Effect of a physical therapist–led, home-based, walking exercise behavior change intervention vs usual care on walking in adults with peripheral artery disease. The MOSAIC randomized clinical trial

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Key points

Question

Does a physical therapist-led, home-based walking exercise behavior change intervention improve walking capacity compared with usual care in adults with peripheral artery disease and intermittent claudication?

Findings

In this randomized clinical trial that included 190 participants with intermittent claudication due to peripheral artery disease, receipt of the intervention, compared with usual care, resulted in a statistically significant adjusted difference in mean six-minute walk distance at 3-months of 16.7m.

Meaning

Among adults with peripheral artery disease, a home-based walking exercise behavior change intervention, compared with usual care, increased six-minute walking distance at 3-months.

Abstract

Importance: Home-based walking exercise interventions are recommended for people with peripheral artery disease (PAD), but evidence of their efficacy has been mixed.

Objective: To investigate the effect of a home-based, walking exercise behavior change intervention in adults with PAD and intermittent claudication, compared with usual care.

Design, Setting, and Participants: Multicentered, randomized clinical trial including 190 adults with PAD and intermittent claudication in six hospitals in the United Kingdom between January 2018 and March 2020, final follow-up 8, September 2020.

Interventions: Participants were randomized to receive a walking exercise behavior change intervention delivered by physical therapists trained to use a motivational approach (N=95) or usual care (N=95).

Main outcomes and measures: The primary outcome was six-minute walking distance at 3-months follow-up (minimal clinically important difference, 8-20 meters). There were 8 secondary outcomes, 3 of which were Walking Estimated-Limitation Calculated by History (WELCH, score range 0 [best performance] to 100), Brief illness Perceptions Questionnaire (score range 0 to 80 [80 indicates negative perception of illness]), Theory of Planned Behaviour Questionnaire (score range 3 to 21 [21 indicates best attitude, subjective norms, perceived behavioral control or intention]) a minimum clinically important difference was not defined for these instruments.

Results: Among 190 randomized participants (mean age 68 years, 30% women, 79% white race, mean baseline six-minute walking distance 361.0m) 148 (78%) completed 3-month follow-up. The six-minute walking distance changed from 352.9m at baseline to 380.6m at 3-months in the intervention and from 369.8m to 372.1m in the usual care group (adjusted mean between-group difference 16.7m (95%CI, 4.2 to 29.2; P=0.009)). Of 8 secondary outcomes, 5 were not statistically significant. At 6-month follow up, baseline WELCH score changed from 18.0 to 27.8 in the intervention group and from 20.7 to 20.7 in the usual care group (adjusted mean between-group

difference 7.4 (95% CI, 2.5 to 12.3; P= 0.003)); score on the Brief illness Perceptions Questionnaire changed from 45.7 to 38.9 in the intervention group and from 44.0 to 45.8 in the usual care group (adjusted mean between-group difference: -6.6 [95%CI, -9.9 to -3.4] P<0.001); scores on the attitude component of the Theory of Planned Behaviour Questionnaire changed from 14.7 to 15.4 in the intervention group and from 14.6 to 13.9 in the usual care group (adjusted mean between-group difference:+1.4 [95%CI, 0.3 to 2.5] P=0.02). Thirteen serious adverse events occurred in the intervention group, compared to 3 in the usual care group. All were determined to be unrelated or unlikely to be related to the study.

Conclusion and relevance: Among adults with PAD and intermittent claudication, a home-based walking exercise behavior change intervention, compared with usual care, resulted in improved walking distance at 3-months. Further research is needed to determine the durability of these findings.

Trial Registration

ISRCTN 14501418; clinicaltrials.gov NCT03238222

Introduction

Lower extremity peripheral artery disease (PAD) is associated with reduced walking capacity and an increased risk of cardiovascular morbidity and mortality[1]. Supervised exercise therapy is recommended to improve walking capacity in people with PAD, but participation rates are low[2,3]. Barriers to participation include lack of time, requirements for transportation to supervised exercise sessions, motivation and resources[2,4,5]. Home-based exercise behavior change interventions that include regular support from a clinician or coach are an acceptable option and may help individuals adhere to walking exercise outside of a supervised setting, but evidence of their effect has been mixed[6,7].

Important components of an intervention to support walking exercise behavior change include an individual's knowledge and understanding of PAD, beliefs about walking as an effective therapy for PAD, confidence and ability to manage their symptoms, and guidance on appropriate walking dosage and environments[8,9]. Targeting these factors using theory-based, behavioral change strategies and exercise advice may increase walking capacity in PAD[10,11].

The Motivating Structured walking Activity in people with Intermittent Claudication (MOSAIC) was a multicenter randomized clinical trial designed to determine whether a home-based, walking behavior change intervention delivered by trained physical therapists improved walking capacity, compared to usual care, in people with PAD and intermittent claudication.

Methods

The National Research Ethics Committee London–Bloomsbury, United Kingdom approved the trial protocol. Participants provided written informed consent. This was an assessor-blinded, multicenter, randomized clinical trial with two parallel groups enrolled participants between January 2018 and March 2020 and conducted follow up for a 6-month period (final follow-up was completed by 8th September 2020). The study protocol[12] (supplementary file 1) and statistical analysis plan (supplementary file 2) are available online.

Participant Identification

Participants were recruited from vascular clinics from six public hospitals in southeast England, United Kingdom (Guy's and St Thomas', King's College, St George's, Royal Free, Royal London, Ashford and St Peter's NHS Foundation Trusts).

Eligibility Criteria

Criteria for study inclusion were 1) participants aged 50 years or over; 2) PAD determined by the consulting clinician based on either (a) Ankle Brachial Pressure Index of 0.90 or less; (b) radiographic evidence of PAD; or (c) clinician reported diagnosis of PAD. People with an ABPI >0.90 were enrolled onto the trial if there was other evidence of PAD (e.g. clinical diagnosis or radiographic evidence of PAD reported determined by the consulting clinician); 3) self-reported claudication identified using the San Diego Claudication Questionnaire[13] and defined as calf pain during walking or atypical symptoms (e.g. symptoms affecting the buttocks or thighs but not the calves),; 4) able to participate in the trial and provide informed consent.

Criteria for study exclusion were 1) unstable PAD defined as self-reported change in symptoms during the previous 3-months in response to the question 'Has there been any change in your symptoms during the past 3-months?'; 2) walking more than 90 minutes/week self-reported on the Brief International Physical Activity Questionnaire[14]; 3) contraindications to exercise determined by the consulting clinician; 4) completed any medically prescribed supervised exercise in the previous 6-months or planned participation in prescribed supervised exercise in the next 6-months.

Randomization and masking

Participants were randomly assigned in a 1:1 ratio to receive either a walking exercise behavior change intervention or usual care using a computer-generated randomization system, with randomly selected block sizes of two and four stratified by center (Figure 1). The outcome assessor

and the trial statistician were masked to group allocation until analyses were completed. It was not possible to mask the participants or treating physical therapists to group allocation after randomization because of the nature of the interventions.

