
Included
Records identified through database searching (n = 16,938)
Additional records identified through other sources (n = 24)
Records after duplicates removed (n = 16,619)
Records screened (n = 16,619)
Records excluded by title and abstract (n = 16,505)
Full-text articles assessed for eligibility (n = 114)
Full-text articles excluded, with reasons (n = 96)
Not RT n=59
Not an RCT n= 25
Not a PAD cohort n= 6
Unable to locate n= 5
Duplicate data n= 1
Studies included in qualitative synthesis (n = 18)
Studies included in quantitative synthesis (meta-analysis) (n = 17)
Records excluded from quantitative analysis
Control data not provided n=1

Figure 1

Study or Subgroup	Resistance Training Mean	Resistance Training SD	Resistance Training Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
A. Constant grade treadmill protocol								
Tebbutt (RT Light-Mod)	20	81	24	0	119.2	18	18.1%	0.20 [-0.41, 0.81]
Parmenter (RT Light)	139.6	299.3	7	77.8	86.3	3	3.7%	0.21 [-1.15, 1.57]
Hobbs (RT Mod 06)	33	22	9	9	70	9	7.7%	0.44 [-0.50, 1.38]
Lundgren (RT INR)	489	380	25	320	351	25	21.5%	0.45 [-0.11, 1.02]
Parmenter (RT High)	117.2	71.9	7	77.8	86.3	4	4.3%	0.47 [-0.78, 1.72]
Stewart (RT INR)	49.4	40	30	15.8	34	30	24.0%	0.89 [0.36, 1.43]
Hobbs (RT Mod 07)	50	40	9	14	19.2	9	6.7%	1.09 [0.08, 2.10]
Dahloff (RT INR)	174	150.3	10	0.01	152.6	8	6.6%	1.10 [0.08, 2.11]
Mannarino (RT INR)	107.2	63	10	36.3	49.4	10	7.2%	1.20 [0.23, 2.17]
Subtotal (95% CI)			**131**			**116**	**100.0%**	**0.64 [0.38, 0.90]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.74$, df = 8 (P = 0.57); $I^2 = 0\%$

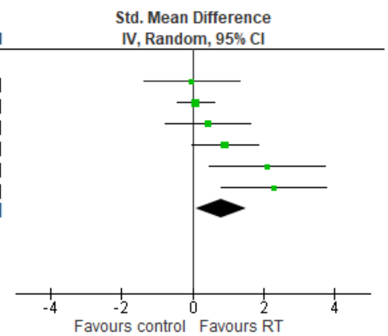
Test for overall effect: Z = 4.83 (P < 0.00001)



Study or Subgroup	Resistance Training Mean	Resistance Training SD	Resistance Training Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
B. Progressive grade treadmill protocol								
Parmenter (RT Light)	62.6	117.3	7	65.2	68.8	3	14.3%	-0.02 [-1.37, 1.33]
McDermott (RT Mod)	86.6	166.9	46	70.2	177.9	20	25.4%	0.10 [-0.43, 0.62]
Parr (RT Mod)	157	358	9	13.7	67	4	16.2%	0.43 [-0.76, 1.63]
McGuigan (RT Mod-High)	153.6	228.6	11	-8.3	10.7	9	19.6%	0.91 [-0.03, 1.84]
Parmenter (RT High)	229.1	72.3	7	65.2	68.8	4	11.5%	2.11 [0.46, 3.75]
Hiatt (RT Mod)	16	20.7	9	-37.4	23.7	5	13.0%	2.30 [0.81, 3.78]
Subtotal (95% CI)			**89**			**45**	**100.0%**	**0.81 [0.09, 1.52]**

Heterogeneity: $Tau^2 = 0.45$; $Chi^2 = 12.89$, df = 5 (P = 0.02); $I^2 = 61\%$

Test for overall effect: Z = 2.22 (P = 0.03)



Study or Subgroup	Resistance Training Mean	Resistance Training SD	Resistance Training Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
C. Six minute walk								
Parmenter (RT Light)	-2.9	262.4	7	-44.6	38.3	3	4.3%	41.70 [-157.46, 240.86]
Parr (RT Mod)	27	71	9	-30	29	4	57.7%	57.00 [2.60, 111.40]
Parmenter (RT High)	77.3	93.1	7	-44.6	59.7	4	20.9%	121.90 [31.46, 212.34]
McGuigan (RT Mod-High)	113	167.3	11	-16	20.9	9	17.1%	129.00 [29.20, 228.80]
Subtotal (95% CI)			**34**			**20**	**100.0%**	**82.23 [40.91, 123.54]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.57$, df = 3 (P = 0.46); $I^2 = 0\%$

