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REVIEW ARTICLE

Effectiveness and Equity in Community-Based Rehabilitation on Pain, Physical Function, and Quality of Life After Unilateral Lower Limb Amputation: A Systematic Review

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Abstract

Objectives: To synthesize evidence for (1) the effectiveness of exercise-based rehabilitation interventions in the community and/or at home after transfemoral and transtibial amputation on pain, physical function, and quality of life and (2) the extent of inequities (unfair, avoidable differences in health) in access to identified interventions.

Data Sources: Embase, MEDLINE, PEDro, Cinahl, Global Health, PsycINFO, OpenGrey, and ClinicalTrials.gov were systematically searched from inception to August 12, 2021, for published, unpublished, and registered ongoing randomized controlled trials.

Study Selection: Three review authors completed screening and quality appraisal in Covidence using the Cochrane Risk of Bias Tool. Included were randomized controlled trials of exercise-based rehabilitation interventions based in the community or at home for adults with transfemoral or transtibial amputation that assessed effectiveness on pain, physical function, or quality of life.

Data Extraction: Effectiveness data were extracted to templates defined a priori and the PROGRESS-Plus framework was used for equity factors.

Data Synthesis: Eight completed trials of low to moderate quality, 2 trial protocols, and 3 registered ongoing trials (351 participants across trials) were identified. Interventions included cognitive behavioral therapy, education, and video games, combined with exercise. There was heterogeneity in the mode of exercise as well as outcome measures employed. Intervention effects on pain, physical function, and quality of life were inconsistent. Intervention intensity, time of delivery, and degree of supervision influenced reported effectiveness. Overall, 423 potential participants were inequitably excluded from identified trials (65%), limiting the generalizability of interventions to the underlying population.

Conclusions: Interventions that were tailored, supervised, of higher intensity, and not in the immediate postacute phase showed greater promise for improving specific physical function outcomes. Future trials should explore these effects further and employ more inclusive eligibility to optimize any future implementation.

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Transfemoral amputation (TFA) and transtibial amputation (TTA) are life-changing events with substantial associated disability and give rise to numerous long-term secondary complications.[1-3] For adults after inpatient rehabilitation after TFA or TTA, there is a high incidence of long-term pain[4-6] and decreased physical function,[2,7-9] which affects community participation and quality of

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life.[10-12] Therefore, rehabilitation after TFA or TTA is considered a lifelong process with regular follow-up in the community and/or at home to identify any additional rehabilitation needs required to maintain adequate quality of life.[13-15]

Previous experimental studies have explored the effectiveness of exercise-based rehabilitation in the community and/or home for adults after TFA or TTA on various outcomes.[16-18] Two previous systematic reviews evaluated the effectiveness of exercise-based rehabilitation (in any setting) on gait performance after lower limb amputation.[19,20] These reviews reported low- to moderate-quality evidence for the effectiveness of exercise-based interventions for adults with TFA and TTA in improving gait. No previous review has synthesized the evidence for the effectiveness of exercise-based rehabilitation in the community and/or home on pain, quality of life, and/or other measures of physical function.

High adherence rates in randomized controlled trials (RCTs) of rehabilitation interventions for adults after TFA or TTA have been reported.[17,21,22] This is in contrast to reports of poor adherence to rehabilitation for this population in current clinical practice.[23-25] The mismatch between RCTs and practice adherence may be due to patients' unwillingness to engage in or access long-term rehabilitation programs offered compared to short-term RCTs. Alternatively, this mismatch may reflect narrow eligibility criteria in RCTs. Of interest is whether such eligibility criteria systematically limit access for patient subgroups that are less likely to adhere to rehabilitation after TFA or TTA and that face poor outcomes in current clinical practice. If so, this could be considered a source of inequity (unfair, avoidable differences in health arising from exclusion) in rehabilitative care. Addressing such systematic inequities in access to appropriate services is a public health priority.[26] Health care services are commissioned based on evidence of clinical efficacy and cost-effectiveness, often from RCTs or meta-analyses of several trials. Once subgroups have been identified, a failure to describe them in the baseline characteristics of trial participants or as trial subgroup analyses means that clinicians and decision makers lack evidence for appropriate management or service commissioning.[27,28]

Therefore, the aim of this systematic review was to synthesize the literature on the effectiveness of exercise-based rehabilitation in the community and/or home on pain, physical function, and quality of life for adults after TFA and TTA. We also sought to determine the role of equity factors in eligibility criteria in RCTs of rehabilitation interventions identified by this review.

Methods

Protocol and registration

We registered the protocol for this review on the International Register of Systematic Reviews (PROSPERO CRD42020171140).[29] We adhered to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement[30] and the Equity extension to the PRISMA statement.[31,32]

List of abbreviations:

LLA	**lower limb amputation**
PRISMA	**Preferred Reporting Items for Systematic Review and Meta-analysis**
RCT	**randomized controlled trial**
TFA	**transfemoral amputation**
TTA	**transtibial amputation**
TUG	**Timed Up and Go**

Eligibility criteria

We included RCTs of rehabilitation interventions based in the community (as an outpatient) or at home for adults with TFA or TTA. We included interventions that included at least 1 physical exercise component of any frequency, intensity, type, or timing, performed individually or in a group, and in any mode; for example, face-to-face or remote. We included RCTs that selected pain, physical function, and/or quality of life as an outcome of interest. We excluded studies that were not RCTs, non-English-language studies, studies on inpatient rehabilitation or pediatric populations, and studies of interventions without a physical exercise component (above that received as part of usual care). No restrictions were imposed based on the type of control group (eg, active, passive, waitlist), geographic location, or status (whether completed or ongoing) of RCTs.

Search

We employed published search terms for the population (amputation),[33,34] intervention (rehabilitation),[35] and study design (RCTs[33]; see Supplementary File A Table A.1, available online only at http://www.archives-pmr.org/). We searched the electronic databases Embase, MEDLINE, PEDro, Cinahl, Global Health, and PsycINFO for published trials; OpenGray for unpublished trials; and ClinicalTrials.gov for registered ongoing trials from inception to August 12, 2021. We reviewed reference lists of included trials and related systematic reviews for other potential trials. We did not search Cochrane Central Register of Controlled Trials.