Interventions

Walking exercise behavior change intervention

The walking exercise behavior change intervention was informed by 2 psychological models (Theory of Planned Behaviour, Common-sense Model of Illness Representations)[15,16]. It consisted of two 60-minute individual in person sessions (weeks 1 and 2) and two 20-minute telephone sessions (weeks 6 and 12) delivered by physical therapists over 3-months[12].

Interventions were delivered by physical therapists who were trained to use a motivational interviewing approach guided by behavior change principles to increase participants intention and commitment to walking exercise. Each intervention session included mandatory components to facilitate accurate participant knowledge about PAD and positive beliefs about walking exercise as a treatment[12]. Content was tailored to the participant's knowledge and current walking exercise behavior, it helped participants to identify their current abilities and the goals the participants wanted to achieve by increasing their walking capacity, their challenges to walking and strategies for overcome these challenges.

Walking exercise goals and plans were agreed upon collaboratively with the physical therapist and included identifying progressive, individualized walking targets to achieve at least 30 minutes walking per day, at a pace that elicited moderate leg symptoms, three times per week[3]. Participants recorded where, when and with whom they would walk[17] and established ways to self-monitor their walking exercise (e.g. recording steps from a pedometer or recording the distance or duration walked in an exercise diary). Participants received a pedometer (Yamax DigiWalker SW-200,) and an intervention manual that included an exercise diary, with goal setting, problem solving, and action

planning worksheets. The intervention was designed to enable participants to continue their walking exercise independently after the final intervention session.

All intervention sessions were audio-recorded, and the physical therapists noted the intervention session components delivered on a checklist.

Sixteen physical therapists received 2 days of training, a physical therapist's manual and intervention session checklists. The training team met with the physical therapists at least every 3-months to provide feedback and advice to optimise fidelity of delivery.

Usual Care

Participants randomized to usual care received no study intervention and received standard care provided by their vascular specialists.

Measurement and procedures

Medical history, ethnic group, and demographics

Self-reported information regarding medical history, race or ethnic group, other demographics and current symptoms (San Diego Claudication Questionnaire[13]) was obtained using questionnaires. Participants self-identified their racial or ethnic group from fixed categories on a questionnaire. This information was collected to assess the generalisability of the results. Body mass index and Ankle-Brachial Pressure Index were measured by the outcome assessor[18].

Primary outcome

The primary outcome was six-minute walking distance at 3-month follow-up[19]. Participants walked as far as possible around two cones, placed 30.48 metres apart in a hospital corridor, using a standardized protocol[20]. The total distance (meters) walked after six minutes was recorded. The walk

test was completed 2 times, at least 30 minutes apart, and the highest six-minute walking distance was used for analysis. The minimum clinically important difference in people with PAD ranged between 8m (small minimum clinically important difference) to 22m (large minimum clinically important difference)[21]. It was not possible to repeat the six-minute walking distance at 6-months due to funding constraints.

Secondary outcomes

Secondary outcomes at 3-and 6-month follow-up were not consistent between the protocol and the statistical analysis plan (Item 6.2 supplement 2). Secondary outcomes (item 5.3.3 in supplement 2) consisted of the following: (1) perceived walking ability, measured by Walking Estimated-Limitation Calculated by History (WELCH, score range, 0 to 100 [100 indicates best], no minimum clinically important difference defined)[22] ; (2) the Self-reported Maximum Walking Distance (range, a small number of meters to >500m [>500m indicates best], no minimum clinically important difference defined)[23]; (3) activities of daily living, measured by the Nottingham Extended Activities of Daily Living scale (score range, 0 to 66 [66 indicates best], no minimum clinically important difference defined)[24]; (4) health-related quality of life assessed with the Vascular Quality of Life Questionnaire-6 (score range, 6 to 24 [24 indicates best] minimum clinically important difference score range between 1.7 and 2.2 points)[25,26]; (5) illness perceptions evaluated by the Brief Illness Perception Questionnaire (score range, 0 to 80 [80 indicates negative perception of health], no minimum clinically important difference defined)[27]; (6) walking treatment beliefs (attitude, subjective norms, perceived behavioral control, intentions) assessed by the Theory of Planned Behaviour Questionnaire (score range for each construct, 3 to 21 [21 indicates best], no minimum clinically important difference defined)[28]; (7) self-regulatory processes estimated using the action planning (score range, from 4 to 16 [16 indicates best]), and action control scale (score range, 6 to 24 [24 indicates best], no minimum clinically important difference defined[17] and (8) physical activity estimated by the brief International Physical Activity Questionnaire (Higher scores indicate greater energy expenditure, no minimum clinically important difference defined[14]. However, the statistical

analysis plan did not pre-specify the attitude, subjective norm, perceived behavioural control and intentions constructs of the Theory of Planned Behavior Questionnaire. At 3-month follow up, responses and results for all secondary outcomes were collected.

Other outcomes

Pain-free walking time was defined as the time (seconds) participants first experienced pain (no minimum clinically important difference defined). Maximal walking capacity was defined as the time (seconds) participant stopped walking (no minimum clinically important difference defined). Pain free walking time and maximum walking capacity were measured during the six-minute walk test. The maximum walking capacity was censored at six minutes if the participant had not stopped walking. At 3 and 6-months exercise adherence was assessed by the Exercise Adherence Rating Scale (score range, 0 to 24 [24 indicates best], the minimum clinically important difference was defined as 5.5 points [29,30] [See Supplement 1 and item 5.3.4 in Supplement 2).

Adverse events

Adverse events were collected by the outcome assessor at 3-and 6-month follow-up as an exploratory outcome.

Fidelity of intervention delivery

Two trained assessors independently rated a 20% randomly selected sample of audio-recorded intervention sessions to assess the extent to which the mandatory components of each session were delivered as intended. The assessors compared their scores and agreed on a score for each intervention session component. High treatment fidelity was achieved if at least 80% of mandatory components were fully/partially delivered in each session.

Randomly selected 20-minute segments of the sampled intervention sessions were rated for motivational interviewing relational (interpersonal style) and technical (techniques) proficiency using

the Motivational Interviewing Treatment Integrity Scale[31]. A score of 3.5 out of 5 and 3 out of 5 represented fair relational and technical proficiency, respectively[31] .

Specific aims to explore the participants' experience of the intervention, assess the feasibility of collecting resource use data, and estimate the MCID for five clinical measures are not reported here.

Sample size

When this study was designed, there was no established MCID for corridor based six-minute walking distance in people with PAD. Therefore, the power calculation used the mean (standard deviation (SD)) six-minute walking distance six-month follow-up by group of a similar trial: control 342.2m (110.8), intervention 399.8 (101.6), giving a difference in means of 58m (SD 111m)[32]. Based on this mean difference, statistical power of 90% and a two-sided significance level of 0.05, the minimum sample size necessary for the primary aim was 154 participants. Anticipating a dropout rate of up to 20% at 3-month follow-up, the desired total sample size was 192 participants.

Statistical analyses

Participants were analyzed according to their assigned randomization group even if they were nonadherent to their assigned intervention. Primary analyses were conducted using complete-case data. The baseline characteristics were summarized using mean (SD) or frequencies and percentages for continuous or categorical variables respectively. Median and interquartile range (IQR) were calculated if data were not normally distributed. The primary outcome was analyzed using multiple regression with the baseline six-minute walking distance and the stratification factor, center, included as covariates. Results for each outcome were reported as the adjusted between-group difference in mean six-minute walking distance with 95% Confidence Interval (CI).