Test for overall effect: Z = 3.90 (P < 0.0001)

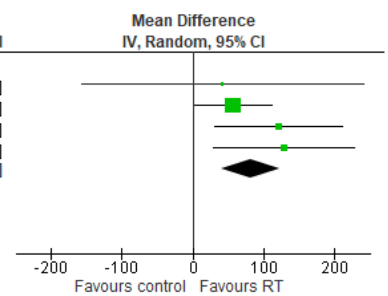
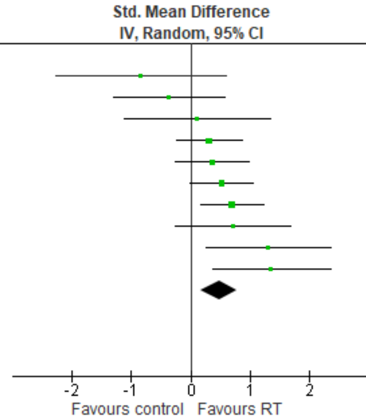


Figure 2

Study or Subgroup	Resistance Training Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
A. Constant grade treadmill protocol								
Parmenter (RT Light)	152.7	412.8	7	677.3	872.1	3	3.9%	-0.84 [-2.27, 0.59]
Hobbs (RT Mod 06)	13	134	9	61	118	9	7.9%	-0.36 [-1.30, 0.57]
Parmenter (RT High)	830.4	1,411.2	7	677.3	872.1	4	5.1%	0.11 [-1.12, 1.34]
Lundgren (RT INR)	474	380	25	361	335	25	15.4%	0.31 [-0.25, 0.87]
Tebbutt (RT Light-Mod)	40	203.5	24	-50	282.8	18	13.8%	0.37 [-0.25, 0.98]
Cheetham (RT INR)	170	243.8	28	71	101.8	28	16.1%	0.52 [-0.01, 1.06]
Stewart (RT INR)	92.4	145	30	16.1	47	30	16.4%	0.70 [0.18, 1.22]
Hobbs (RT Mod 07)	119	128	9	43	66.4	9	7.6%	0.71 [-0.25, 1.67]
Dahloff (RT INR)	362	205	10	0.01	324.5	8	6.6%	1.31 [0.26, 2.35]
Mannarino (RT INR)	168.6	81.3	10	56.9	76.5	10	7.2%	1.36 [0.36, 2.35]
Subtotal (95% CI)			**159**			**144**	**100.0%**	**0.48 [0.18, 0.78]**

Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 13.49$, df = 9 (P = 0.14); $I^2 = 33\%$

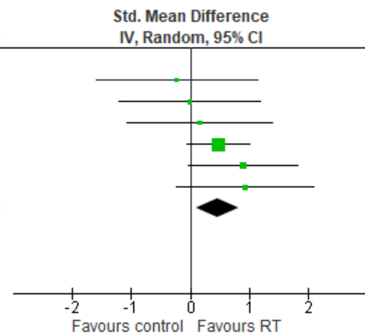
Test for overall effect: Z = 3.10 (P = 0.002)



Study or Subgroup	Resistance Training Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
B. Progressive grade treadmill protocol								
Parmenter (RT Light)	10.6	137	7	47.9	171	3	7.4%	-0.23 [-1.59, 1.13]
Parr (RT Mod)	7	19.8	8	7.3	46	4	9.5%	-0.01 [-1.21, 1.19]
Parmenter (RT High)	73.5	132.3	7	47.9	171	4	9.0%	0.16 [-1.07, 1.39]
McDermott (RT Mod)	124.3	197.4	46	35.5	144.5	20	48.4%	0.48 [-0.05, 1.01]
McGuigan (RT Mod-High)	186.8	269	11	0.01	0.01	9	15.7%	0.89 [-0.04, 1.83]
Hiatt (RT Mod)	106.8	138.2	9	-5.3	3.4	5	10.0%	0.93 [-0.24, 2.10]
Subtotal (95% CI)			**88**			**45**	**100.0%**	**0.46 [0.09, 0.83]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.26$, df = 5 (P = 0.66); $I^2 = 0\%$