Selection

We imported citations into Covidence for the removal of duplicates and screening.[a] Three review authors (KS, AW, KC) independently screened titles, abstracts, and full texts to determine trial eligibility against predefined criteria. Conflicts were resolved by consensus (KS, AW, KC).

Data extraction

One author (AW) extracted data into a predefined template including author, year, and location; study design, sample size, eligibility criteria, and baseline characteristics; cause, type, and time since amputation; and intervention, setting, control, outcomes, intervention effect (intergroup), follow-up, and equity factors in eligibility criteria. Data from protocols and registered ongoing trials were extracted solely to inform the analysis related to equity factors and not the intervention effect. We defined equity factors by the Cochrane and Campbell Collaboration Equity Methods group's PROGRESS-Plus framework.[31,36] PROGRESS is an acronym for Place of residence, Race/ethnicity/language/culture, Occupation, Gender (sex), Religion, Education, Socioeconomic status and Social capital.[31,36] PLUS captures other factors that affect equity, namely, age, disability, and time-dependent relationships.[31,36] A second author (KS) independently extracted data from a sample set (n=3). There were no discrepancies in data extraction between authors.

Risk of bias

Three reviewers (AW, KS, RMC) independently assessed risk of bias using the Cochrane Risk of Bias Tool,[37] which considers potential for bias in participant selection, performance (participants and personnel), detection, attrition, and reporting of results. Conflicts were resolved by consensus.

Synthesis of results

We report trial characteristics as counts and proportions. There was variation in eligibility criteria, prognostic factor measurement, intervention characteristics, and outcome measurement across trials, which made it implausible to combine the results and perform a meta-analysis. Therefore, we report results using a narrative review approach.[38] We summarize the evidence in text and tables.

Results

RCT selection

We identified 5549 trials after removal of duplicates (n=7171). Figure 1 shows the process of study selection, which yielded 14 studies for 13 RCTs (8 completed trials,[17,21,22,39-44] 2 protocols,[45,46] 3 registered ongoing trials[47-49]). Two studies reported different outcomes for the same trial.[43,44]

Completed trial characteristics

All completed trials included in the review were published after 2015. These trials were performed in 5 countries: Turkey (n=3),[39-41] United States (n=2),[21,42] South Africa (n=1),[17] Canada (n=1),[22] and the UK (n=1).[43,44] Most participants were male (n=256, 73%) and had an amputation because of vascular disease (n=223, 63.5%), trauma (n=116, 33.0%), tumor (n=9, 2.5%), or infection (n=3, 0.8%). All were prosthetic users with unilateral TFA (n=133, 37.9%) or TTA (n=218, 62.1%). The mean time since amputation was more than 10 years for 91 participants (25.9%) and less than 6 months for 192 participants (54.7%).

Risk of bias within completed trials

All RCTs were at low risk of bias for random sequence generation and selective reporting (n=8), and most were at low risk of bias for incomplete outcome data (n=6[17,21,22,41-44]; Figure 2). There

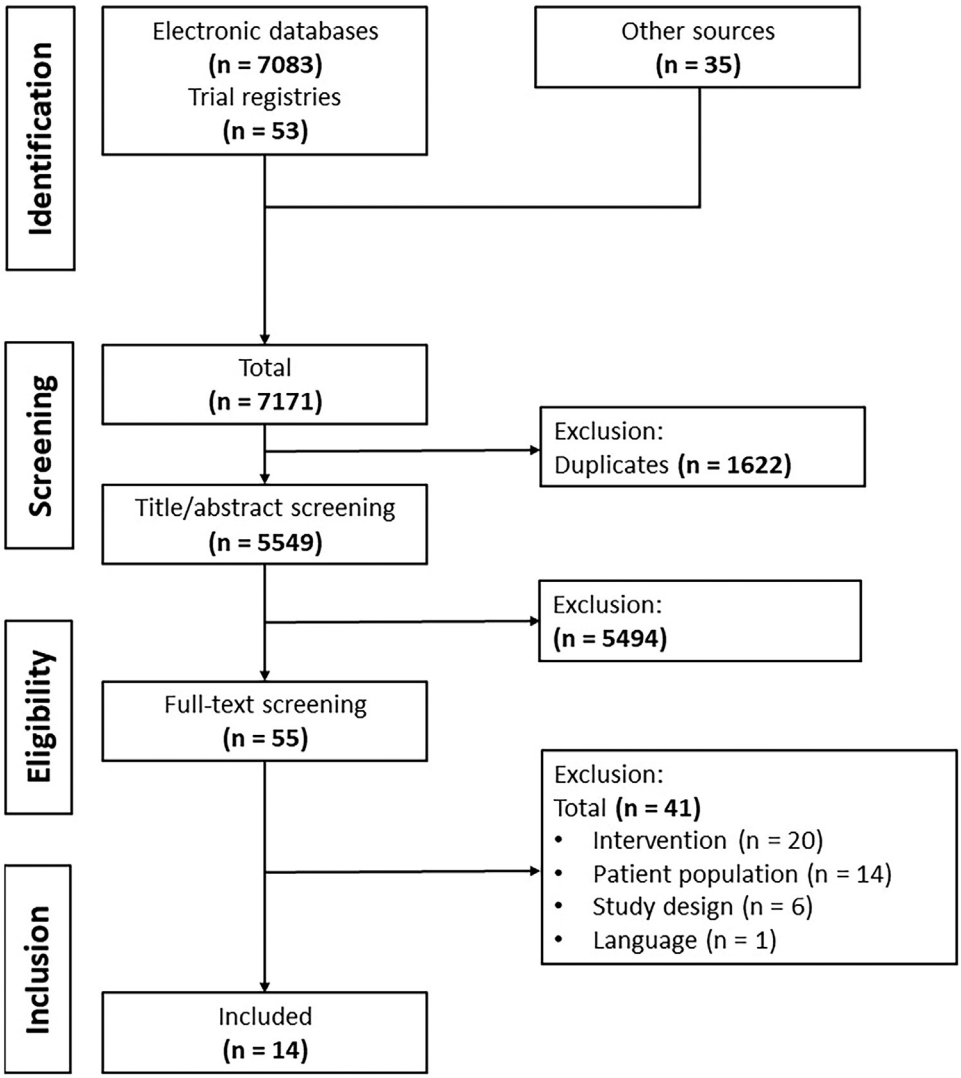

Fig 1 PRISMA flowchart of study selection.