In pre-specified analyses the primary outcome was analyzed according to adherence to the protocol ('Per protocol'). The per protocol analyses consisted of participants who attended both the in-person sessions and at least one telephone session. Model assumptions were checked using normal quantile-quantile plot to evaluate whether residuals followed a normal distribution. When this assumption was not met, a generalized linear model with appropriate distribution family and link was used. There was no pre-specified plan to impute missing data.

Post-hoc Exploratory Analyses

Post-hoc exploratory analyses included: i) comparison of baseline characteristics in those with and without primary outcome data, ii) using a linear mixed model for the primary outcome with center as a random effect, iii) multiple imputation of the primary outcome using baseline data to predict missingness (Supplementary file 3 e-table 1), iv) repat primary analyses among participants with an ankle-brachial pressure index of 0.9 or less at baseline study visit.

All analyses were 2-sided and statistical significance was defined as $P<0.05$. The statistical modelling used R package v4.0.3 and Stata software v16.

Because of the potential for type 1 error due to multiple comparisons, findings for analyses of secondary endpoints should be considered exploratory.

Trial changes in response to the COVID-19 pandemic

Due to the COVID-19 pandemic, recruitment ceased on 12th March 2020, two participants short of the target (192 participants). It was also not possible to collect the six-minute walking distance on fifteen participants at 3-month follow-up.

Results

Among 190 participants randomized (mean age 68 years, 30% female, 79% White race) primary outcome data were complete for 148/190 participants (78%) at 3-month follow-up. Loss to follow up was primarily due to the COVID-19 pandemic (Table 1, Figure 1). Self-reported outcomes were completed for 161/190 participants (85%) at 3-months. At 6-month follow-up, 166/190 participants (87%) contributed data for one or more secondary outcomes (Figure 1).

At baseline, 173 participants had an ankle-brachial pressure index ≤0.90 and 17 participants had an ankle-brachial pressure index >0.90.

85% participants attended at least three intervention sessions (82/95) and 67% participants attended all intervention sessions (64/95) (Supplementary file 3 e-table 2).

Primary Outcome

At 3-month follow-up, compared with usual care, the 6-minute walking distance was significantly improved in the walking exercise behavior-change group. The 6-minute walking distance changed from 352.9m at baseline to 380.6m at 3-months and from 369.8m to 372.1m in the intervention and usual care groups, respectively (adjusted between-group difference 16.7m [95%CI,4.2 to 29.2] P=0.009) (Table 2, Figure 2).

In per protocol analyses, the intervention group significantly improved the six-minute walk, compared to usual care (between-group difference 19.2m [95%CI,6.3 to 32.1] P=0.004 (Supplementary file 3 e-table 3).

Secondary outcomes

At six-month follow-up, compared to usual care, the intervention group had a significantly greater WELCH score (between-group difference 7.4 [95%CI,2.5 to 12.3] P=0.003), Brief Illness Perceptions

Questionnaire score (between-group difference -6.6 [95%CI,-9.9 to -3.4] P<0.001) and attitude score (between-group difference 1.4 [95%CI,0.3 to 2.5] P=0.02).

There were no significant between-group differences in Self-reported maximum walking distance (315m [95% CI,-14.3 to 644.3] P=0.20), Nottingham extended activities of daily living score score (-1.4 [95% CI,-4.4 to 1.6] P=0.37),Vascular quality of life score (-6, 0.6 [95% CI,-0.4 to 1.6] P=0.33), subjective norms score (0.3 [95% CI,-1.1 to 1.7) P=0.67), perceived behavioural control score (-0.2 [95%CI,-1.4 to 1.0] P=0.78), intention score (-0.3 [95%CI,1.5 to 0.9] P=0.64), action planning score (0.2 [95%CI -0.1 to 0.5] P=0.16), action control score (0.1 [95%CI,-0.1 to 0.4] P=0.36) or IPAQ score (-2.0 [95%CI,-1034 to 1029] P>0.99) (Table 2).

Other outcomes

At 3-month follow-up, compared to usual care, the intervention group significantly improved the WELCH score (between-group differences 10.2 [95%CI,5.7 to 14.7] P<0.001), Self-reported maximum walking distance (between-group difference 181.0m [95%CI,60 to 302) P=0.003), Nottingham Extended activity of Daily Living score (between-group difference 2.8 [95%CI,0.1 to 5.4] P=0.04), Painfree walking time (between-group differences 30.3 seconds [95%CI:5.4 to 55.3] P=0.02), Brief illness perceptions questionnaire score (between-group difference -5.8 [95%CI,-8.6 to -2.9] P<0.001), attitude score (between-group difference 1.1 [95%CI,0.2 to 2.0] P=0.02), subjective norms score (between-group difference 1.3 [95%CI,0.1 to 2.6] P=0.03), intention score (between-group difference 0.9 [95% CI,0.0 to 1.9] P=0.048), action planning score (between-group difference 0.5 [95%CI,0.2 to 0.8] P=0.001), action control score (between-group difference 0.7 [95%CI,0.5 to 1.0] P<0.001) and Exercise Adherence Rating Scale score (between-group difference 2.0 [95%CI,0.5 to 3.5] P=0.01).

At 3-month follow-up, compared to usual care, there was no effect of the walking exercise behaviour change intervention on the Maximum walking capacity (12.0 [95%CI:-16.9 to 40.8]

P=0.42), Vascular quality of Life score (0.6 [95%CI,-0.2 to 1.4] P=0.17), perceived behavioural control score (-0.3 (95%CI,-1.3 to 0.8) P=0.06) or International Physical Activity Questionnaire (+532 [95%CI,-855 to 1919] P=0.45).

At 6 month follow-up, compared to usual care, there was no significant effect of the intervention on the Exercise Adherence Rating Scale score (+1.2 [95%CI,-0.7 to 3.1] P=0.21) (Table 3).

Post-hoc Exploratory Analyses

Compared to participants who did not complete the six-minute walk at 3-month follow-up, those who completed the six-minute walk at 3-month follow-up had significantly greater baseline six-minute walking distance (mean (SD) 369.5m (77.5) versus 332.8m (94.7) P=0.01) (Supplementary file 3 e-table 4). Results for the primary outcome (+16.7m (95% CI, 4.2 to 29.2) P=0.009) did not meaningfully change when the analyses were repeated using a mixed model with center modelled as a random effect (+16.3m (95%CI,3.9 to 28.6) P=0.010) or when analyses were repeated using multiple imputation (+18.9m (5.5 to 32.3) P=0.006) (Supplementary file 3 e-table 1). Results did not meaningfully change when the analyses were limited to those with a baseline study visit ankle-brachial pressure index of 0.9 or less (15.9 [95%CI, 2.6 to 29.2]; P = 0.02).

