REVIEW

The Impact of Supervised Exercise Training on Traditional Cardiovascular Risk Factors in Patients With Intermittent Claudication: A Systematic Review and Meta-Analysis

Nils Cornelis [a,*], **Julie Nassen** [a], **Roselien Buys** [a,b], **Inge Fourneau** [b], **Véronique Cornelissen** [a]

[a] Department of Rehabilitation Sciences, KU Leuven, Leuven, Belgium
[b] Department of Cardiovascular Sciences, KU Leuven, Leuven, Belgium

---

WHAT THIS PAPER ADDS
This systematic review and meta-analysis shows for the first time that supervised exercise training in patients with intermittent claudication has the potential to reduce cardiovascular risk factors in addition to improving pain free and maximum walking distance. Moreover, this report highlights the lack of data on the effect of claudication limited exercise on cardiovascular risk factors. Therefore, this paper can encourage other exercise researchers to evaluate cardiovascular risk outcomes and therefore study the added value of exercise in secondary prevention of peripheral artery disease.

Background: Patients with intermittent claudication (IC) are at increased risk of cardiovascular (CV) morbidity and mortality. Whereas extensive evidence supports the beneficial effects of supervised exercise training (SET) on walking capacity, little is known about the effect of SET on the CV risk profile of IC patients. Therefore, the aim was to evaluate the effects of SET on CV risk factors in IC patients by using meta-analysis techniques.
Methods: A systematic search in the electronic databases MEDLINE, EMBASE, CINAHL, and CENTRAL was conducted from the earliest date available until October 2, 2018. Randomised and non-randomised controlled trials lasting $\geq$ four weeks and investigating the effect of SET on CV risk factors in IC patients were included. Traditional CV risk factors were studied as primary outcomes; pain free walking distance (PFWD) and maximum walking distance (MWD) were included as secondary outcomes. Data were pooled using random effects models with summary data reported as weighted means and 95% confidence interval (CIs).
Results: Fifteen trials were included, involving 18 study groups (nine walking, four resistance, two aerobic training, and three combined groups), totalling 725 patients (mean age 66.3 years; mean ankle brachial index, 0.64). Exercise reduced systolic blood pressure (-5.8 mmHg; CI -9.89 to 1.67, $p < .01$) whereas all other CV risk factors (i.e., body weight, body mass index, diastolic blood pressure, and blood lipids) remained statistically unaltered. Exercise also improved PFWD ($+132$ m; CI 70—194, $p < .001$) and MWD ($+183$ m; CI 98—268, $p < .001$).
Conclusion: This meta-analysis supports the beneficial effects of SET on walking capacity. Little evidence for an improvement of the CV risk profile was found following exercise in patients with IC. However, given the scarcity of data, high quality RCTs that include an assessment of CV risk factors are urgently required to determine the effect of exercise therapy in the secondary prevention of CV disease of IC patients.

---

* **Corresponding author.** Research Group for Rehabilitation in Internal Disorders, O&N IV Herestraat 49 - box 1510, 3000 Leuven, Belgium.
E-mail address: nils.cornelis@kuleuven.be (Nils Cornelis).

INTRODUCTION

Lower extremity artery disease (LEAD), as specified by the most recent European Society of Cardiology (ESC) and European Society for Vascular Surgery (ESVS) guidelines on peripheral arterial diseases,[1] is characterised by a

progressive atherosclerotic build up in arteries supplying the lower limbs. Worldwide 202 million patients are diagnosed with LEAD, with a 23.5% increase within the last decade because of a higher overall life expectancy and concomitant global rise in risk factors.[2,3] Of these 202 million LEAD patients, up to 35% present with the cardinal symptom of intermittent claudication (IC), characterised by a cramp like pain when walking which only resolves through rest.[4] Although not initially life threatening, the debilitating nature of IC initiates a vicious cycle of physical inactivity[5,6] impacting functional capacity,[7] and quality of life,[8] and probably aggravating the already increased cardiovascular (CV) risk in these patients. Research shows that a considerable number of LEAD patients also have damage in other vessel sites, underscoring the systemic impact of atherosclerosis. Moreover, the comorbidity rate of CV and/or cerebrovascular diseases in LEAD is estimated at 61%, with the presence of LEAD itself considered as an independent risk factor equivalent to well known lifestyle related risk factors.[9] It is thus most noteworthy that only a minority (20—30%) of LEAD patients will die from a non-cardiovascular disease.[4]

Current treatment guidelines in LEAD patients with IC highlight the importance of supervised[10] exercise training (SET) and risk factor management as a first line treatment to improve symptomatic claudication and to slow down the progressive nature of atherosclerosis.[1] Yet, a remarkable care gap regarding optimum medical treatment, risk prevention support, and healthy lifestyle promotion is still present in LEAD patients.[2,11—13] There is overwhelming evidence from well controlled randomised studies that SET improves both pain free walking distance (PFWD), maximum walking distance (MWD), and quality of life in patients with IC.[14] However, less attention has been paid to whether SET can also impact on the CV risk profile of these patients.[15] Interestingly, one small retrospective study has shown that SET significantly altered CV morbidity and mortality in 64 patients completing SET compared with those who did not.[16] The primary driver behind this observation remains unclear, but the impact of exercise on traditional CV risk factors, and therefore risk of future morbidity and mortality, has already been established in patients presenting with similar CV risk profiles.[17—19] As most contemporary SET programs in IC patients are tailored to improve claudication symptoms, the systemic benefit of SET in IC remains to be determined. Therefore, this systematic review with meta-analysis will study the effect of SET on traditional CV risk factors in LEAD patients with IC. Secondary outcomes of this study will include the effect of SET on walking performance measures.

METHODS

The Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines were followed to conduct this systematic review and meta-analysis.[20] Supplementary information S1 shows the protocol of the study.

Database and search strategy

Four electronic databases (MEDLINE, EMBASE, CINAHL and Cochrane Central Register of Controlled Trials [CENTRAL]) were searched for articles published in English from the earliest date available until October 2, 2018. The full search strategy for each of these databases is provided in Supplementary information S2. Additionally, the reference list of eligible articles and meta-analyses on the topic were manually scrutinised for other potentially eligible papers.

Eligibility

The current analysis was limited to (1) randomised controlled trials and controlled clinical trials of SET only, lasting ≥ four weeks; (2) in adult humans aged ≥ 18 years with LEAD and IC (typically classified as Rutherford 1—3 or Fontaine 2a or 2b); (3) reporting before and after mean and SD (or standard error) in exercise and control groups or mean change and SD (or standard error) in exercise and control groups or median and range in exercise and control groups of at least one traditional CV risk factor; i.e., weight, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC), high density lipoprotein (HDL-C), low density lipoprotein (LDL-C), triglycerides (TGs), and fasting blood glucose (FBG); (4) published in English in a peer reviewed journal.

Study selection

After removal of duplicates, screening of all titles and abstracts from the first search (earliest date available of databases to April 27, 2017) was performed by two independent reviewers (N.C. and J.N.). Secondly, all identified articles were assessed by both reviewers and papers were selected for inclusion after consensus. An updated search was performed from April 2017 to the October 2, 2018. A third reviewer (V.C.) was consulted in case of disagreement.