was insufficient information to assess allocation concealment for 5 trials.[39-44] Lack of blinding of personnel and participants was the only reason for high bias assignment for 6 trials.[17,21,39,41-44] The RCT by Anaforoğlu et al was assigned a high risk of bias because of a lack of blinding of personnel and participants as well as lack of blinding of outcome assessors.[39] Another RCT by Anaforoğlu et al was not assigned a high risk of bias for any domain; however, there was insufficient information to assess 4 of 6 domains of bias in this RCT.[40]

Completed trial intervention characteristics

Interventions comprised stretching and strengthening of lower limb and/or trunk muscles,[17,21,22,39,42] cycle ergometery,[42-44] aerobic exercises,[22,42-44] balance and gait training,[17,22,41-44] and cognitive behavioral therapy.[21] The frequency of rehabilitation interventions ranged from daily[40] to once a week.[21] The length of the interventions ranged from 2 weeks[39] to 12 weeks.[17,21,43,44] Session duration (where specified) ranged from 15 minutes[39] to 60 minutes.[39,41,42] Mode of intervention delivery was face to face in all trials. Where reported, methods used to encourage participant adherence during the intervention and follow-up included consultations via telephone,[17,22,40] in person at weekly meetings,[21] or direct supervision by a physiotherapist.[41-44] Dropout rates of participants during the follow-up period of completed trials ranged from 0%[39,40] to 33%[42] with adverse events/complications reported in 4 trials (all were attributed to preexisting medical conditions).[17,22,42,43]

Five trials compared the intervention to active controls (dual task vs single task,[41] health education program,[39] cognitive games,[22] attention control,[21] and mirror therapy[40]), and 3 trials compared the intervention to passive controls (usual care[17,43,44])

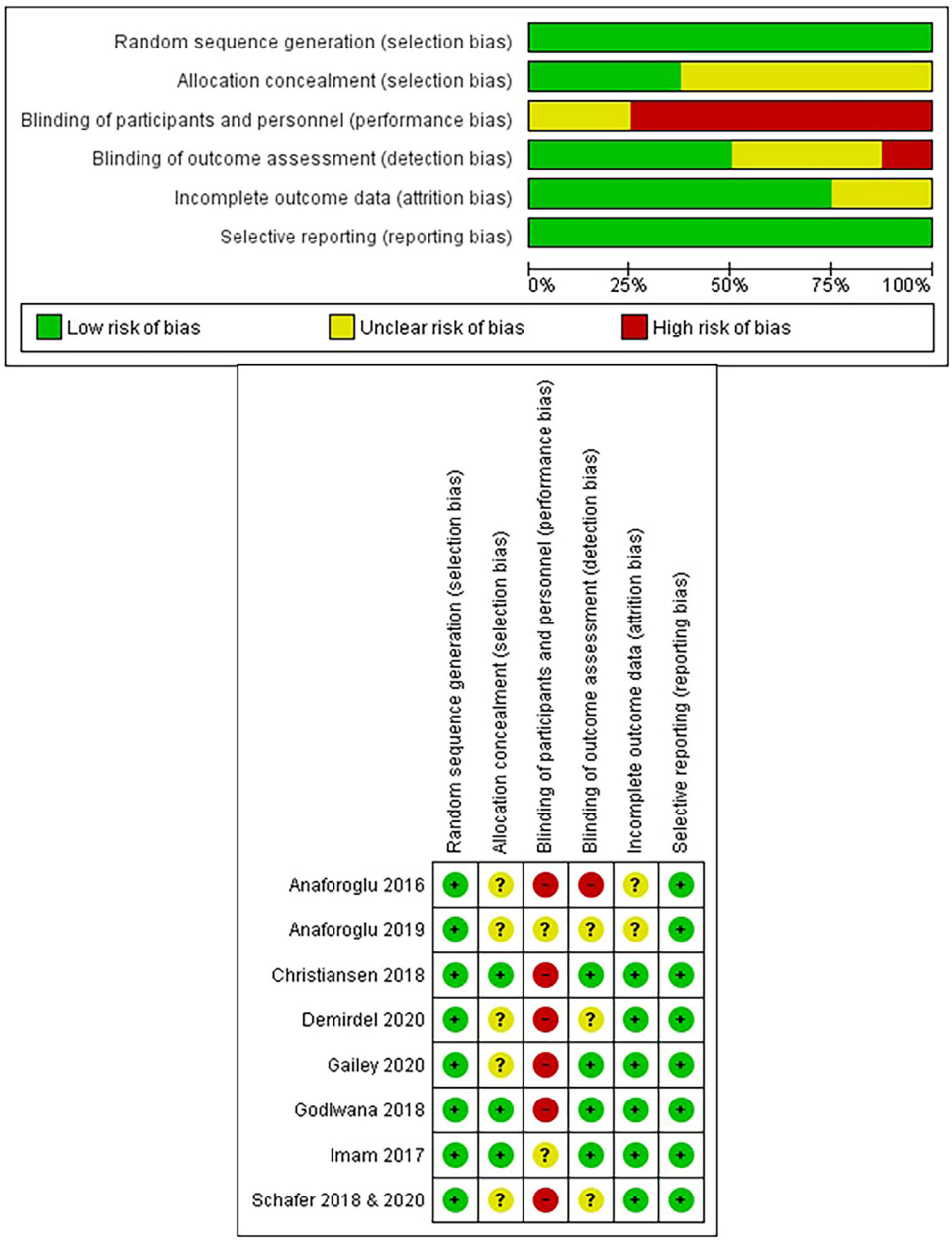

Fig 2 Risk of bias.

and waitlist control.[42] Follow-up evaluation of the intervention was reported in 6 out of the 8 trials and ranged from 3 weeks[22] to 12 months.[43,44] Further details may be found in Table 1.

Pain

Two trials employed pain (back pain,[39] phantom limb pain,[40] and back pain−related disability[39]) as an outcome. Of the 2 trials, 1 reported an improvement in back pain and related disability after a 2-week supervised exercise program and education compared with education alone at 1-month and 3-month follow-ups ($P<.05$).[39] The other trial favored mirror therapy compared to exercises in reducing phantom limb pain at 1-month, 3-month, and 6-month follow-ups ($P<.001$[40]; Table 1).