Fidelity of intervention delivery

Fifteen physical therapists delivered the walking exercise behavior change intervention. Sixty-two randomly selected intervention sessions were rated (21%). Overall, 79% sessions were delivered with fidelity. High fidelity was achieved in both in-person sessions (session 1,100%; session 2, 88%), but fidelity was lower in the telephone sessions (session 3, 67%; session 4, 54%). Fair technical motivational interviewing proficiency was achieved in all sessions (3.2-3.9 on a scale of 5) and fair relational motivational interviewing proficiency in both in-person sessions (both 3.5 on a scale of 5

for both sessions), but the telephone sessions did not attain at least fair relational motivational interviewing proficiency (session 1=3.1/5; session 2=3.2/5) (Supplementary file 3 e-table 5).

Adverse events

There were 37 adverse events (25 intervention, 12 usual care). Twenty-one non-serious adverse events were reported by 19 participants (12 intervention, nine usual care). Falls (three intervention and three usual care) were the most common non-serious adverse event. None were determined to be related to the study. Sixteen serious adverse events due to hospitalisation were reported by 15 participants (13 intervention, three usual care). All serious adverse events were judged to be either unrelated or unlikely to be related to the study by the Trial Steering/Data Monitoring and Ethics Committee (Supplementary file 3 e-table 6-8).

Discussion

In this trial of 190 participants with PAD and symptoms of intermittent claudication, a walking exercise behavior change intervention significantly improved mean 6-minute walk distance, compared with usual care, at 3-month follow-up. Out of eight secondary outcomes, three outcomes improved at 6-month follow-up, self-reported walking capacity measured by the WELCH score, illness perceptions measured by the Brief illness perceptions questionnaire and walking treatment beliefs (attitude score) measured by the Theory of Planned behaviour questionnaire significantly improved in the intervention group compared with usual care.

Results of prior randomized clinical trials of home-based exercise therapy for people with PAD have been mixed, with multiple prior clinical trials showing benefits of home-based exercise for PAD[32-35], but at least two showing no effect of a home-based exercise intervention for PAD[36,37]

The difference in 6 minute walking distance following this intervention was greater than a small minimal clinically important difference for people with PAD but did not meet the threshold for a large minimal clinically important difference in people with PAD[21]. Factors that may have

contributed to the success of the intervention of the current trial include the following. First, it was designed to address theory-based, psychological factors that influenced walking exercise behavior in people with PAD[8,9,11]. Previous work reported that positive walking beliefs, defined by the Theory of Planned Behaviour, are positively associated with motivation to walk[8,38]. An individuals' accurate understanding of their illness and perceptions about the causes and ability to control PAD are associated with greater motivation and are associated with better 6 minimal clinically important difference [8]. Second, the intervention included evidence-based, behavior change principles that may have helped participants translate intention to walk for exercise into actual behaviour[10,17,39]. Third, the intervention was tailored to each participant's knowledge, skills and environment.

Compared to prior effective home-based walking exercise interventions for PAD that improved the six-minute walk by 45-53 meters, compared to the control group, [33-35] the effect size for the current intervention was smaller (i.e. 16.7 meters). This could be because social restrictions during the COVID-19 pandemic hindered participants' planned walking. However, most participants had completed the primary outcome prior to the start of the pandemic. Alternatively, the smaller effect size may have been because the participants did not walk at sufficient intensity to produce large improvements in six-minute walking distance [35]or because there was an insufficient number of intervention sessions to support large intervention effects. However, a prior highly effective 12-week home-based exercise intervention had a similar number of intervention sessions[34]. Further study is needed to determine whether, for the current intervention, more sessions would have a more potent effect.

Another potential explanation for the lower potency of the current intervention, compared to prior home-based exercise interventions in PAD[32,34,35], may be the relatively low fidelity of delivery and motivational interviewing proficiency in the telephone sessions of the current trial. Higher levels of treatment fidelity are associated with better treatment outcomes[40]. There are several possible explanations for this. First, at the start of this trial, it was not typical for physical therapy to be delivered remotely. Lack of familiarity with remote interventions may have affected the therapist's

confidence and ability to deliver the mandatory components. Second, the telephone consultations, a mean of 20 minutes, may have been too brief to deliver the mandatory components. However, another highly effective home-based exercise intervention for PAD used intervention telephone calls that were shorter than 20 minutes[35]. Third, during the trial, some therapists may have drifted from the motivational interviewing approach. However, regular meetings with the training team should have mitigated this. Fourth, low participant recruitment at some sites may have compromised therapist proficiency and effectiveness, due to less experience delivering the intervention over time. Fifth, therapist training may have been suboptimal. Training may not have differentiated between mandatory and optional components sufficiently or the therapists may not have understood the importance of delivering the mandatory components at every intervention session. Further study is needed to determine whether better interventionist training, monitoring, and feedback could improve the potency of the intervention.

Despite the positive effect of the intervention on six-minute walking distance, most secondary outcomes did not improve at 6-months compared to usual care. Improving quality of life is a key clinical and health priority. The lack of change in quality of life at 6-month follow-up, after this intervention was completed, may be because only two of the items in the Vascular quality of life -6 assessed physical health and improvement in mental health may lag behind improvements in physical function. Alternatively, people may underestimate changes in quality of life following exercise programmes because improvements are slower and less noticeable than with other interventions, such as revascularisation, and other co-morbidities can also affect quality of life.

Limitations

This study has several limitations. First, it was not possible to collect the primary outcome on all participants. This contributed to a large loss to follow-up for the 6- minute walking distance (22%). Post-hoc power calculations showed this had negligible effect on power (88% vs 90% planned). Further, participants without six-minute walking distance at follow-up had a lower baseline 6-

minute walking distance than those with the primary outcome. The post-hoc multiple imputation models for the 6- minute walking distance showed a greater magnitude of improvement between the intervention and the control groups in analyses that included multiple imputation. Third, most participants were white males. This limits the generalizability of these results. Fourth, the 3-month follow-up period is relatively short. The durability of the intervention is unknown. Fifth, the comparator to the intervention was not an attention control group. Sixth, relatively low fidelity of delivery in the telephone intervention sessions may have limited the intervention effect. Seventh, no actual walking activity data was collected.

Conclusion

Among adults with PAD and intermittent claudication, a physical therapist-led, home-based walking exercise behavior change intervention, compared with usual care, improved walking distance at 3-months. Further research is needed to determine the durability of these findings.