Test for overall effect: Z = 2.45 (P = 0.01)



Study or Subgroup	Resistance Training Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
C. Six minute walk								
Parr (RT Mod)	13	21	9	2	33	4	32.6%	11.00 [-24.13, 46.13]
McDermott (RT Mod)	-2	37.9	46	-15	38.7	20	48.5%	13.00 [-7.19, 33.19]
Parmenter (RT Light)	8.8	192.2	7	-9.9	38.6	3	3.5%	18.70 [-130.23, 167.63]
Parmenter (RT High)	59.9	166.3	7	-9.9	60.3	4	4.1%	69.80 [-66.83, 206.43]
McGuigan (RT Mod-High)	85	127.2	11	-23	30.1	9	11.2%	108.00 [30.30, 185.70]
Subtotal (95% CI)			**80**			**40**	**100.0%**	**25.56 [-3.12, 54.24]**

Heterogeneity: $Tau^2 = 335.18$; $Chi^2 = 6.09$, df = 4 (P = 0.19); $I^2 = 34\%$

Test for overall effect: Z = 1.75 (P = 0.08)

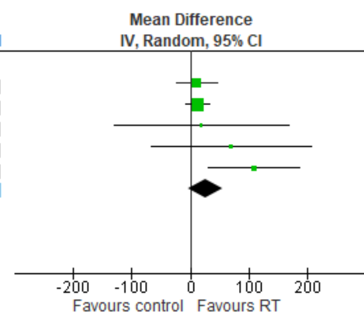
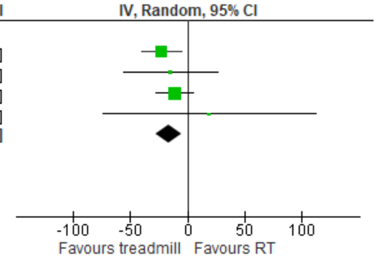
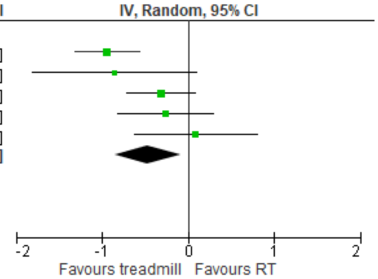


Figure 3

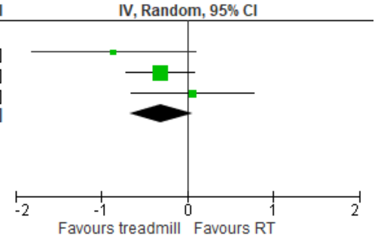
Study or Subgroup	Resistance Training Mean	Resistance Training SD	Resistance Training Total	Treadmill Training Mean	Treadmill Training SD	Treadmill Training Total	Weight	Mean Difference IV, Random, 95% CI
A. 6MWT RT versus Trd								
McDermott (Trd Walk)	-2	37.9	46	21	48.6	50	43.4%	-23.00 [-40.36, -5.64]
Szymczak (Trd Walk)	27.1	71.4	26	41.8	78.1	24	7.6%	-14.70 [-56.29, 26.89]
Gardner (Trd Walk)	4	40	60	15	52	60	47.5%	-11.00 [-27.60, 5.60]
Delaney (Trd Walk)	51	165	13	32	47	14	1.5%	19.00 [-74.01, 112.01]
Subtotal (95% CI)			**145**			**148**	**100.0%**	**-16.04 [-27.48, -4.60]**
Heterogeneity: Tau² = 0.00; Chi² = 1.52, df = 3 (P = 0.68); I² = 0%								
Test for overall effect: Z = 2.75 (P = 0.006)								