Assessment of risk of bias

Studies were assessed for quality by both reviewers (N.C. and J.N.) using the Tool for the assEssment of Study qualiTy and reporting in EXercise (TESTEX scale).[21] This scale is a validated tool specifically developed for the assessment of study quality and reporting in exercise training studies. The total TESTEX score of 15 points is composed of five points on assessment of study quality and 10 points regarding study reporting. A higher score reflects a better quality. Inter-observer agreement was determined using Kappa statistics.[22] Disagreements were resolved by discussion with a third reviewer (V.C.).

Data extraction

A standardised Access Database file (Microsoft, Redmond, WA, USA) was used by both reviewers (N.C. and J.N.) to extract data related to trial and patient characteristics, intervention details, and primary and secondary outcome

data. For three and five papers, data on pain free (PFWD in metres) and maximum walking distance (MWD in metres), respectively, were calculated using reported time and speed on the treadmill test. When only median and interquartile data were reported,[23] these values were converted using approximation methods.[24] Data presented graphically were transposed to numerical data by means of digital scaling and measurement of plots in Adobe Acrobat Reader (Adobe Systems Incorporated, San Jose, CA, USA). A request for missing data was sent to 11 authors, of which one provided the missing information.

Statistics

All meta-analyses were performed using Comprehensive Meta-Analysis software V2.2 (Biostat, Englewood, NJ, USA). When assessments were performed at different time periods, the last assessment in the analyses was used. Descriptive data are reported as weighted mean. Both Hedges' g, mean differences, and their 95% confidence intervals (CIs) were calculated as effect sizes. Each effect size was weighted by the inverse of its variance. Given the clinical heterogeneity of included studies, random effects models were used to pool the data. A two sided $p \leq .05$ was considered statistically significant.

Heterogeneity among trials was assessed using Cochran Q tests with an alpha value of 0.1 indicating significant heterogeneity. In addition, the I^2 statistic was used to quantify inconsistency of treatment effect across trials. A value for $I^2 > 50\%$ was considered to indicate substantial heterogeneity. Additionally, sensitivity analyses were performed by removing studies from the model one by one. A mixed effects subgroup analysis was performed to evaluate whether exercise modes influenced the results. Publication bias was evaluated by means of visual inspection of the funnel plots of variables reported in at least five studies, supplemented by Duval and Tweedie's Trim and Fill tests to obtain an estimate of the unbiased effect size.

RESULTS

Study selection

A PRISMA flow diagram of the literature search and selection is presented in Fig. 1. The initial search identified 8316 potentially relevant studies of which 117 were retrieved for full text review. Eleven studies were omitted from the meta-analysis since five of them were ancillary studies of included trials[25—29] and another six did not report the required data. One extra eligible study was identified after updating the initial search.[30] Details on this updated search can be found in Supplementary information S2. In total, 15 publications were included for the quantitative analyses.

Study design and participant characteristics

A summary of the study characteristics of the included trials is shown in Table 1. All 15 trials were published between 2000 and 2018. Twelve trials were randomised controlled trials and the remaining three (20%) were non-randomised

controlled trials.[31—33] Except for one that applied a cross over design[33] all studies used a parallel design. Sample sizes of the studies ranged from 10 to 177 (median 45) totalling 725 randomised patients (mean age 66.3 years; range 61.8—70.5). The majority of the included patients in the studies were male (72%; range 40—100%). The total dropout rate was 17% (range 0—36%), resulting in 604 patients that completed the allocated intervention.

Eleven studies reported ABI, ranging from 0.56 to 0.78 (mean 0.64), with IC class reported in seven trials as Fontaine II or Rutherford 1—3. Fig. 2 provides an overview of the studies reporting on each of the risk factors. In studies that reported the presence of specific risk factors, 23% (range 0—43%) of the patients were diagnosed with diabetes, with one trial excluding diabetic patients.[34] 73% of participants (range 33—91%) had hypertension. Baseline values suggested that all trials included pre- and/or hypertensive patients (SBP range, 134—152 mmHg). In addition, almost 80% (range 30—96%) of patients had hypercholesterolaemia. PFWD and MWD were reported in eight and 13 studies respectively, with seven of them using the Gardner protocol for assessment.

Outcome assessment and intervention characteristics

The median duration of the interventions was 12 weeks (range 8—52 weeks). Training frequency was three times per week, except in three studies performing two sessions a week.[23,30,35] As shown in Fig. 3, half (9/18) of the supervised interventions provided a walking program.[23,31,34—40] Four studies implemented a resistance training intervention,[30,33,41,42] two involved an aerobic training program,[40,43] and three applied a combination of exercise modalities.[32,40,42] Most control groups received usual care including advice to exercise.

Risk of bias

The median quality of the trials was 11 (range 6—14), with incomplete reporting of point measures in seven of 15 and blinding of assessors in four of 15 studies only. Interobserver agreement, calculated using the kappa statistics, was 0.89 between both reviewers. TESTEX results and funnel plots are shown in Supplementary information S3. SBP was suggestive of publication bias. A visible trend was noted in 11 interventions, with smaller studies presenting a larger effect size left to the mean. Five studies need to be imputed according to the Duval and Tweedie's Trim and Fill to establish symmetry with an estimated Hedges' g of −0.041 (CI −0.292 to 0.210).