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Table 1 Baseline Characteristics of Participants with Peripheral Arterial Disease

	Walking exercise behavior change intervention (N=95)	Usual Care (N=95)
Age mean (SD) (years)	67.6 (8.7)	68.2 (9.0)
Sex N (%)		
Male	66 (69)	67 (71)
Female	29 (31)	28 (29)
Ethnic group N (%)		
Asian or Asian British	2 (2.1)	0 (0)
Black, African, Caribbean or Black British	11 (12)	7 (7)
Mixed or multiple ethic groups	4 (4.2)	0 (0)
White	72 (76)	78(82)
Other ethnic group[a]	5 (5.3)	6 (6.3)
Ankle brachial pressure index[b] mean (SD)	0.63 (0.12)	0.63 (0.15)
Body mass index[c] mean (SD)	26.7 (5.7)	26.9 (5.8)
Co-morbidities[d] **N (%)**		
High blood pressure	56 (59)	60 (63)
Cardiovascular disease	46 (48)	39 (41)
Diabetes	34 (36)	30 (32)
History of cardiac arrest	19 (20)	15 (16)
History of cerebrovascular accident	13 (14)	6 (6.3)
Kidney disease	11 (12)	6 (6.3)
Any other medical comorbidity[e]	9 (9.5)	9 (9.5)
Current or former smoker N(%)	82 (86)	85 (90)
History of lower extremity revascularization N(%)	28 (30)	24 (25)
Medication N(%)		
Using antiplatelet medication	21 (22)	20 (21)
Using statin medication	9 (9)	13 (14)
Using vasodilator medication	1 (1)	1 (1)
San Diego Claudication Questionnaire[f] N(%)		
Exertional leg pain-stop (classic or atypical claudication)	85 (89)	89 (94)
Exertional leg pain (classic claudication)	42 (44)	57 (60)
Exertional leg pain-carry on (atypical claudication)	8 (8.4)	2 (2.1)
Pain at rest	2 (2.1)	4 (4.2)
No exertional leg pain	0 (0)	0 (0)
6-minute walk distance[g] mean (SD) (metres)	352.9 (87.1)	369.8 (77.8)
Walking Estimated-Limitation Calculated by History score[g] median (IQR)[h]	16 (8;24)	20 (9; 27)
Self-reported Maximum Walking Distance[i]**,** median (IQR) (metres)	100 (45; 300)	150 (69; 255)
Nottingham Extended Activities of Daily Living score[j] median (IQR)	60 (51;66)	60 (54;66)
Vascular Quality of Life Questionnaire-6 score[k] median (IQR)	13 (11;15)	14 (11;16)
Brief illness perceptions questionnaire score[l]	45.7 (11.5)	44.0 (10.1)

Attitude score[m]	14.7 (3.1)	14.6 (3.4)
Subjective norms score[m]	16.2 (4.9)	15.8 (4.6)
Perceived behavioral control score[m]	17.5 (3.7)	17.0 (3.8)
Intention score[m]	19.3 (2.8)	19.0 (2.6)
Action planning score[n]	2.5 (1.2)	2.3 (1.1)
Action control score[n]	2.4 (0.9)	2.4 (1.0)
International Physical Activity Questionnaire[o] (MET minutes/week)	2846 (6359)	2615 (5903)

Abbreviations: SD, standard deviation; N, number; IQR, interquartile range; MET minutes/week, metabolic equivalent of task-minutes /week.

[a] Other ethnic group: Arab or any other self-reported ethnic group that could not be described using any of the previously listed categories.

[b]Calculated by dividing the mean of the dorsalis pedis and post tibial pressures in each leg by the mean of all four brachial pressures.

[c]Calculated as weight in kilograms divided by height in meters squared.

[d] Represents self-reported diagnosed medical conditions on a predetermined list on a questionnaire with checkboxes

[e]Represents any other diagnosed medical condition in response to one free text question for participants to record other conditions not listed in the pre-determined list.

[f]Represents participants evaluation of claudication pain based on location and extent of pain combined with activity level associated with pain on the San Diego Claudication questionnaire[13].

[g]Represents participants maximum walking distance in 6 minutes (ranges from small number of meters to further than 500m)[20]. Minimal clinically important distances are between 8m and 22m[21].

[h]Measures participants reported walking limitation at different speeds in comparison to friends and relatives (*i.e.,* slower/same/faster) on a four-item questionnaire. Scores range from 0 (able to walk for a maximum of 30 seconds at slow speed) to 100 (able to walk 3 hours or more at fast speed); 100 indicates best[22]. A minimal clinically important difference has not been defined.

[i]Measures self-reported walking distance in response to the question 'What is the maximum distance (in metres) you can walk at your usual pace on a flat surface before leg pain forces you to stop?' Ranges from a small number of meters to over 500m; over 500m indicates best[23]. A minimal clinically important difference has not been defined.

[j]Measures participants reported ease of completing activities of daily living on a 22-item questionnaire[24]. Score range from 0 to 66; 66 indicates best. A minimal clinically important difference has not been defined.

[k]Measures participants reported health related quality of life on a five-subscale questionnaire. Scores range from 6 to 24;24 indicates best[25]. The minimal clinically important difference ranges between 1.7 and 2.2 points[26].

[l]Measures participants cognitive and emotional representations of their illness on a 9-item questionnaire [27]. Scores range from 0 to 80; 0 indicates best. A minimal clinically important difference has not been defined.

[m]Measures participants attitude; subjective normative beliefs; perceived behavioral control beliefs and intention to walk on 12-item questionnaire[28]. Scores for each construct ranges from 3 to 21; 21 indicates best. A minimal clinically important difference has not been defined.

[n]Measures participants ability to plan and self-regulate their walking behavior on a 4-item (scores range 4 to 16) and 6-item scale (scores range from 6-24)[17]. Higher scores indicate best. A minimal clinically important difference has not been defined.

[o]Measures participants reported energy expenditure completed over the past seven days (metabolic equivalent of task-minutes /week) on a 7-item questionnaire. Higher scores indicate greater energy expenditure[14]. A minimal clinically important difference has not been defined.

Table 2 Effects of home-based walking exercise behavior change intervention on primary and secondary outcomes at 3-month or 6-month follow up

	Walking exercise behavior change intervention			Usual Care			Walking exercise behavior change vs Usual Care	
	Mean (SD)		Within-group change, mean (95% CI)	Mean (SD)		Within-group change, mean (95% CI)	Adjusted mean between group difference (95% CI)[a]	P value
	Baseline N=95	3-mo follow-up		Baseline N=95	3-mo follow-up			
PRIMARY OUTCOME								
6-min walk distance[b] (meters)	352.9 (87.1)	380.6 (87.7) [N=74]	22.3 (0.5 to 44.2)	369.8 (77.8)	372.1 (77.3) [N=74]	9.2 (-15.2 to 33.6)	16.7 (4.2 to 29.2)	0.009
SECONDARY OUTCOMES	**Baseline**	**6-mo follow-up**		**Baseline**	**6-mo follow-up**			
Walking Estimated-Limitation Calculated by History score[c]	18.0 (12.6) [N=94]	27.8 (18.5) [N=71]	6.6 (2.4 to 10.8)	20.7 (13.9)	20.7 (14.2) [N=72]	-1.4 (-4.8 to 2.1)	7.4 (2.5 to 12.3)	0.003
Self-reported Maximum Walking Distance[d] (meters)	199 (241)	586 (1430) [N=83]	378 (72 to 685)	275 (549)	305 (588) [N=83]	71 (-44 to 185)	104 (-56 to 264)	0.20
Nottingham Extended Activities of Daily Living score[e]	51.3 (15.7)	56.3 (13.1) [N=74]	-0.6 (-1.4 to 0.2)	54.3 (11.0)	58.4 (8.5) [N=73]	-0.3 (-1.0 to 0.3)	-1.4 (-4.4 to 1.6)	0.37
Vascular Quality of Life Questionnaire-6 score[f]	13.3 (3.5) [N=94]	15.2 (3.9) [N=83]	1.5 (0.7 to 2.2)	13.9 (3.1)	14.6 (3.9) [N=82]	0.8 (0.1 to 1.6)	0.5 (-0.5 to 1.5)	0.33
Brief illness perceptions questionnaire score[g]	45.7 (11.5)	38.9 (11.3) [N=72]	-4.3 (-6.9 to -1.7)	44.0 (10.1)	45.8 (12.2) [N=73]	2.0 (-0.2 to 4.2)	-6.6 (-9.9 to -3.4)	<0.001
Attitude score[h]	14.7 (3.1)	15.4 (3.7) [N=70]	0.7 (-0.3 to 1.7)	14.6 (3.4)	13.9 (3.6) [N=72]	-0.6 (-1.4 to 0.2)	1.4 (0.3 to 2.5)	0.017