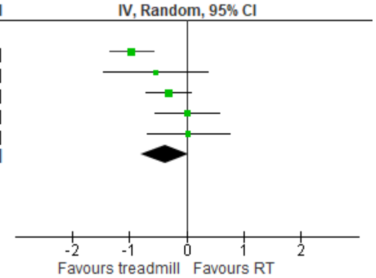
Study or Subgroup	Resistance Training Mean	Resistance Training SD	Resistance Training Total	Treadmill Training Mean	Treadmill Training SD	Treadmill Training Total	Weight	Std. Mean Difference IV, Random, 95% CI
B. Progressive treadmill COD RT versus Trd								
Gardner (Trd Walk)	15	121.4	60	149.6	160.2	60	26.6%	-0.94 [-1.32, -0.56]
Hiatt (Trd Walk)	16	20.7	9	181.6	252.4	10	11.2%	-0.86 [-1.81, 0.09]
McDermott (Trd Walk)	86.6	166.9	46	156.8	261.8	50	25.7%	-0.31 [-0.72, 0.09]
Szymczak (Trd Walk)	61.7	134.7	26	90.2	64.1	24	20.4%	-0.26 [-0.82, 0.29]
Ritti-Dias (Trd Walk)	146	224	15	127	182	15	16.0%	0.09 [-0.63, 0.81]
Subtotal (95% CI)			**156**			**159**	**100.0%**	**-0.47 [-0.85, -0.08]**
Heterogeneity: Tau² = 0.11; Chi² = 9.87, df = 4 (P = 0.04); I² = 59%								
Test for overall effect: Z = 2.38 (P = 0.02)								



Study or Subgroup	Resistance Training Mean	Resistance Training SD	Resistance Training Total	Treadmill Training Mean	Treadmill Training SD	Treadmill Training Total	Weight	Std. Mean Difference IV, Random, 95% CI
C. Progressive Trd COD mod-high RT versus Trd								
Hiatt (Trd Walk)	16	20.7	9	181.6	252.4	10	14.4%	-0.86 [-1.81, 0.09]
McDermott (Trd Walk)	86.6	166.8	46	156.8	261.8	50	61.4%	-0.31 [-0.72, 0.09]
Ritti-Dias (Trd Walk)	146	339.5	15	127	285.4	15	24.2%	0.06 [-0.66, 0.77]
Subtotal (95% CI)			**70**			**75**	**100.0%**	**-0.30 [-0.68, 0.07]**
Heterogeneity: Tau² = 0.02; Chi² = 2.30, df = 2 (P = 0.32); I² = 13%								
Test for overall effect: Z = 1.59 (P = 0.11)								



Study or Subgroup	Resistance Training Mean	Resistance Training SD	Resistance Training Total	Treadmill Training Mean	Treadmill Training SD	Treadmill Training Total	Weight	Std. Mean Difference IV, Random, 95% CI
D. Progressive Trd WD RT versus Trd								
Gardner (Trd Walk)	19.4	139.9	60	168	167.2	60	25.5%	-0.96 [-1.34, -0.58]
Hiatt (Trd Walk)	106.8	138.2	9	272.3	378.6	10	12.6%	-0.54 [-1.46, 0.38]
McDermott (Trd Walk)	124.3	197.5	46	218.1	364	50	24.8%	-0.31 [-0.72, 0.09]
Szymczak (Trd Walk)	148.4	223.3	26	146	137.8	24	20.6%	0.01 [-0.54, 0.57]
Ritti-Dias (Trd Walk)	157	282	15	149	231	15	16.6%	0.03 [-0.69, 0.75]
Subtotal (95% CI)			**156**			**159**	**100.0%**	**-0.38 [-0.80, 0.04]**
Heterogeneity: Tau² = 0.14; Chi² = 11.76, df = 4 (P = 0.02); I² = 66%								
Test for overall effect: Z = 1.79 (P = 0.07)								



Study or Subgroup	Resistance Training Mean	Resistance Training SD	Resistance Training Total	Treadmill Training Mean	Treadmill Training SD	Treadmill Training Total	Weight	Std. Mean Difference IV, Random, 95% CI
E. Progressive Trd WD mod-high RT versus Trd								
Hiatt (Trd Walk)	106.8	138.2	9	272.3	378.6	10	12.7%	-0.54 [-1.46, 0.38]
McDermott (Trd Walk)	124.3	197.5	46	218.1	364	50	66.3%	-0.31 [-0.72, 0.09]
Ritti-Dias (Trd Walk)	157	417.4751	15	149	353.3523	15	21.0%	0.02 [-0.70, 0.74]
Subtotal (95% CI)			**70**			**75**	**100.0%**	**-0.27 [-0.60, 0.06]**
Heterogeneity: Tau² = 0.00; Chi² = 1.01, df = 2 (P = 0.60); I² = 0%								
Test for overall effect: Z = 1.63 (P = 0.10)								