Physical function

Seven trials assessed the effectiveness of exercise-based rehabilitation in the community or home on physical function. We report the intervention effect by domains of physical function (Table 1).

Endurance

Two trials reported a beneficial effect of the intervention on endurance (6-minute walk test[42] and 2-minute walk test[22]) after (1) an 8-week evidence-based amputation rehabilitation exercise intervention compared to waitlist control at intervention end ($P<.05$)[42] and (2) a 4-week Wii Fit balance board intervention compared to a seated cognition improvement program (cognitive games) at intervention end and 3-week follow-up ($P<.05$).[22] In contrast, no effect on endurance (2-minute walk test) was observed after a 3-month behavior change intervention composed of cognitive behavioral therapy and home-based exercises compared to an attention control at intervention end and 12-week follow-up ($P>.05$).[21]

Physical activity level

Two trials reported a beneficial effect of the intervention on physical activity (daily step count[21,22] and time spent in sedentary activity[21]) after (1) a 3-month behavior change intervention composed of cognitive behavioral therapy and home-based exercises compared to an attention control at intervention end and 12-week follow-up ($P<.05$)[21] and (2) a 4-week Wii Fit balance board intervention compared to a seated cognitive game at ($P<.05$).[22] However, the latter trial also reported no change in physical activity level when measured by the Physical Activity Scale for the Elderly ($P>.05$).

Gait parameters

Two trials reported a beneficial effect of the intervention on gait speed after (1) a 4-week dual-task balance training intervention compared to single-task balance training at intervention end ($P<.05$)[41] and (2) a 12-week supervised and personalized exercise program compared to usual care control at 12-month follow-up ($P<.05$).[43] In contrast, Christiansen et al[21] reported no change in gait speed after a 3-month behavior change intervention composed of cognitive behavioral therapy and home-based exercises compared to an attention control at intervention end and 12-week follow-up ($P>.05$).

Schafer et al[43] reported a beneficial effect of the intervention on temporal-spatial parameters, peak sagittal and frontal plane joint angles, sagittal plane joint moments and powers, and ground reaction forces after their 12-week supervised and personalized exercise program compared to usual care control at 12-month follow-up.

Functional mobility

Two trials reported a beneficial effect of the intervention on functional mobility and 2 trials reported no effect. A beneficial effect was observed after (1) an 8-week evidence-based amputation rehabilitation exercise intervention compared to waitlist control at intervention end ($P<.05$; Amputee Mobility Predictor with and without prosthesis)[42] and (2) a 3-month education and exercise intervention compared to usual care at intervention end ($P<.05$; Locomotor Capability Index).[17] No effect was observed after (1) a 3-month behavior change intervention composed of cognitive behavioral therapy and home-based exercises compared to an attention control at intervention end and 12-week follow-up ($P>.05$; Prosthesis Evaluation Questionnaire-Mobility Scale)[21] and (2) a 4-week Wii Fit balance board intervention compared to a seated cognitive game at intervention end and 12-week follow-up ($P>.05$; Locomotor Capability Index).[22]

Lower extremity functioning

Three trials reported no effect on lower extremity functioning (Timed Up and Go [TUG] test[17,21] and Short Physical Performance Battery[22]) after (1) a 3-month behavior change intervention composed of cognitive behavioral therapy and home-based exercises compared to an attention control at intervention end and 12-week follow-up ($P>.05$),[21] (2) a 4-week Wii Fit balance board intervention compared to at a seated cognitive game at intervention end and 12-week follow-up ($P>.05$),[22] and (3) a 3-month education and exercise intervention compared to usual care at intervention end and 3-month follow-up ($P>.05$).[17] In contrast, Demirdel and Erbahçeci[41] reported a beneficial effect of the intervention on lower extremity functioning (TUG test) using a cognitive dual task after a 4-week dual-task balance training intervention compared to single-task balance training at intervention end ($P<.05$).

Falls and balance

Two trials reported a beneficial effect on balance outcomes. Schafer et al reported a reduction in falls incidence[43] and improvement in postural control (equilibrium, strategy score, and vestibular ratio)[44] after a 12-week supervised and personalized exercise program compared to usual care control at 12-month follow-up ($P<.05$). Demirdel and Erbahçeci[41] reported improvement in static and dynamic balance (1-leg stance time and 4-square step test, respectively) using cognitive and/or motor dual tasks after a 4-week dual-task balance training intervention compared to single-task balance training at intervention end ($P<.05$). In contrast, no effect on postural control (somatosensory ratio, visual sensory ratio, latency score) and balance confidence (Activity-specific Balance Confidence Scale) was noted at 12-month follow-up for the RCT by Schafer et al[44] ($P>.05$). This is in keeping with findings from Imam et al[22] in which no effect on balance confidence (Activity-specific Balance Confidence Scale) was reported after a 4-week Wii Fit balance board intervention compared to a seated cognitive game at intervention end and 3-week follow-up ($P>.05$).

Other measures of physical function

Improved flexibility was observed (change in distance between 2 anatomic reference points before and after the movement) after a 2-week supervised exercise program and education compared

Table 1 Effectiveness of exercise-based rehabilitation in the community and/or at home on pain, physical function, and quality of life after TFA or TTA