Subjective norms score[h]	16.2 (4.9)	16.7 (4.9) [N=69]	-0.0 (-1.3 to 1.2)	15.8 (4.6)	16.0 (4.4) [N=72]	0.0 (-1.0 to 1.0)	0.3 (-1.1 to 1.7)	0.67
Perceived behavioral control score[h]	17.5 (3.7)	16.8 (3.4) [N=70]	-0.8 (-1.8 to 0.3)	17.0 (3.8)	16.8 (3.9) [N=72]	-0.2 (-1.2 to 0.9)	-0.2 (-1.4 to 1.0)	0.78
Intention score[h]	19.3 (2.8)	18.0 (3.5) [N=70]	-1.1 (-2.1 to -0.1)	19.0 (2.6)	18.3 (3.7) [N=72]	-0.8 (-1.7 to 0.1)	-0.3 (-1.5 to 0.9)	0.64
Action planning score[i]	2.5 (1.2)	3.0 (0.9) [N=70]	0.5 (0.2 to 0.7)	2.3 (1.1)	2.8 (1.0) [N=72]	0.4 (0.1 to 0. 7)	0.2 (-0.1 to 0.5)	0.16
Action control score[i]	2.4 (0.9)	3.1 (0.8) [N=70]	0.7 (0.4 to 0.9)	2.4 (1.0)	3.0 (0.8) [N=71]	0.6 (0.3 to 0.8)	0.1 (-0.1 to 0.4)	0.36
International Physical Activity Questionnaire[j] (MET minutes/week)	2846 (6359)	2764 (4198) [N=82]	-57 (-877 to 992)	2615 (5903)	2599 (5534) {N=82]	-110 (-599 to 819)	-2 (-1034 to 1029)	>0.99

Abbreviations: N,number; SD,standard deviation; 95% CI, 95% confidence interval; MET minutes/week, metabolic equivalent of task-minutes/week.

[a]Multiple regression using complete cases with baseline value, trial arm, centre as covariates; generalized linear model with same covariates used for non-normal outcomes.

[b]Represents participants maximum walking distance in 6 minutes (ranges from small number of meters to greater than 500m)[20]. Minimal clinically important distances are between 8m and 22m[21].

[c]Measures participants reported walking limitation at different speeds in comparison to friends and relatives (*i.e.,* slower/same/faster) on a four-item questionnaire. Scores range from 0 (*i.e.,* able to walk for a maximum of 30 seconds at slow speed) to 100 (able to walk 3 hours or more at fast speed); 100 indicates best[22]. A minimal clinically important difference has not been defined.

[d]Measures reported walking distance in response the question 'What is the maximum distance (in metres) you can walk at your usual pace on a flat surface before leg pain forces you to stop?' Ranges from a small number of meters to over 500m; over 500m indicates best[23]. A minimal clinically important difference has not been defined.

[e]Measures participants reported ease of completing activities of daily living on a 22-item questionnaire[24]. Scores range from 0 to 66; 66 indicates best. A minimal clinically important difference has not been defined.

[f]Measures participants reported health related quality of life on a five-subscale questionnaire. Scores range from 6 to 24;24 indicates best[25]. The minimal clinically important difference ranges between 1.7 to 2.2 points[26].

[g]Measures participants cognitive and emotional representations of their illness on a 9-item questionnaire [27]. Scores range from 0 to 80; 0 indicates best. A minimal clinically important difference has not been defined.

[h]Measures participants attitude; subjective normative beliefs; perceived behavioral control beliefs and intention to walk on 12-item questionnaire[28]. Scores for each construct ranges from 3 to 21; 21 indicates best. A minimal clinically important difference has not been defined.

[i]Measures participants ability to plan and self-regulate their walking behavior on a 4-item (scores range 4 to 16) and 6-item scale (scores range from 6 to 24)[17]. Higher scores indicate best). A minimal clinically important difference has not been defined.

[j]Measures participants reported energy expediture completed over the past seven days (metabolic equivalent of task-minutes /week) on a 7-item questionnaire. Higher scores indicate greater energy expenditure[14]. A minimal clinically important difference has not been defined.

32 **Table 3 Effects of home-based walking exercise behavior change intervention on other outcomes at 3-month or 6-month follow up**

	Walking exercise behavior change intervention			Usual Care			Walking exercise behavior change intervention vs Usual Care	
	Mean (SD)		Within-group change, mean (95% CI)	Mean (SD)		Within-group change, mean (95% CI)	Adjusted mean difference between groups (95% CI)[a]	P value
	Baseline N=95	3-mo follow-up		Baseline N=95	3-mo follow-up			
Walking Estimated-Limitation Calculated by History score[b]	18.0 (12.6) [N=94]	29.5 (18.3) [N=81]	9.7 (5.6 to 13.9)	20.7 (13.9)	20.0 (13.5) [N=80]	-1.0 (-3.8 to 1.7)	10.2 (5.7 to 14.7)	<0.001
Self-reported Maximum Walking Distance[c] (meters)	199 (241)	500 (1140) [N=90]	298 (75 to 521)	275 (549)	277 (402) {N=89]	51 (-40 to 141)	181 (60 to 302)	0.003
Nottingham Extended Activities of Daily Living score[d]	51.3 (15.7)	58.3 (8.4) [N=81]	0.2 (-0.3 to 0.7)	54.3 (11.0)	56.2 (12.6) [N=83}	-0.8 (-1.5 to -0.0)	2.8 (0.1 to 5.4)	0.04
Vascular Quality of Life Questionnaire-6 score[e]	13.3 (3.5)	14.8 (3.8) [N=91]	1.4 (0.7 to 2.0)	13.9 (3.1)	14.6 (3.5) [N=90]	0.6 (0.1 to 1.2)	0.6 (-0.2 to 1.4)	0.17
Pain free walking time[f] (seconds)	159.0 (77.2) [N=87]	208.0 (86.4) [N=65]	52.8 (33.7 to 72.0)	163.0 (83.8) [N=91]	173.0 (81.4) [N=68]	22.7 (4.2 to 41.3)	30.3 (5.4 to 55.3)	0.017
Maximum walking[g] (seconds)	301.5 (93.3)	324.4 (82.6) [N=74]	10.9 (-7.6 to 29.5)	289.7 (100.0)	308.7 (87.9) [N=74]	21.7 (1.9 to 41.5)	12.0 (-16.9 to 40.8)	0.42
Brief illness perceptions questionnaire score[h]	45.7 (11.5)	40.4 (11.5) [N=81]	-4.2 (-6.6 to -1.7)	44.0 (10.1)	45.6 (10.7) [N=82]	1.7 (-0.2 to 3.6)	-5.8 (-8.6 to -2.9)	<0.001
Attitude score[i]	14.7 (3.1)	15.7 (2.9) [N=81]	1.0 (0.2 to 1.7)	14.6 (3.4)	14.5 (4.0) [N=82]	-0.1 (-0.8 to 0.5)	1.1 (0.2 to 2.0)	0.016
Subjective norms score[i]	16.2 (4.9)	17.2 (4.1) [N=81]	0.9 (-0.1 to 1.8)	15.8 (4.6)	15.6 (4.9) [N=82]	0.0 (-1.0 to 1.0)	1.3 (0.1 to 2.6)	0.029