SYNTHESIS OF RESULTS
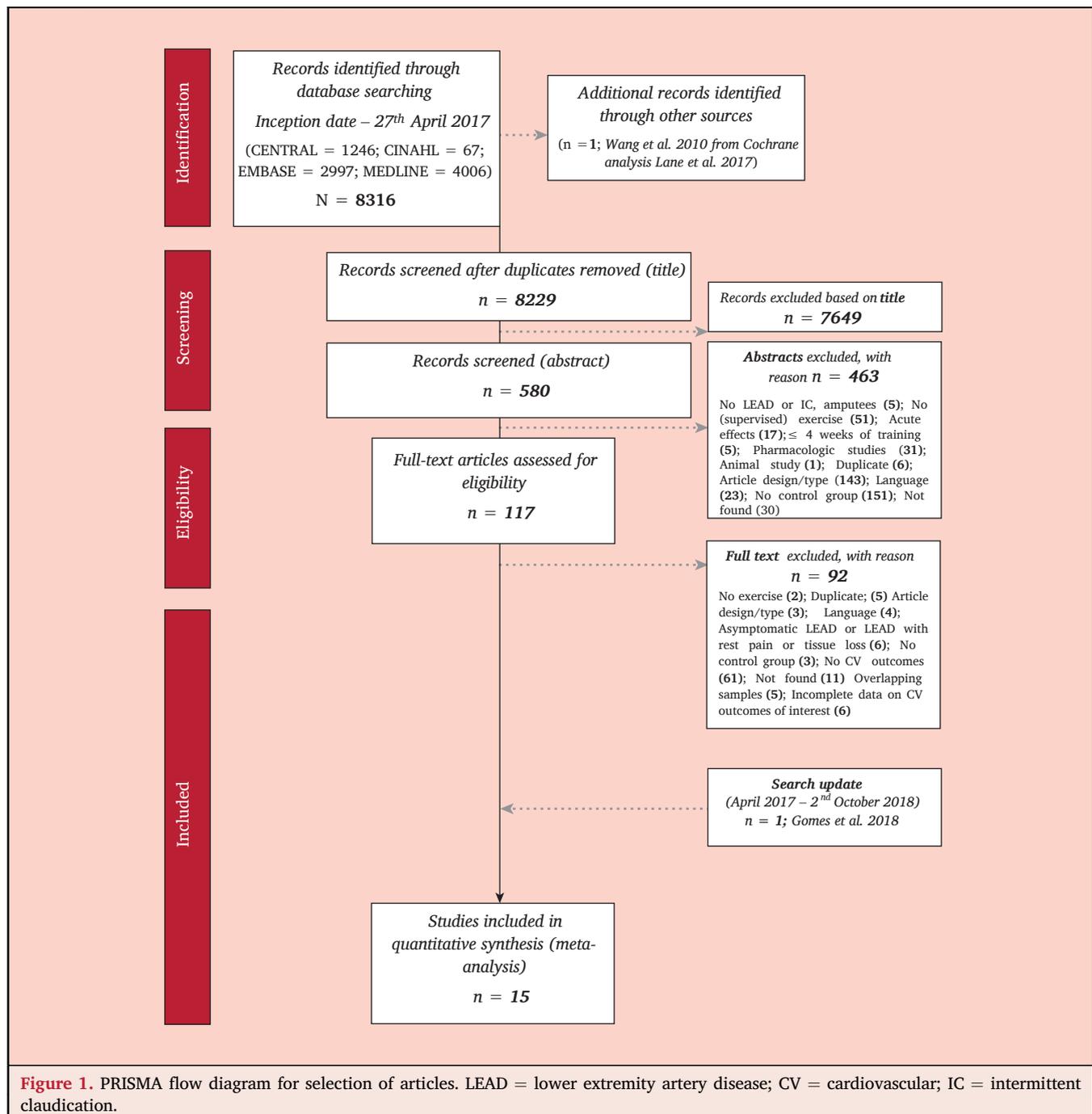
Primary outcome: cardiovascular risk factors

A summary of the main effect sizes of the primary outcomes is presented in Table 2. Compared with controls, exercise training induced a significant decrease in office SBP with a mean reduction of −5.8 mmHg (−9.9 to −1.7). Heterogeneity and inconsistency were low for SBP. A subgroup

analysis showed only a non-significant trend towards a reduction in SBP (-4.8 mmHg; range -11.1 to 1.5; $p = .14$; $I^2 = 45.7$) in the six studies that provided walking training. Conversely, the two more intense aerobic interventions,[40,43] comprising 24 exercise and 19 control patients, showed a significant reduction in SBP of 11.6 mmHg (-22.3 to -1.0, $p = .03$; $I^2 = 0.0$). Five trials reporting on DBP found no effect after training (-2.2 mmHg; range -5.2 to 0.7). Changes in weight and BMI were reported in seven and four study groups respectively. There was no impact of the exercise interventions on each of these parameters compared with the control. No evidence of statistical heterogeneity was present ($I^2 = 0\%$ for both). The lipid profile was only investigated following walking interventions.[23,31,34,38,39] Pooling results across these studies showed no effect on TC, HDL-C, LDL-C, and triglycerides compared with the control. Heterogeneity and inconsistency were high for TC and LDL-C and low for HDL-C and triglycerides.

Secondary outcomes: pain free and maximum walking distance

PFWD (132 m; range 70–194, $p < .01$) and MWD (183 m; range 98–268, $p < .01$) improved significantly compared with the control. As shown in Table 2, a separate analysis of studies using the Gardner protocol indicated even higher effect sizes. Further, pooling data from the walking interventions (7 for

Figure 1. PRISMA flow diagram for selection of articles. LEAD = lower extremity artery disease; CV = cardiovascular; IC = intermittent claudication.

Table 1. Included studies with trial and participant characteristics based on reported baseline data

Reference, country of origin	Trial characteristics			Patient Characteristics						
	Design	Duration (weeks)	FITT	n (male/ female)	Mean age (years)	Mean ABI	DM (%)	HTN (%)	BMI (kg/m²)	HCL (%)
Chehuen et al., 2017,[35] Brazil	●	12	**Treadmill walking:** 2/w, %HR_{max} at pain threshold, 30 min (15 × 2 min intervals, 2 min rest) **Control:** attention-control stretching 2/w, 30 min	42 (42/0)	62.5	0.60	26.2	83.3	26.2	95.2
			Standard care: recommendation to walk 30 min every day (assessed by weekly recall) **Test protocol:** Gardner protocol (3.2 km/h with 2% increase in inclination every 2-min)							
Crowther et al., 2008,[36,b] Australia	●	52	**Treadmill walking:** 3/w, intense to maximum pain (CPS 3–4/4), 25–40 min **Control:** not specified	21 (10/11)	69.1	0.67	19.0	33.3	28.0	N/A
			Standard care: recommendations for lifestyle changes **Test protocol:** Gardner protocol (3.2 km/h with 2% increase in inclination every 2 min)							
Gardner et al., 2001,[37] USA	●	26	**Treadmill walking:** 3/w, intense pain (CPS 3/4), at 50–80% $Workload_{max}$ 15–40 min **Control:** did not receive any recommendations regarding exercise	52 (47/5)	70.5	0.68	42.3	80.8	29.9	75.0
			Mutual: usual medical care **Test protocol:** Gardner protocol (3.2 km/h with 2% increase in inclination every 2 min)							
Gelin et al., 2001,[38,b] Sweden	●	52	**Walking:** first 26 w; 3/w and last 26 w; 2/w, 30 min **Control:** not specified	177 (118/59)¤	67.0	0.56	14.7	PoS	N/A	PoS
			Standard care: recommendations to quit smoking and risk factor management **Test protocol:** progressive increase of slope from 0–12%							
Gomes et al., 2018,[30] Brazil	●	12	**Resistance exercise:** 2/w, 8 exercises, 3 sets of 10 repetitions, 5–7/10 on OMNI resistance exercise scale, 40 min **Control:** whole body stretching and relaxation exercises, 40 min **Test protocol:** no treadmill test	30 (18/12)¤	63.5	0.72	43.3	73.3	25.9	33.3
Izquierdo-Porrera et al., 2000,[31] USA	○	26	**Treadmill walking:** 3/w, intense pain (CPS 3/4) at 50–80% $Workload_{max}$, 15–40 min **Control:** non-exercising control from longitudinal studies **Test protocol:** Gardner protocol (3.2 km/h with 2% increase in inclination every 2-min)	48 (44/4)	68	0.62	37.5	77.1	28.4	79.2