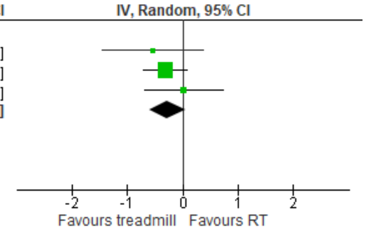


Figure 4

Study or Subgroup	Resistance Training Mean	Resistance Training SD	Resistance Training Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
A. Below Knee								
Parmenter (RT Light)	0	11.5	7	8	6.5	3	3.7%	-0.69 [-2.10, 0.72]
Hiatt (RT Mod)	4.3	11.6	9	2.7	12.1	5	6.1%	0.13 [-0.97, 1.22]
McDermott (RT Mod)	117	212.6	46	78.2	194	20	26.5%	0.19 [-0.34, 0.71]
Parmenter (RT High)	12	19	7	8	6.5	4	4.8%	0.23 [-1.01, 1.46]
McGuigan (RT Mod-High)	55	81.4	11	6.6	8.6	9	8.7%	0.76 [-0.16, 1.68]
Subtotal (95% CI)			**80**			**41**	**49.7%**	**0.22 [-0.17, 0.60]**
Heterogeneity: Tau² = 0.00; Chi² = 2.98, df = 4 (P = 0.56); I² = 0%								
Test for overall effect: Z = 1.11 (P = 0.27)								
B. Above Knee								
Parmenter (RT Light)	25	155.8	7	34	96.1	3	4.0%	-0.06 [-1.41, 1.30]
McGuigan (RT Mod-High)	63.5	94	11	9.3	12.2	9	8.7%	0.74 [-0.18, 1.65]
McDermott (RT Mod)	94.9	105.4	46	14.7	93.3	20	24.9%	0.78 [0.23, 1.32]
Parmenter (RT High)	112	59.9	7	34	96.1	4	4.2%	0.96 [-0.36, 2.29]
Subtotal (95% CI)			**71**			**36**	**41.7%**	**0.71 [0.29, 1.13]**
Heterogeneity: Tau² = 0.00; Chi² = 1.44, df = 3 (P = 0.70); I² = 0%								
Test for overall effect: Z = 3.31 (P = 0.0009)								
C. Whole Body								
Parmenter (RT Light)	-89	605	7	-88	439.2	3	4.0%	-0.00 [-1.35, 1.35]
Parmenter (RT High)	275	578	7	-88	439.2	4	4.5%	0.62 [-0.65, 1.89]
Subtotal (95% CI)			**14**			**7**	**8.5%**	**0.33 [-0.60, 1.25]**
Heterogeneity: Tau² = 0.00; Chi² = 0.43, df = 1 (P = 0.51); I² = 0%								
Test for overall effect: Z = 0.70 (P = 0.49)								
Total (95% CI)			**165**			**84**	**100.0%**	**0.43 [0.16, 0.70]**
Heterogeneity: Tau² = 0.00; Chi² = 7.76, df = 10 (P = 0.65); I² = 0%								
Test for overall effect: Z = 3.12 (P = 0.002)								
Test for subgroup differences: Chi² = 2.91, df = 2 (P = 0.23), I² = 31.3%								

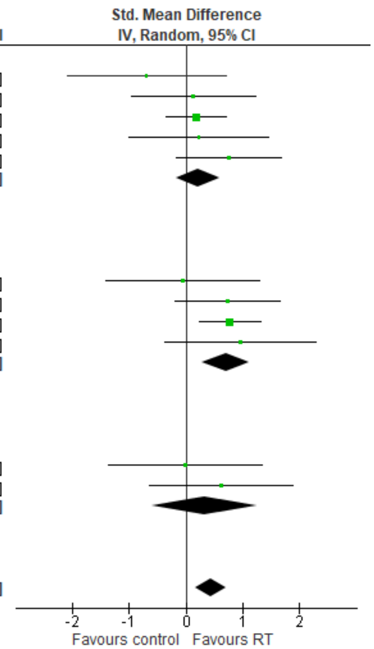


Figure 5