Perceived behavioral control score[i]	17.5 (3.7)	17.2 (3.5) [N=81]	-0.5 (-1.4 to 0.4)	17.0 (3.8)	17.3 (3.5) [N=82]	0.3 (-0.7 to 1.3)	-0.3 (-1.3 to 0.8)	0.60
Intention score[j]	19.3 (2.8)	19.5 (2.2) [N=81]	0.3 (-0.4 to 1.0)	19.0 (2.6)	18.5 (3.8) [N=82]	-0.5 (-1.3 to 0.3)	0.9 (0.0 to 1.9)	0.048
Action planning score[j]	2.5 (1.2)	3.2 (0.9) [N=81]	0.8 (0.5 to 1.1)	2.3 (1.1)	2.7 (1.1) [N=82]	0.4 (0.1 to 0.6)	0.5 (0.2 to 0.8)	0.001
Action control score[j]	2.4 (0.9)	3.5 (0.6) [N=81]	1.1 (0.9 to 1.3)	2.4 (1.0)	2.7 (1.0) [N=82]	0.3 (0.1 to 0.5)	0.7 (0.5 to 1.0)	<0.001
International Physical Activity Questionnaire[k] (MET minutes/week)	2874 (6387) [N=94]	3846 (6192) [N=91]	838 (-500 to 2175)	2615 (5903)	3207 (5035) [N=90]	424 (-658 to 1506)	532 (-855 to 1919)	0.45
Exercise Adherence Rating Scale score[l]	13.9 (5.8)	17.3 (5.1) [N=81]	3.3 (2.0 to 4.7)	13.6 (5.7)	15.3 (5.7) [N=82]	1.4 (0.0 to 2.7)	2.0 (0.5 to 3.5)	0.011

	Walking exercise behavior change intervention			**Usual Care**			**Walking exercise behavior change intervention vs Usual Care**	
	Mean (SD)		**Within-group change, mean (95% CI)**	**Mean (SD)**		**Within-group change, mean (95% CI)**	**Adjusted mean difference between groups (95% CI)**[a]**:**	**P value**
	Baseline	**6-mo follow-up**		**Baseline**	**6-mo follow-up**			
Exercise Adherence Rating Scale score[l]	13.9 (5.8)	16.0 (5.4) [N=70]	1.7 (0.1 to 3.3)	13.6 (5.7)	14.7 (6.3) [N=72]	0.6 (-1.0 to 2.3)	1.2 (-0.7 to 3.1)	0.21

Abbreviations: N, number; SD, standard deviation; 95% CI, 95% confidence interval; MET minutes/week, metabolic equivalent of task-minutes/week.

[a]Multiple regression using complete cases with baseline value, trial arm, centre as covariates; generalized linear model with same covariates used for non-normal outcomes.

[b]Measures participants reported walking limitation at different speeds in comparison to friends and relatives (*i.e.,* slower/same/faster) on a four-item questionnaire. Scores range from 0 (*i.e.,* able to walk for a maximum of 30 seconds at slow speed) to 100 (able to walk 3 hours or more at fast speed); 100 indicates best[22]. A minimal clinically important difference has not been defined.

[c]Measures reported walking distance in response the question 'What is the maximum distance (in metres) you can walk at your usual pace on a flat surface before leg pain forces you to stop?' Ranges from a small number of meters to over 500m; over 500m indicates best[23]. A minimal clinically important difference has not been defined.

[d]Measures participants reported ease of completing activities of daily living on a 22-item questionnaire[24]. Scores range from 0 to 66; 66 indicates best. A minimal clinically important difference has not been defined.

[e]Measures participants reported health related quality of life on a five-subscale questionnaire. Scores range from 6 to 24;24 indicates best[25]. The minimal clinically important difference ranges between 1.7 and 2.2 points[26].

[f]Represents the time in seconds that participants first experienced pain during 6-minute walk test. Ranges from small number of seconds to 360 seconds; 360 seconds indicates best. A minimal clinically important difference has not been defined.

[g]Represents time in seconds that participants stopped walking due to pain during 6-minute walk test Ranges from small number of seconds to 360 seconds; 360 seconds indicates best. A minimal clinically important difference has not been defined.

[h] Measures participants cognitive and emotional representations of their illness on a 9-item questionnaire [27]. Scores range from 0 to 80; 0 indicates best. A minimal clinically important difference has not been defined.

[i]Measures participants attitude; subjective normative beliefs; perceived behavioral control beliefs and intention to walk on 12-item questionnaire[28]. Scores for each construct ranges from 3 to 21; 21 indicates best. A minimal clinically important difference has not been defined.

[j]Measures participants ability to plan and self-regulate their walking behavior on a 4-item (scores range 4-16) and 6-item scale (scores range from 6 to24)[17]. Higher scores indicate best). A minimal clinically important difference has not been defined.

[k]Measures participants reported energy expediture completed over the past seven days (metabolic equivalent of task-minutes /week) on a 7-item questionnaire. Higher scores indicate greater energy expenditure[14]. A minimal clinically important difference has not been defined.

[l]Measures participants reported adherence to exercise on a 6-item questionnaire. Scores range from 0 to 24; 24 indicates best[29]. The minimal clinically important is 5.5 points[30].

Figure 1 Participants screening, randomization, and analysis in the MOSAIC trial of a home-based walking exercise behaviour change intervention for people with peripheral artery disease