Continued

Table 1-*continued*

Reference, country of origin	Trial characteristics			Patient Characteristics						
	Design	Duration (weeks)	FITT	*n* (male/ female)	Mean age (years)	Mean ABI	DM (%)	HTN (%)	BMI (kg/m²)	HCL (%)
McGuigan et al., 2001,[41] Australia	●	24	**Resistance exercise:** 3/w, 8 exercises, 2 sets with variable number of repetitions (8–15) (linear periodisation), weights **Control:** non-exercising control group **Test protocol:** no data on PFWD or MWD	20 (9/11)[¤]	68.2	0.64	N/A	PoS	27.5	N/A
Mika et al., 2011,[34] Poland	●	12	**Treadmill walking:** 3/w, onset of claudication (CPS 2/5), 30–55 min (3–5 min intervals with 3 min rest) **Control:** advised not to change their usual level of activity	61 (53/8)	62.8	0.78	0.0	N/A	27.7	PoS
			Standard care: encouraged to stop smoking **Test protocol:** Gardner protocol (3.2 km/h with 2% increase in inclination every 2-min)							
Mosti et al., 2011,[32] Norway	○	8	**Combined exercise:** 3/w, 60 min **1)** Plantar flexion ergometre: 80% Workload$_{max}$, 4×4 min each leg at 55–65 rpm **2)** Maximum strength training: horizontal dynamic leg press, %1 RM 85–90, 4 sets with 5 repetitions **Control:** non-randomised, recommendation to follow AHA exercise guidelines (Hirsch et al., 2006) **Test protocol:** Hiatt protocol (3.2 km/h with a 3.5% increase in inclination every 3-min)	20 (14/6)	65.5	N/A	20.0	45.0	28.0	50.0[a]
Murphy et al., 2012,[39,b] USA	●	26	**Treadmill walking:** 3/w, mild-moderate pain (CPS 3–4/5), 15–50 min **Control:** no supervised exercise	65 (37/28)[¤]	63.5	0.68	20.0	90.8	27.8	83.1
			Standard care: optimal medical management + cilostazol + recommendations for risk factor management (incl. unsupervised exercise with written and verbal instructions) **Test protocol:** Gardner protocol (3.2 km/h with 2% increase in inclination every 2-min)							

Table 1-*continued*

Reference, country of origin	Trial characteristics			Patient Characteristics						
	Design	Duration (weeks)	FITT	*n* (male/ female)	Mean age (years)	Mean ABI	DM (%)	HTN (%)	BMI (kg/m^2)	HCL (%)
Parr et al., 2009,[42] South Africa	●	6	**A. Resistance exercise:** 3/w, 10 weight plated upper-body exercises and 4 dumbbell exercises with 15 (comfortably) and 10 repetitions (starting at 1.5 kg increased by 1.8−7.3 kg/week) respectively, 45 min **B. Combined exercise:** 3/w, 45 min 1) Treadmill walking: speed and incline with onset of claudication in 5−10 min, 10−20 min 2) Stationary cycling: 5 min 3) Circuit training/Floor exercises/Spinning class: 1/w, 15 min and stretching for 5 min **Control:** advice to walk as much as possible at home **Test protocol:** Gardner protocol (3.2 km/h with 2% increase in inclination every 2-min)	25 (17/8)	61.8	N/A	N/A	N/A	28.0	N/A
Schlager et al., 2012,[23] Austria	●	26	**Walking:** 2/w, walking speed to elicit claudication pain in 3−5 min (intermittent walking), 35−50 min **Control:** no supervised exercise **Standard care:** best medical treatment with detailed information on LEAD, risk factor management and lifestyle changes **Test protocol:** Constant test (3.2 km/h with a 12% inclination)	53 (33/20)[¤]	69.5	0.58	39.6	PoS	26.8	96.2[a]
Treat-Jacobson et al., 2009,[40] USA	●	12	**A. Aerobic exercise:** arm-ergometer, 3/w, 10 Watts below Workload$_{max}$ at 50 rpm, 60 min (2−5 min exercise, 1−2 min rest) **B. Treadmill walking:** 3/w, moderately severe pain (CPS 4/5), with increase in inclination and speed when walking > 8 min, 60 min **C. Combined exercise:** 3/w, 60 min 1) Arm ergometer: 20 min 2) Treadmill walking: 40 min **Control:** continue prescribed medical care + specific standardised written walking instructions and daily exercise records (reviewed weekly) **Test protocol:** 3.2 km/h with a 3.5% inclination increase every 3 min. When 10.5% inclination was reached, speed was increased with 0.8 km/h every 3-min	41 (29/12)	67.5	0.67	36.6	80.5	28.3	90.2

Table 1-*continued*

Reference, country of origin	Trial characteristics			Patient Characteristics						
	Design	Duration (weeks)	FITT	n (male/female)	Mean age (years)	Mean ABI	DM (%)	HTN (%)	BMI (kg/m^2)	HCL (%)
Wang et al., 2008, [43] Norway	●	8	**Aerobic exercise:** plantar flexion ergometer, 3/w, 80% Workload$_{max}$, 40 min (4 × 4 min each leg) at 55–65 rpm **Control:** recommendation to follow AHA exercise guidelines (Hirsch et al., 2006) **Test protocol:** Hiatt protocol (3.2 km/h with a 3.5% increase in inclination every 3 min)	25 (19/6)	66.4	N/A	12.0	40.0	30.0	N/A
Wang et al., 2010, [33] Norway	○	8	**Resistance exercise:** horizontal dynamic leg press, 3/w, %1RM 85–90, 4 sets with 5 repetitions **Control:** non-randomised, recommendation to follow AHA exercise guidelines (Hirsch et al., 2006) **Test protocol:** Hiatt protocol (3.2 km/h with a 3.5% increase in inclination every 3 min)	10 (9/1)	67.0	N/A	20.0	40.0[a]	31.4	30.0[a]