Study	Location	Sample Size	Population	Intervention	Control	Outcomes	Effect
Completed trials							
Anaforoğlu et al[39]	Turkey	40	Male, age 38.0 (10.8) years (intervention) and 36.0 (10.3) years (control) posttraumatic, unilateral TFA, prostheses ≥1 year, diagnosis of LBP	2-week (1 h/d, 5 d/wk) supervised back health education (anatomy, biomechanics, spinal ergonomics) and exercise (ergonomics during activities, strengthening, stretching, spinal stabilization, dynamic stump) program	Sham control	Pain Back pain (VAS) Back pain—related disability (ODI) Physical function Spinal flexibility (tape measurement)	1-Month follow-up: VAS, ODI scores, and trunk lateral flexion to right increased improved for intervention vs control (P<.05). No intergroup change in trunk flexion, extension, lateral flexion to left, rotation (P>.05) 3-Month follow-up: VAS, ODI scores, and trunk flexion, lateral flexion to right, and rotation to right improved for intervention vs control (P<.05). No intergroup change in extension, flexion to left, and rotation to left (P>.05)
Anaforoğlu et al[40]	Turkey	40	Male (n=25) and female (n=15), age 32.60 (7.39; MT) and 29.60 (6.87; PE), posttraumatic, unilateral TTA, experiencing PLP regularly (with an average intensity of at least 40 on VAS)	PE* Toe and ankle movements followed by knee and hip movements, daily or in case of recurrence of PLP in a day, performed bilaterally (in opposite direction) with 15 repetitions or until felt relaxation/PLP disappeared (whichever is earlier), 1 session daily for 4 weeks)	MT	Pain PLP (VAS) Quality of life SF-36	IAI: VAS and SF-36 scores improved for MT group vs PE group (P<.05) 3-Month follow-up: VAS and SF-36 scores improved for MT group vs PE group (P<.05). 6-Month follow-up: VAS and SF-36 scores improved for MT group vs PE group (P<.05)
Christiansen et al[21]	United States	38	Male (n=35) and female (n=3) age 62 (59, 65; intervention) and 65 (60, 71; control) unilateral TTA <6 months with type II DM and/or PAD, household ambulators (or better), prosthetic users, living within 45 min of a participating clinic	3-Month behavior change intervention (30-min weekly sessions), based on social cognitive and control theories of behavior change targeting physical exercise, walking activity, and disease self-management	Attention control	Physical function Functionality (TUG test) Walking activity (activity monitor) Endurance (2-MWT) Gait speed (5-MWT) Ability to perform functional tasks (PEQ-MS)	IAI: Daily step count increased for intervention vs control (P<.05). No intergroup change in other outcomes (P>.05) 12-Week follow-up: Time spent in sedentary activity decreased for intervention vs control (P<.05). No intergroup change in other outcomes (P>.05)
Demirdel and Erbahçeci[41]	Turkey	20	Male (n=14) and female (n=6) age 18-65 years, unilateral TFA, prosthesis >1 year, able to walk 10 meters without walking aids, Montreal Cognitive Assessment Score≥21, using a mechanical, hydraulically controlled prosthetic knee joint	Balance and mobility exercises with cognitive and motor dual tasks for 4 weeks (45-60 min each session, 3 sessions per week).	Single task balance training	Physical function Gait speed (10-MWT) Balance (OLST and FSST) Mobility (TUG test)	IAI: 10-MWT, TUG test, OLST, and FSST under dual-task conditions improved for intervention vs control (P<.05). No intergroup change in any of the outcomes under single task (P>.05) No follow-up
Gailey et al[42]	United States	16	Male (n=13) and female (n=3) age 63.4 (11.5; intervention) and 63.0 (7.1; control) traumatic or dysvacular unilateral TTA ≥1 year, prosthesis ≥6 months, completed traditional postamputation rehabilitation and prosthetic training	8-Week EBAR program (60 min, 3 times/wk) comprising cardiopulmonary aerobic and warm-up exercises, ergometry, treadmill walking, trunk and lower limb stretching and strengthening, balance and coordination exercises, weight-bearing and stance control, and prosthetic gait training	Waitlist control	Physical function Functional capability to ambulate (AMPPro and AMPnopro score) Endurance and overall mobility (6-MWT)	IAI: AMPPro score, AMPnopro score, and 6-MWT distance improved for intervention vs control (P<.05) No follow-up
Godlwana et al[17]	South Africa	154	Male (n=100) and female (n=54), age 58.58 (9.92; intervention) and 57.78 (9.66; control), dysvascular (diabetes or PVD), first-time major unilateral LLA	Usual care+home education and exercise program for 3 months that includes stump positioning, safe transfer techniques, stretching and	Usual care	Physical function Functional independence (Barthel Index) Basic mobility (TUG test) Ability to perform locomotor	IAI: Modified LCI-5 and Euroqol-5D improved for intervention vs control (P<.05). No intergroup change in other outcomes (P>.05)

(*continued on next page*)

Table 1 (*Continued*)

Study	Location	Sample Size	Population	Intervention	Control	Outcomes	Effect
				strengthening exercises, and balance reeducation		activities (Modified LCI-5) Quality of life Euroqol-5D	3-Month follow-up: No intergroup change in any of the outcomes ($P>.05$)
Imam et al[22]	Canada	28	Male (n=18) and female (n=10) age≥50 years, unilateral TTA or TFA ≥1 year, prosthesis ≥2 h/d for past 6 months, not participating in formal exercise/training programs	4-Week Wii.n.Walk program (40 min, 3 times/wk) consisted of Nintendo Wii Fit activities (participants required to stand on the Wii Fit balance board) including yoga (static and dynamic single and double leg poses), balance games (lateral, posterior and anterior weight shifting), strength training (dynamic single and double leg), and aerobics (running on the spot and step class)	Sham control	Physical function Walking capacity (2-MWT) Lower limb functionality (SPPB) Physical activity level (PASE) Balance confidence (ABC scale) Daily step count (activity monitor) Ability to perform locomotor activities (LCI-5)	IAI: 2-MWT distance and daily step count increased for intervention vs control ($P<.05$). No intergroup change in other outcomes ($P>.05$) 3-Week follow-up: 2-MWT distance and daily step count increased for intervention vs control ($P<.05$). No intergroup change in other outcomes ($P>.05$)
Schafer et al[43] Schafer et al[44]	UK	15	Male (n=11) and female (n=4), age 60 (12; intervention) and 65 (16; control) unilateral TTA or TFA, daily prosthesis users, able to ambulate independently along level surfaces with or without mobility aids, with a history of falls during past 2 years or deemed at risk of falling	12-Week supervised, circuit-style group exercise session and personalized home-based training targeting gait endurance and speed, flexibility, strength (squats, sit-ups, step-ups, calf raises, hip abduction, with optional use of Therabands, kettlebells, or dumbbells), dynamic balance, and cardiovascular fitness (cycle ergometer)	No care or usual care	Physical function Falls incidence Postural control (equilibrium, strategy score, sensory ratio, latency score) Balance confidence (ABC scale) Gait parameters (Temporal-spatial: speed, double support, step length, cadence, and stance; joint kinetics and kinematics of hip, knee, and ankle joint in different phases of gait)	12-Month follow-up: Number of falls reduced and strategy score, equilibrium score, and vestibular ratio improved for intervention vs control ($P<.05$) Increased walking speed, cadence (intact limb), terminal stance peak hip extension angle (bilaterally), ankle plantarflexion in preswing (intact limb), concentric powers at the hip (bilaterally), eccentric powers at the hip (affected limb), ankle joint power (intact limb), peak vertical GRF in preswing (intact limb), peak propulsive GRF during push-off (affected limb), and decreased peak hip flexion angle in preswing (affected limb), power absorption and generation (intact and affected hip joint, and intact ankle joint) for intervention vs control ($P<.05$) No intergroup change in step length, stance, double support durations, somatosensory ratio, visual sensory ratio, latency scores, and ABC scale ($P>.05$)
Protocols and registered ongoing trials							
Bourque et al[45]	United States	60	Male and female age≥18 years, unilateral TTA, prosthesis ≥6 months, balance confidence (ABC scale) <80	8-Week (1.5 h/session, 1 session/wk) training sessions with a virtual reality active gaming component (ie, PT component) and CBT strategies	Sham control	Physical function Functional ability (BBS and L-test) Balance confidence (ABC scale) Community integration (activity monitor and FAI) Quality of life SF-36 PEQ	Protocol