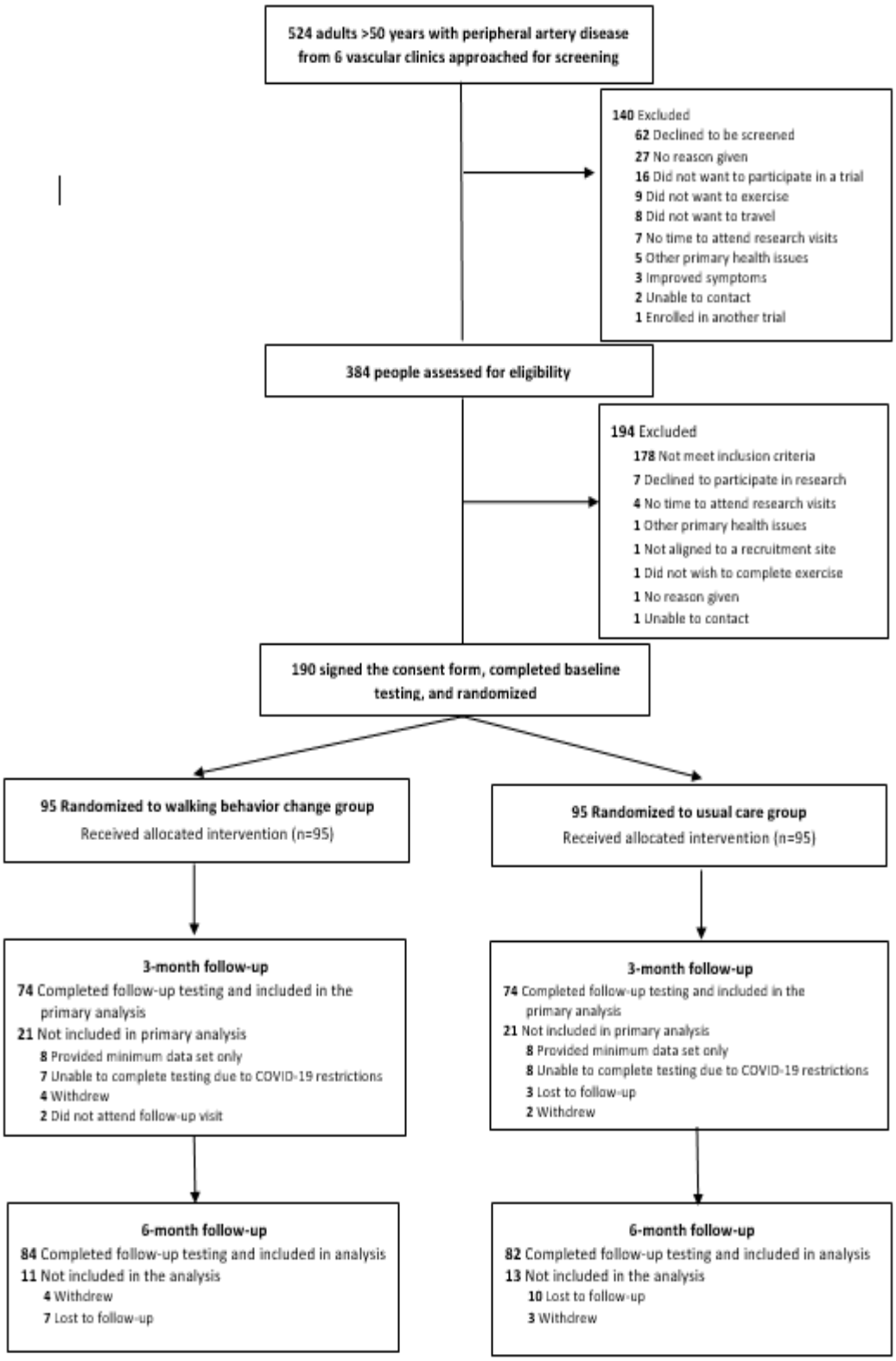

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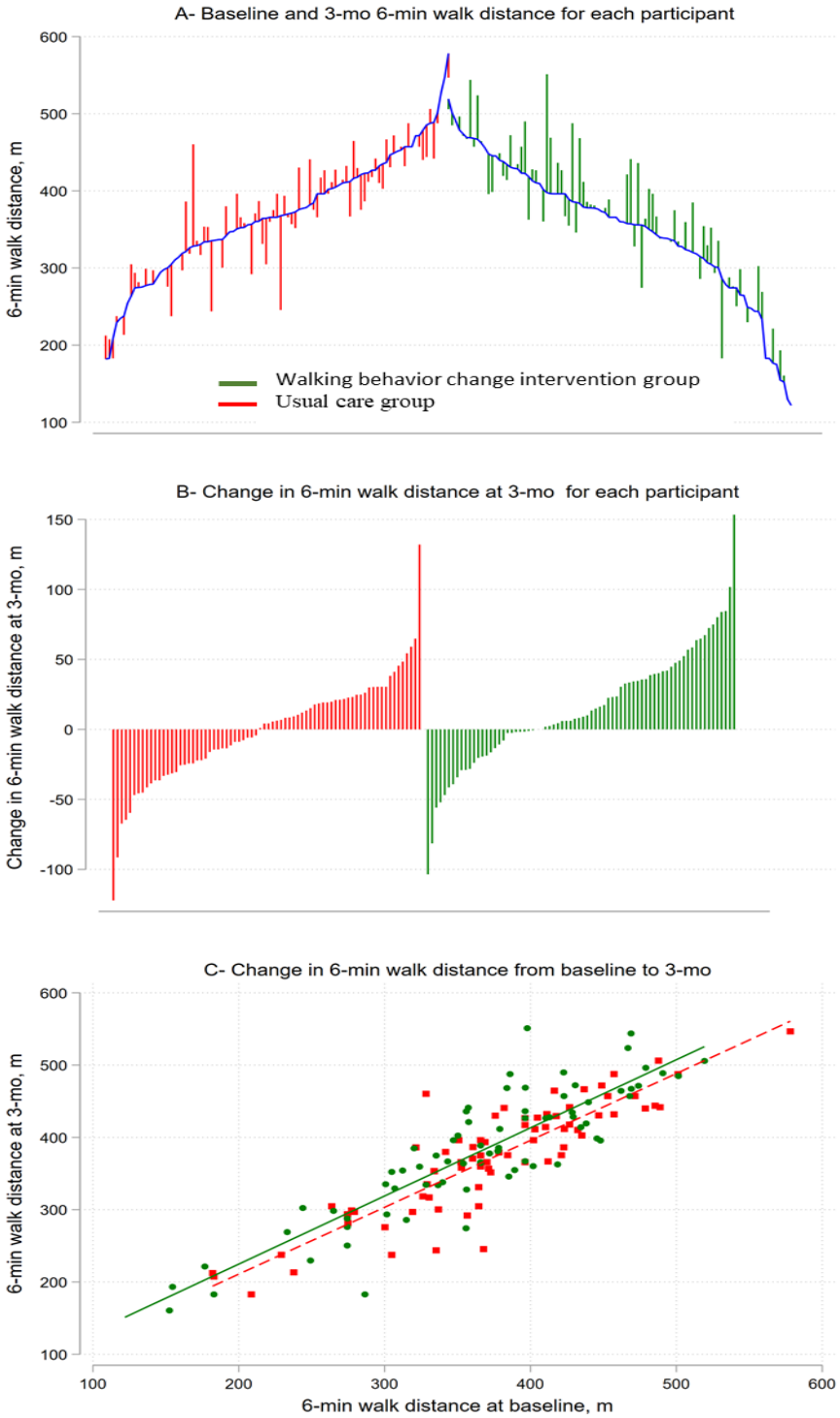
Figure 2. Baseline, 3-Month Follow-up, and Change in 6-Minute Walk Distance at 3- Months Among Participants With Peripheral Artery Disease



A, Each vertical line represents an individual participant, with participants ordered by baseline value and the vertical line extending up (improvement) or down (deterioration) to the 3-month value.

B, Vertical lines extending up denote the degree of improvement in 6-minute walk distance at 3-month follow-up. Vertical lines extending down denote the degree of decline in 6-minute walk distance.

C, Each point represents an individual participant. The vertical distance between the two regression lines represents the estimated difference between the two groups from the analysis of covariance between baseline and 3-months.