Note. Study design was a randomised controlled trial, ●, or a prospective non-randomised controlled trial, ○. FITT characteristics are summarised for every intervention group. FITT = frequency, intensity, time, and type of training; n = analysed or randomised numbers; CPS = claudication pain scale; ABI = ankle brachial index; BMI = body mass index; DM = diabetes mellitus; HTN = hypertension; OBS = obesity; HCL = hypercholesterolaemia; AHA = American Heart Association; 1RM = one-repetition maximum; rpm = revolutions per minute; PFWD = pain free walking distance; MWD = maximal walking distance; HR = heart rate.
[a] PoS = part of sample was used to indicate that, based on baseline data or reported medication use, at least part of the sample was diagnosed with the respective comorbidity.
[b] Crowther et al. had a LEAD free control group, n = 11. Gelin and Murphy et al. both studied a revascularisation group, n = 87 and n = 46 not included in the analyses. LEAD = lower extremity artery disease.
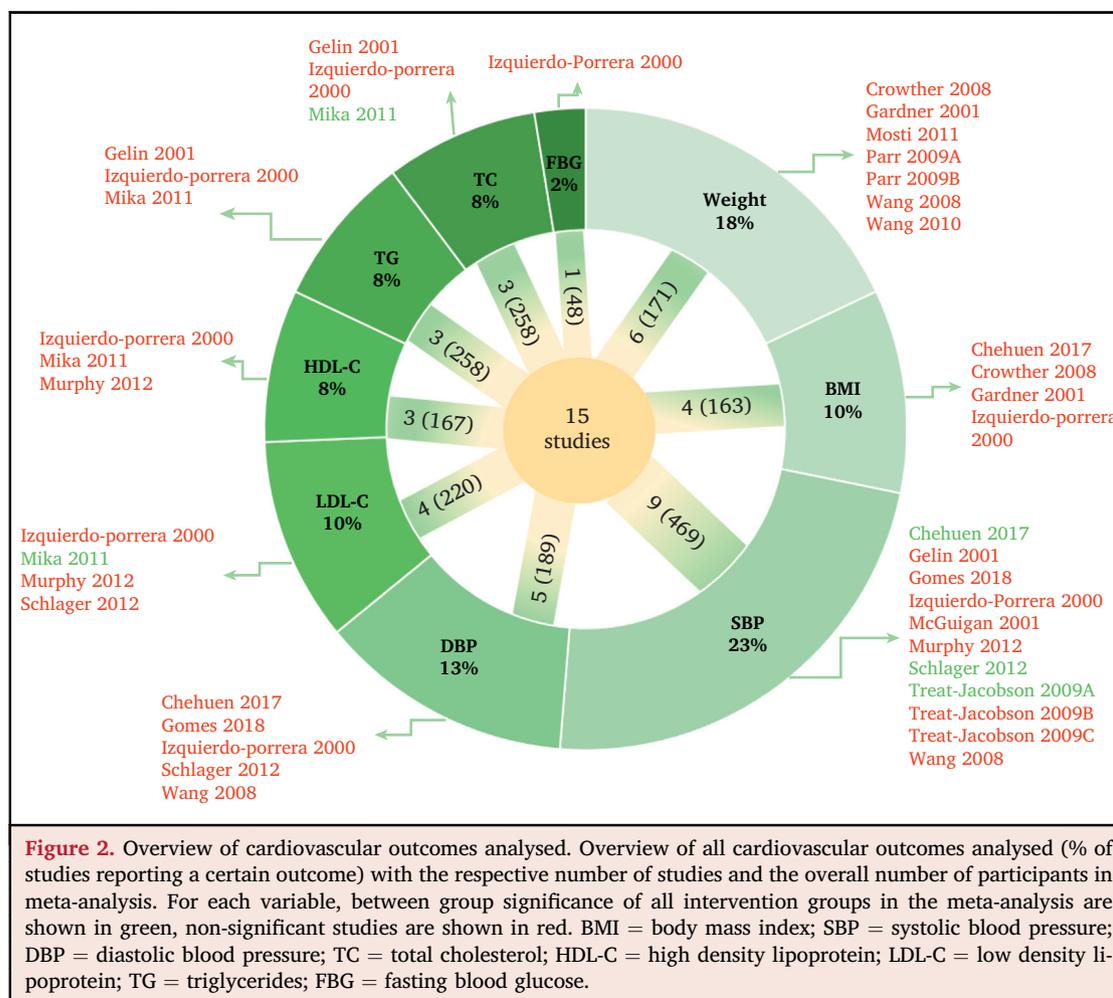
PFWD and 9 for MWD) showed an improvement of 160 m (89–231 m, $p < .01$ and $I^2 = 80\%$) in PFWD and 214 m (93–335, $p < .01$ and $I^2 = 96\%$) in MWD in favour of the walking group. No statistical differences were present when comparing exercise modes. The high heterogeneity with regard to MWD was reduced when omitting two studies[23,38] that found no effect of SET ($I^2 = 96\%$ vs. $I^2 = 0\%$). Similarly, omitting the study of Mika et al.[34] shifted heterogeneity for PFWD to non-significant ($I^2 = 80\%$ vs. $I^2 = 0\%$). Three interventions that combined modes of exercise[32,40,42] found a significant improvement in PFWD and MWD 73 m, range 1–145, $p < .05$ and $I^2 = 0.0$; and 176 m, range 109–243, $p < .01$ and $I^2 = 0.0$). Combining also data of both aerobic training interventions (24 exercise and 19 control patients) showed a significant increase in MWD, whereas no effect on MWD was established for the two resistance exercise trials (19 exercise and 18 control patients). PFWD was only evaluated in two single studies regarding the aforementioned exercise modes.[40,42]

DISCUSSION

This systematic review with meta-analysis is the first to pool data on CV risk factors following SET in a population of IC patients. The results confirm the findings from previous systematic reviews showing improved PFWD and MWD following SET.[10,14] However, only little evidence was found to support the potential of SET as an adjunctive therapy in the secondary prevention of IC patients.
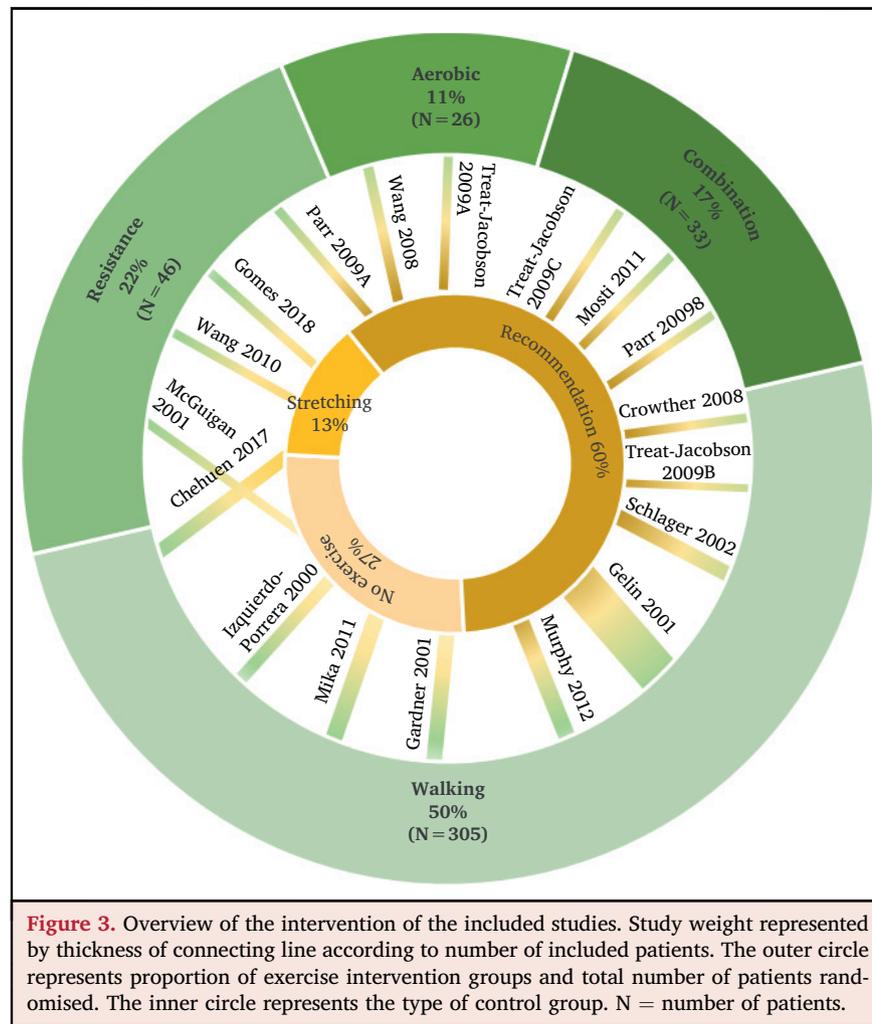
An abundance of studies highlights the key role of regular physical activity and exercise in the prevention of all cause and CV mortality in the general population and in patients with established cardiac diseases.[44] The benefits of exercise on the presence and severity of CV risk factors is one of the main drivers underlying this inverse association.[45] In this meta-analysis little evidence was found to support these findings in IC patients, with engagement in exercise training being associated with a significant and clinically relevant decrease in SBP (−5.8 mmHg). A recent meta-analysis in coronary artery disease patients demonstrated similar reductions in SBP following endurance training.[19] Walking was the most applied exercise mode, involving 74% of included IC participants. This would suggest that low intensity exercise could already suffice to improve blood pressure levels. In line with this, Cornelissen and Smart[46] found no significant differences in BP reductions in subgroups of healthy individuals participating in low, moderate, or high intensity endurance training. However, effect sizes were smallest in the low intensity group. In IC patients included in this meta-analysis, exercise intensity was mostly prescribed based on pain