(*continued on next page*)

Table 1 (*Continued*)

Study	Location	Sample Size	Population	Intervention	Control	Outcomes	Effect
Wasser et al[46]	United States	40	Male and female, age 18-60 years, traumatic unilateral TTA >1 year, prosthesis ≥6 months, chronic LBP >3 months with at least 3 pain episodes per week), having regular access to a computer for Skype or a mobile phone or iPAD, prosthesis K-level of K2 or greater	12-Week exercise program emphasizing core strength, dynamic hip and pelvis stability, and lumbar endurance and strength, organized as 6 phases (2 weeks per phase), 8-12 repetitions for each exercise (first phase: 2 days/week, other 5 phases: 3 days/week)	Waitlist control	Pain Back pain severity (NPS) Physical function Gait parameters (3D motion analysis for temporal-spatial parameters of gait and GRF) Muscle strength (1-RM) Step count (7-day average count) Quality of life Effect of pain on QoL (pain medications used, SF-36, ODI, RMDQ	Protocol
ClinicalTrials.gov[47]	Turkey	22	Male and female, age 18-65 years, unilateral TTA ≥6 months, prosthetic users, quadriceps and hamstring strength of the residual limb (Lovett's manual muscle test)≥4	Usual care+spinal (core) stabilization exercises for 8 weeks	Usual care	Physical function Energy expenditure and exercise capacity (6-minute step test) Fatigue (Modified Borg Scale) Strength of deep spinal muscles (stabilizer) Mobility (PEQ)	Registered ongoing trial
ClinicalTrials.gov[48]	Brazil	26	Male and female age 18-50 years, unilateral TTA, prosthesis >3 months, discharge from the rehabilitation program	8-Eeek concurrent training (strength training and aerobic interval training on cycle ergometer)	No care or usual care	Physical function Dynamic functional capacity (sit to stand test) Functional mobility (TUG test) Muscular strength (isokinetic dynamometry) Cardiopulmonary capacity ($\dot{V}o_2max$) Dynamic and static balance (Balance Master System version 8.1—Dual force platform system)	Registered ongoing trial
ClinicalTrials.gov[49]	Turkey	40	Male and female age 30-60 years, unilateral TTA, using active vacuum system prosthesis and carbon foot >1 year, mobility level K2-K3, Montreal Cognitive Assessment Score≥21	A structured exercise program supported by telerehabilitation (online supervision through mobile telecommunication applications and videos) 3 days per week for 6 weeks+home exercise program for remaining days of the week	Sham control	Physical function Mobility (TUG test) Leg strength and endurance (sit to stand test) Balance confidence (ABC scale) Quality of life TAPES	Registered ongoing trial

NOTES.

* Superiority trial.1-RM, 1-repetition maximum; 2-MWT, 2-minute walk test; 5-MWT, 5-meter walk test; 6-MWT, 6-minute walk test; 10-MWT, 10-meter walk test; ABC, activity-specific balance; AMPPro/AMPnopro, amputee mobility predictor with prosthesis/without prosthesis; BBS, Berg Balance Scale; CBT, cognitive behavioral therapy DM, diabetes mellitus; EBAR, evidence-based amputee rehabilitation; FAI, Frenchay Activity Index; FSST, 4-square step test; GRF, ground reaction force; IAI, immediately after intervention; LBP, low back pain; LCI-5, locomotor capabilities index in amputees; MT, mirror therapy; NPS, numeric pain scale; ODI, Oswestry Disability Index; OLST, 1-leg stance test; PAD, peripheral arterial disease; PASE, Physical Activity Scale for the Elderly; PE, phantom exercises; PEQ, Prosthesis Evaluation Questionnaire; PEQ-MS, Prosthesis Evaluation Questionnaire-Mobility Scale; PLP, phantom limb pain; PT, physical therapy; PVD, peripheral vascular disease; QoL, quality of life; RMDQ, Roland Morris Disability Questionnaire; SF-36, Medical Outcomes Short Form 36; SPPB, Short Physical Performance Battery; TAPES, Trinity Amputation and Prosthesis Experiences Scale; VAS, visual analog scale.

with education alone at 1-month (trunk lateral flexion to right, $P<.05$) and 3-month (trunk flexion, lateral flexion to right, and rotation to right, $P<.05$) follow-ups.[39] Activities of daily living (Barthel index) was not improved after 3-month education and exercise intervention compared to usual care at intervention end and 3-month follow-up ($P>.05$).[17]

Quality of life

Quality of life was employed as an outcome in 2 trials.[17,40] One trial reported improvement in quality of life after a 3-month education and exercise intervention compared with usual care at intervention end ($P<.05$) but not at 3-month follow-up ($P>.05$).[17] The other trial favored mirror therapy compared to exercises in improving quality of life of adults with TTA experiencing phantom limb pain ($P<.05$[40]; Table 1).