Figure 2. Overview of cardiovascular outcomes analysed. Overview of all cardiovascular outcomes analysed (% of studies reporting a certain outcome) with the respective number of studies and the overall number of participants in meta-analysis. For each variable, between group significance of all intervention groups in the meta-analysis are shown in green, non-significant studies are shown in red. BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; TC = total cholesterol; HDL-C = high density lipoprotein; LDL-C = low density lipoprotein; TG = triglycerides; FBG = fasting blood glucose.

perception, which makes interpretation of intensity difficult. Yet, based on GPS data, Le Faucheur et al.[47] found IC patients to walk at approximately 3.6 km/h outdoors, with a quarter of patients exceeding 4.2 km/h. Combined with the evidence that most LEAD patients are physically inactive[5] and that the metabolic cost of walking after pain onset is increased,[48] one could assume that walking is performed at least at a moderate intensity by many IC patients. The lack of an effect on DBP can be explained by the fact that baseline DBP was already in the optimal range (76 mmHg) and the scant number of studies ($n = 5$) reducing the power.

Previous research in patients with hypercholesterolaemia suggests a decrease of 6–18% in triglycerides and 7–16% increase in HDL-C.[45] As most lipid changes are expected with a >900 kcal/week energy expenditure, prolonged exercise sessions for at least 40 weeks are recommended.[49] The meta-analyses did not establish any significant improvement in the blood lipid profiles of IC patients. However, baseline values of HDL-C and TG were already in the (high) normal range. Recent recommendations state that the greatest improvements in blood lipid profile may be anticipated in patients with the worst blood lipid profile, which could explain the lack of results.[49] Moreover, walking interventions in a broad range of health conditions did not find any effect on HDL-C or triglycerides.[50,51]

Next, obesity in IC patients is an important risk factor since it is directly associated with walking ability,[52] improvement during SET,[52,53] sedentary behaviour,[54] and subsequent development of other CV risk factors.[55] More specifically, this progression of CV risk factors is linked with body composition and the visceral distribution of fat mass**.**[55] No effect of the exercise interventions was found on body weight in the overall overweight IC patients. This is in contrast with a recent review showing that walking lowered BMI in sedentary but otherwise healthy individuals with −0.53 kg/m^2.[51] A possible explanation for this discrepancy could be the higher walking frequency in this review (median, five days/week vs. three days/week), resulting in a higher total energy expenditure.[51] More specifically, a recent consensus statement from the EXPERT panel recommends an aerobic exercise volume of more than 250 min/week to target obesity.[49] Therefore, SET induced body weight changes in IC patients seem to be hampered by low exercise volumes and the lack of whole body workouts included in analysis. Further, overall body weight changes do not reflect changes at a tissue level.[49] This illustrates the limitations of using BMI and body weight without measuring body composition and waist circumference. Therefore, as no studies investigated changes in waist circumference or fat percentage and

Figure 3. Overview of the intervention of the included studies. Study weight represented by thickness of connecting line according to number of included patients. The outer circle represents proportion of exercise intervention groups and total number of patients randomised. The inner circle represents the type of control group. N = number of patients.

distribution, future studies in IC patients are warranted to elucidate the effect on body composition.

Finally, the findings confirm the results from a recent systematic review that also documented a significant improvement in PFWD and MWD at 140 and 210 m respectively.[10] Significant heterogeneity observed in ambulatory outcomes can be explained by the various exercise interventions included, although heterogeneity was

Table 2. Changes in primary and secondary outcomes

Variable	Studies	Sample size (Ex/Con)	Baseline, mean ± SD	Mean difference	CIs (95%)	Hedges' g	CIs (95%)	I^2 (%)
Weight (kg)	6	89/82	85.1 ± 5.8	−0.46	−4.8; 3.9	−0.031	−0.321; 0.260	0
BMI (kg/m)	4	94/69	28.3 ± 1.5	0.00	−1.3; 1.3	0.003	−0.306; 0.312	0
SBP (mmHg)	9	261/208	143 ± 5.3	−5.8	−9.9; −1.7	−0.283	−0.502; −0.065	17.1
DBP (mmHg)	5	108/81	75.9 ± 5.3	−2.2	−5.2; 0.74	−0.202	−0.489; 0.085	0
TC (mmol/L)	3	137/121	6.5 ± 0.94	−0.19	−0.92; 0.53	−0.291	−1.105; 0.523	86.6[a]
LDL-C (mmol/L)	4	129/91	3.1 ± 0.70	−0.25	−0.64; 0.14	−0.320	−0.812; 0.171	70.0[a]
HDL-C (mmol/L)	3	102/65	1.1 ± 0.16	0.03	−0.055; 0.12	0.090	−0.235; 0.415	1
TG (mmol/L)	3	137/121	2.1 ± 0.26	−0.19	−0.43; 0.058	−0.204	−0.451; 0.043	5.98
PFWD (m)	8	212/160	174 ± 65	132	70.0; 194	1.115	0.562; 1.667	83.6[a]
PFWD Gardner (m)	7	179/136	176 ± 70	157	90.5; 224	1.208	0.489; 1.927	76.4[a]
MWD (m)	13	346/293	404 ± 288	183	98.4; 268	1.049	0.568; 1.531	92.7[a]
MWD Gardner (m)	7	179/136	431 ± 145	269	214; 324	1.418	0.683; 2.154	33.0

Note. Weighted means were calculated using baseline values and analysed numbers. BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; TC = total cholesterol; LDL-C = low density lipoprotein; HDL-C = high density lipoprotein; TG = triglycerides; PFWD = pain free walking distance; and MWD = maximum walking distance; Gardner = walking distance was assessed by means of Gardner protocol; SD = standard deviation; CI = confidence interval; I^2 = percentage of variation; Ex/Con = exercise/control.
[a] Significant heterogeneity Cochran Q-test (<0.10).

also found when isolating walking interventions. This was due to two studies in which no effect of walking training was found,[23,38] possibly caused by a large dropout rate (51%) in the exercise group,[38] the approximation method which was used to convert non-parametric outcomes, and a non-optimal walking frequency of two days/week.[23] Moreover, both studies had a lower mean ABI than the other studies (0.56 and 0.58).