Protocols and registered ongoing trials

Two protocols[45,46] and 3 registered ongoing trials[47-49] were included. Proposed interventions included strengthening exercises,[46-49] cycle ergometry,[48] aerobic exercises,[48] and virtual reality games[45] (Table 1). In contrast to other studies that propose face-to-face delivery, 1 registered ongoing trial plans for telerehabilitation.[49] These trials will measure back pain,[46] physical function,[45-49] and quality of life[46,49] as the outcomes of the proposed intervention (Table 1).

Role of equity factors in eligibility criteria

The number of PROGRESS-Plus factors contributing to eligibility criteria of completed, protocol, or registered ongoing trials ranged from 4[17,21,40,42-44,47-49] to 7[22,46] across trials (Tables 2 and 3). All completed trials excluded participants based on the PROGRESS factor place of residence (not registered in selected hospital/prosthetic center/clinic/amputee group, not a residence in trial catchment area) and Plus factors disability and time-dependent relationships (minimum age, maximum age, time using prosthesis, time since amputation) or age. One trial excluded potential participants based on sex.[39] Occupation and religion did not contribute to eligibility criteria for any of the included trials. Of the 8 completed trials, 5 reported the exclusion of 423 potential participants because of equity-related factors (65%).[21,22,39,41,43] The remaining 3 trials did not specify either the criteria for exclusion[39] or the criteria and number of potential participants excluded.[17,40]

Discussion

Main findings

Fourteen studies including 13 RCTs (8 completed trials, 2 protocols, and 3 registered ongoing trials) of exercise-based rehabilitation in the community or at home for adults after unilateral lower limb amputation (LLA) were identified. All participants included in the completed trials were prosthetic users with comparatively

Table 2 Contribution of PROGRESS-Plus equity factors to eligibility criteria in RCTs of exercise-based rehabilitation in the community and/or at home after TFA or TTA

	Exclusion Criteria		
	N	(%)	References
Total	13	(100)	
PROGRESS-Plus factors*			
Place of residence			
Not registered in selected hospital/prosthetic center/clinic/amputee support group	11	(84.6)	17,21,22,39-43,45–47
Outside trial catchment area	3	(23.1)	21,22,39
Race/ethnicity/language/culture			
Language barrier	1	(7.7)	22
Gender (Sex)			
Gender (Sex)	1	(7.7)	39
Education			
Low technology literacy	1	(7.7)	46
Inability to understand instructions/provide consent	2	(15.4)	17,22
Socioeconomic status			
No internet and communication technology at home	1	(7.7)	46
Social capital			
Use of rehabilitation services	6	(46.2)	22,40,43,45,46,49
Type of prosthesis	2	(15.4)	41,49
Plus: time dependent relationships			
Time since amputation	5	(38.5)	21,22,42,46,47
Time using prosthesis	9	(69.2)	22,39,41-43,45,46,48,49
Plus: age			
Minimum age	12	(92.3)	17,21,22,39-49
Maximum age	9	(69.2)	21,36-39,46-49
Plus: disability			
Disability (see Table 3 for details)			

* Occupation and religion did not contribute to eligibility criteria in any RCT of exercise-based rehabilitation in the community or home after transfemoral/transtibial amputation.

Table 3 Contribution of the Plus equity factors (disability) to eligibility criteria in RCTs of exercise-based rehabilitation in the community and/or at home after TFA or TTA

	Exclusion Criteria		
	N	(%)	References
Total	13	(100)	
Plus: Disability			
Patient-related			
Cognitive impairment	5	(38.5)	17,40,41,43,49
Using a walking aid/assistive device	4	(30.8)	39-41,46
Ill-fitting/ill-functioning prosthesis	4	(30.8)	22,42,45,47
Pregnancy	1	(7.7)	46
Mobility/functional impairment	8	(61.5)	17,21,41,43,45-47,49
Medical/surgical condition limiting exercise	7	(53.8)	22,41,45,46-49
Higher functional/mobility level	1	(7.7)	42
Higher balance confidence	1	(7.7)	45
Not a prosthetic user	11	(84.6)	21,22,39,41-43,45-49
Not completed traditional/conventional prosthetic training	2	(15.4)	42,48
Comorbidities			
Systemic disease	5	(38.5)	39-41,48,49
Radiating pain	1	(7.7)	39
Lumbar disk herniation	2	(15.4)	39,46
Inflammatory back pain	1	(7.7)	39
History of spinal surgery	2	(15.4)	39,46
Structural spinal deformities	1	(7.7)	39
Neuropathic pains except PLP	1	(7.7)	40
History of surgery due to pain	1	(7.7)	40
Chronic diseases	2	(15.4)	43,48
Uncontrolled asthma	1	(7.7)	43
Uncontrolled diabetes	1	(7.7)	43
High blood pressure	1	(7.7)	48
Severe osteoporosis	1	(7.7)	43
Severe pulmonary disease	1	(7.7)	42
Severe cardiac disease	1	(7.7)	42
Poorly controlled metabolic disease	1	(7.7)	42
Neurological disorders	6	(46.2)	41,42,46-49
Unstable heart condition	1	(7.7)	42
Acute back injury	1	(7.7)	46
Chronic back pathologies	1	(7.7)	46
History of neurodegenerative disease	1	(7.7)	46
History of stroke	1	(7.7)	46
Musculoskeletal conditions	3	(23.1)	42,48,49
Hearing, vision, and speech impairments	1	(7.7)	49
Not having low back pain	2	(15.4)	39,46
Not having PLP	1	(7.7)	39
Not having type II diabetes and/or PAD	1	(7.7)	21
Not satisfying a predefined outcome	7	(53.8)	41,42,45-49
Not sustained a fall/no risk of fall	1	(7.7)	43
Injury-related			
Trauma-related amputation	2	(15.4)	17,21
Cancer-related amputation	4	(30.8)	17,21,39,40
Vascular-related amputation	4	(30.8)	17,39,40,46
Bilateral amputation	13	(100)	17,21,22,39-43,45-49
Complications			
Nonhealing wounds	1	(7.7)	42
Open wounds on weight-bearing surfaces	1	(7.7)	46
Stump pain and/or edema	2	(15.4)	40,47
Cardiac complications	1	(7.7)	43

NOTE. PAD, peripheral arterial disease; PLP, phantom limb pain.