Limitations

The results presented in this meta-analysis should be interpreted with the following limitations: (1) The number of studies that could be included and their sample sizes is small, which limits the statistical power for most parameters. (2) Whereas almost 75% of exercise patients were included in walking groups, data on the impact of other types of exercise are scarce or absent. Since exercise characteristics are known to influence the impact of exercise on specific CV risk factors, more studies are warranted investigating the effect of other modes of exercise in IC patients. (3) Most outcome measures were secondary, which could have resulted in selective reporting. (4) The results cannot be generalised to all LEAD patients, as only LEAD patients with IC were included. (5) A lack of data on risk factor management can limit the interpretation of results. However, the majority of studies (11/15) either reported that patients were stable, had no change in pharmacological treatment, or had optimal medical treatment as standard care. (6) As different treadmill protocols were used to evaluate MWD and PFWD, mean differences presented might lack external validity. Therefore, standardised Hedges' g values complement crude outcomes. In addition, the majority of trials (11/13) used either the Gardner or the (adjusted) Hiatt protocol to evaluate MWD. These protocols tend to have a similar energy expenditure[56] and therefore pooled mean differences are intuitively meaningful. Furthermore, a separate analysis of the studies that used the Gardner protocol further confirmed the beneficial effect of exercise therapy on walking capacity. In summary, although being the best representation of available evidence through increasing power and assessing heterogeneity, meta-analysis reviews should always be complemented with rigorous RCTs evaluating the subject. Therefore future research to include and report CV measures in exercise trials in LEAD patients should be encouraged.

CONCLUSION

In summary, the findings emphasise the importance of exercise training in IC patients to improve ambulatory capacity. In addition, some evidence was found suggesting that CV risk factors could ameliorate after SET. However, studies reporting on CV risk outcomes are scarce. Therefore, high quality RCTs are required to elucidate the CV risk-reducing effect of different exercise programs in IC patients.

CONFLICT OF INTEREST

None.

FUNDING

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2018.12.014.

REFERENCES

1 Aboyans V, Ricco J-B, Bartelink M-LEL, Björck M, Brodmann M, Cohnert T, et al. 2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European Society for Vascular Surgery (ESVS). *Eur J Vasc Endovasc Surg* 2018;**55**:305−68.

2 Berger JS, Ladapo JA. Underuse of prevention and lifestyle counseling in patients with peripheral artery disease. *J Am Coll Cardiol* 2017;**69**:2293−300.

3 Fowkes FGR, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *The Lancet* 2013;**382**: 1329−40.

4 Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FGR. Inter-society consensus for the management of peripheral arterial disease (TASC II). *J Vasc Surg* 2007;**45**:S5−67.

5 Barbosa JPAS, Henriques PM, Barros MVGB, Wolosker N, Ritti Dias RM. Physical activity level in individuals with peripheral arterial disease: a systematic review. *J Vasc Bras* 2011;**11**:22−8.

6 Garg PK, Tian L, Criqui MH, Liu K, Ferrucci L, Guralnik JM, et al. Physical activity during daily life and mortality in patients with peripheral arterial disease. *Circulation* 2006;**114**:242−8.

7 Leeper NJ, Myers J, Zhou M, Nead KT, Syed A, Kojima Y, et al. Exercise capacity is the strongest predictor of mortality in patients with peripheral arterial disease. *J Vasc Surg* 2013;**57**:728−33.

8 Regensteiner JG, Hiatt WR, Coll JR, Criqui MH, Treat-Jacobson D, McDermott MM, 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.

9 Criqui MH, Aboyans V. Epidemiology of peripheral artery disease. *Circ Res* 2015;**116**:1509−26.

10 Hageman D, Fokkenrood HJ, Gommans LN, van den Houten MM, Teijink JA. Supervised exercise therapy versus home-based exercise therapy versus walking advice for intermittent claudication. Cochrane Vascular Group. *Cochrane Database Syst Rev* 2018;**4**: CD005263.

11 Cimminiello C, Arpaia G, Friz HP, Boracchi P, Marano G, Spezzigu G, et al. A prospective multicentre study on the treatment of cardio-vascular risk factors and claudication symptoms in patients with peripheral artery disease (the IDOMENEO study). *VASA Z Gefasskrankheiten* 2015;**44**:371−9.

12 Sigvant B, Hasvold P, Kragsterman B, Falkenberg M, Johansson S, Thuresson M, et al. Cardiovascular outcomes in patients with peripheral arterial disease as an initial or subsequent manifestation of atherosclerotic disease: results from a Swedish nationwide study. *J Vasc Surg* 2017;**66**:507−14.e1.

13 Subherwal S, Patel MR, Kober L, Peterson ED, Bhatt DL, Gislason GH, et al. Peripheral artery disease is a coronary heart disease risk equivalent among both men and women: results from a nationwide study. *Eur J Prev Cardiol* 2015;**22**:317−25.

14 Lane R, Harwood A, Watson L, Leng GC. Exercise for intermittent claudication. *Cochrane Database Syst Rev* 2017;**12**:CD000990.

15 Skorkowska-Telichowska K, Pilch U, Szuba A. Analysis of up-to-date studies investigating effects of physical rehabilitation on traditional and novel biochemical parameters in PAD patients with intermittent claudication: a review. *Acta Angiol* 2015;**21**: 66−74.

16 Sakamoto S, Yokoyama N, Tamori Y, Akutsu K, Hashimoto H, Takeshita S. Patients with peripheral artery disease who complete 12-week supervised exercise training show reduces cardiovascular mortality and morbidity. *Circ J* 2009;**73**:167—73.

17 Pattyn N, Cornelissen VA, Eshghi SRT, Vanhees L. The effect of exercise on the cardiovascular risk factors constituting the metabolic syndrome: a meta-analysis of controlled trials. *Sports Med* 2013;**43**:121—33.

18 Kelley GA, Kelley KS, Franklin B. Aerobic exercise and lipids and lipoproteins in patients with cardiovascular disease: a meta-analysis of randomized controlled trials. *J Cardiopulm Rehabil* 2006;**26**:131—9.

19 Chen Y-C, Tsai J-C, Liou Y-M, Chan P. Effectiveness of endurance exercise training in patients with coronary artery disease: a meta-analysis of randomised controlled trials. *Eur J Cardiovasc Nurs* 2017;**16**:397—408.

20 Moher D, Liberati A, Tetzlaff J, Altman DG, for the PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;**339**:b2535.

21 Smart NA, Waldron M, Ismail H, Giallauria F, Vigorito C, Cornelissen V, et al. Validation of a new tool for the assessment of study quality and reporting in exercise training studies: TESTEX. *Int J Evid Based Healthc* 2015;**13**:9—18.

22 Viera AJ, Garrett JM. Understanding interobserver agreement: the kappa statistic. *Fam Med* 2005;**37**:360—3.

23 Schlager O, Hammer A, Giurgea A, Schuhfried O, Fialka-Moser V, Gschwandtner M, et al. Impact of exercise trainting on inflammation and platelet activation in patients with intermittent claudication. *Swiss Med Wkly* 2012;**142**:w13623.

24 Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014;**14**:135.

25 Crowther R, Leicht AS, Spinks WL, Sangla K, Quigley F, Golledge J. Effects of a 6-month exercise program pilot study on walking economy, peak physiological characteristics, and walking performance in patients with peripheral arterial disease. *Vasc Health Risk Manag* 2012;**8**:225—32.

26 Leicht A, Crowther R, Golledge J. Influence of regular exercise on body fat and eating patterns of patients with intermittent claudication. *Int J Mol Sci* 2015;**16**:11339—54.

27 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—64.

28 Helgerud J, Wang E, Mosti MP, Wiggen ØN, Hoff J. Plantar flexion training primes peripheral arterial disease patients for improvements in cardiac function. *Eur J Appl Physiol* 2009;**106**:207—15.

29 Crowther RG, Spinks WL, Leicht A, Sangla K, Quigley F, Golledge J. The influence of a long term exercise program on lower limb movement variability and walking performance in patients with peripheral arterial disease. *Hum Mov Sci* 2009;**28**:494—503.

30 Gomes AP, Correia MA, Soares AH, Cucato GG, Lima AH, Cavalcante BR, et al. Effects of resistance training on cardiovascular function in patients with peripheral artery disease: a randomized controlled trial. *J Strength Cond Res* 2018;**32**:1072—80.

31 Izquierdo-Porrera AM, Gardner AW, Powell CC, Katzel LI. Effects of exercise rehabilitation on cardiovascular risk factors in older patients with peripheral arterial occlusive disease. *J Vasc Surg* 2000;**31**:670—7.

32 Mosti MP, Wang E, Wiggen ØN, Helgerud J, Hoff J. Concurrent strength and endurance training improves physical capacity in patients with peripheral arterial disease: strength and endurance training in PAD. *Scand J Med Sci Sports* 2011;**21**:e308—14.

33 Wang E, Helgerud J, Loe H, Indseth K, Kaehler N, Hoff J. Maximal strength training improves walking performance in peripheral arterial disease patients. *Scand J Med Sci Sports* 2010;**20**:764—70.

34 Mika P, Wilk B, Mika A, Marchewka A, Niżankowski R. The effect of pain-free treadmill training on fibrinogen, haematocrit, and lipid profile in patients with claudication. *Eur J Cardiovasc Prev Rehabil* 2011;**18**:754—60.

35 Chehuen M, Cucato GG, Carvalho CRF, Ritti-Dias RM, Wolosker N, Leicht AS, 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—92.

36 Crowther RG, Spinks WL, Leicht AS, Sangla K, Quigley F, Golledge J. Effects of a long-term exercise program on lower limb mobility, physiological responses, walking performance, and physical activity levels in patients with peripheral arterial disease. *J Vasc Surg* 2008;**47**:303—9.

37 Gardner AW, Katzel LI, Sorkin JD, Bradham DD, Hochberg MC, Flinn WR, et al. Exercise rehabilitation improves functional outcomes and peripheral circulation in patients with intermittent claudication: a randomized controlled trial. *J Am Geriatr Soc* 2001;**49**:755—62.

38 Gelin J, Jivegård L, Taft C, Karlsson J, Sullivan M, Dahllöf A-G, et al. Treatment efficacy of intermittent claudication by surgical intervention, supervised physical exercise training compared to No treatment in unselected randomised patients I: one year results of functional and physiological improvements. *Eur J Vasc Endovasc Surg* 2001;**22**:107—13.

39 Murphy TP, Cutlip DE, Regensteiner JG, Mohler ER, Cohen DJ, Reynolds MR, et al. Supervised exercise versus primary stenting for claudication resulting from aortoiliac peripheral artery disease: six-month outcomes from the claudication: exercise versus endoluminal revascularization (CLEVER) study. *Circulation* 2012;**125**:130—9.

40 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—13.

41 McGuigan MR, Bronks R, Newton RU, Sharman MJ, Graham JC, Cody DV, 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**:B302—10.

42 Parr BM, Noakes TD, Derman EW. Peripheral arterial disease and intermittent claudication: efficacy of short-term upper body strength training, dynamic exercise training, and advice to exercise at home. *S Afr Med J* 2009;**99**:800—4.

43 Wang E, Hoff J, Loe H, Kaehler N, Helgerud J. Plantar flexion: an effective training for peripheral arterial disease. *Eur J Appl Physiol* 2008;**104**:749—56.

44 Warburton DER, Bredin SSD. Health benefits of physical activity: a systematic review of current systematic reviews. *Curr Opin Cardiol* 2017;**32**:541—56.

45 Vanhees L, Geladas N, Hansen D, Kouidi E, Niebauer J, Reiner Z, et al. Importance of characteristics and modalities of physical activity and exercise in the management of cardiovascular health in individuals with cardiovascular risk factors: recommendations from the EACPR (Part II). *Eur J Prev Cardiol* 2011;**19**:1005—33.

46 Cornelissen VA, Smart NA. Exercise Training for Blood Pressure: a Systematic Review and Meta-analysis. *J Am Heart Assoc* 2013;**2**:e004473.

47 Le Faucheur A, Abraham P, Jaquinandi V, Bouye P, Saumet JL, Noury-Desvaux B. Measurement of walking distance and speed in patients with peripheral arterial disease: a novel method using a global positioning system. *Circulation* 2008;**117**:897—904.

48 Gardner AW, Ritti-Dias RM, Stoner JA, Montgomery PS, Khurana A, Blevins SM. Oxygen uptake before and after the onset of claudication during a 6-minute walk test. *J Vasc Surg* 2011;**54**:1366—73.

49 Hansen D, Niebauer J, Cornelissen V, Barna O, Neunhäuserer D, Stettler C, et al. Exercise prescription in patients with different combinations of cardiovascular disease risk factors: a consensus

statement from the EXPERT working group. *Sports Med* 2018;**48**: 1781−97.

50 Hanson S, Jones A. Is there evidence that walking groups have health benefits? A systematic review and meta-analysis. *Br J Sports Med* 2015;**49**:710−5.

51 Murtagh EM, Nichols L, Mohammed MA, Holder R, Nevill AM, Murphy MH. The effect of walking on risk factors for cardiovascular disease: an updated systematic review and meta-analysis of randomised control trials. *Prev Med* 2015;**72**:34−43.

52 Dörenkamp S, Mester I, de Bie R, Tejink J, van Breukelen G. Patient characteristics and comorbidities influence walking distances in symptomatic peripheral artery disease: a large one-year physiotherapy cohort study. *PLOS One* 2016;**11**:e0146828.

53 Gardner AW, Parker DE, Montgomery PS. Predictors of improved walking after a supervised walking exercise program in men and women with peripheral artery disease. *Int J Vasc Med* 2016:1−8.

54 Farah BQ, Ritti-Dias RM, Cucato GG, Montgomery PS, Gardner AW. Factors associated with sedentary behavior in patients with intermittent claudication. *Eur J Vasc Endovasc Surg* 2016;**52**:809−14.

55 Van Gaal LF, Mertens IL, De Block CE. Mechanisms linking obesity with cardiovascular disease. *Nature* 2006;**444**:875−80.

56 Nicolaï S, Viechtbauer W, Kruidenier L, Candel M, Prins M, Teijink J. Reliability of treadmill testing in peripheral arterial disease: a meta-regression analysis. *J Vasc Surg* 2009;**50**:322−9.