higher functional status. Interventions were comprehensive exercise programs with a few trials incorporating strategies such as cognitive behavioral therapy, education, or video gaming in addition to exercises. Evidence was inconclusive for an effect of these interventions on pain and quality of life. Two studies that employed pain as an outcome investigated 2 pain types (back pain[39] and phantom limb pain[40]) that are different in terms of underlying pathophysiology, clinical presentation, management, and outcomes. Of the 2 studies that reported positive effects on quality of life, baseline quality of life was higher in the intervention group compared to the control group in 1 study.[17] Studies that employed physical function as an outcome varied in terms of participant and intervention characteristics and outcome measures used, limiting the ability to draw conclusions on the intervention effect. Interventions that were tailored, supervised, of higher intensity, and not in the immediate postacute phase showed greater promise for improving specific physical function outcomes (endurance, physical activity level, balance, and gait speed). However, where an effect was noted, it was often by a sole RCT or 2 RCTs, and there was heterogeneity in interventions and outcomes, limiting the ability to determine optimal rehabilitation parameters. Moreover, where reported, 423 potential participants were excluded from trials because of equity-related factors (65%), the most frequent of which were age, place of residence, and disability.

Interpretation

Similar to the present review, 2 previous reviews reported beneficial effects of exercise interventions in improving gait parameters from low- to moderate-level evidence.[19,20] This is comparable with findings of the present review, which identified 2 RCTs (with methodological concerns) reporting beneficial effects of interventions on gait speed at intervention end[41] and 12-month follow-up[43] and 1 RCT that identified a beneficial effect of additional gait parameters at 12-month follow-up.[43] However, we also noted 1 RCT that reported no significant effect on gait speed.[21] Those that demonstrated a beneficial effect included supervised exercise programs with a higher proportion of functional tasks, and the RCT by Christiansen et al[21] included home-based unsupervised exercises with limited functional tasks. Given methodological concerns and the absence of longer follow-up, further high-quality research is required to confirm these findings.

Interventions that included higher intensity exercise components (eg, ergometry, squats, step-ups) more often saw a beneficial effect than lower intensity exercise interventions (eg, stump positioning, transfer techniques, stretching). This is consistent with the findings of a recent systematic review that reported a beneficial effect of more demanding functional exercises on gait speed compared to less demanding, structure-focused exercises.[19] This aligns with the overload principle of exercise training; for an organism to adapt, the biological system must be stressed above habitual levels.[50] Therefore, we suggest tailoring exercise prescription to baseline physical function in future trials. In contrast to the above evidence, 1 study included in the present review favored mirror therapy (which is less physically demanding compared to exercises) over phantom exercises for phantom limb pain and quality of life.[40] However, there was insufficient information to assess the methodological quality of this study, which reduced the validity of the results. Similarly, 2 previous systematic reviews found that there is a lack of high-quality evidence to support the positive effects of mirror therapy on outcomes after LLA.[51,52]

For the 2 RCTs that included participants in the acute stage (<6 months postoperative), no beneficial effects were noted on physical function (TUG test,[17,21] endurance,[21] and gait speed[21]). In contrast, RCTs that included participants with a longer history of amputation (at least 6 months) saw beneficial effects of their interventions on these outcomes (TUG test,[41] endurance,[22,42] and gait speed[41,43]). The difference in observed benefit may be due to differences in the quality of the underlying evidence; trials that included participants in the acute stage were of higher quality (low risk of bias across all domains except for blinding of participants and personnel).[17,21] Alternatively, differences may be due to the high level of disability often experienced in the acute stage after LLA, which decreases thereafter.[53,54] Moreover, the psychological effect of TFA and TTA may be greater in the early postoperative phase, which may inhibit engagement in an early postoperative exercise program.[55] Therefore, the optimal components of an intervention may vary depending on the timing of its delivery.

For the current review, 2 RCTs[17,21] focused exclusively on participants after vascular LLA noted a potential benefit of rehabilitation on walking activity and quality of life, and 2 RCTs[39,40] focused exclusively on participants after traumatic amputation noted a potential benefit of rehabilitation on back pain, phantom limb pain, flexibility, and quality of life. However, most of these potential benefits were observed by 1 trial, often with some methodological concerns, therefore requiring replication in future research. It was more common for RCTs to enroll participants after LLA irrespective of underlying mechanism (vascular or trauma; n=4[22,41-44]), with no subgroup analysis by said mechanisms. This is despite the known differences in potential outcomes among those with a vascular history compared to those with a traumatic history; that is, lower gait speed[56] and balance outcomes[57] among those with a vascular history compared to those with a traumatic history. Moreover, studies that included participants with TFA and TTA used similar intervention components and outcome measures for both groups and the data were analyzed together, again despite the known difference in functional levels between these 2 groups.[58,59] Therefore, to determine the influence of amputation mechanisms on outcomes of rehabilitation, these groups should be studied separately, or subgroup analysis be planned in future trial analysis plans a priori.

Where a beneficial effect of interventions was noted, there was limited evidence of preserved effectiveness because follow-up times were short (≤3 months) in most of the trials (n=6).[17,21,22,39,41,42] For the 2 trials that included longer term follow-up (6 months[40] and 12 months[43,44]), a retention of intervention effect was reported. Of the 2 trials, 1 favored mirror therapy over exercise and the other 1 favored exercise over usual care, which hinders the ability to make a conclusion. Reporting on follow-up effects is key for rehabilitation interventions based in the community where continuous follow-up is difficult.

We identified 39 different outcome measures across 13 RCTs. Two completed RCTs with a comparatively smaller number of participants (n=20[41] and n=38[21]) used 5 and 6 outcomes, respectively, to test the effect of the intervention, which might have resulted in false-positive results.[60] To minimize this effect, it is recommended that, when employing multiple outcomes, statistical level should be adjusted for each statistical test (used to find the effect of intervention on each outcome) and the sample size calculation should be performed for each outcome separately.[61,62] We also observed the effect of an intervention on physical activity when measurements with different outcome measures in the same

trial yielded different results.[22] This indicates the necessity for a core outcome set with recommendations for appropriate measures for each core outcome for trials after TFA or TTA. Ambler et al[63] are developing a core outcome set for trials involving patients undergoing major LLA for peripheral artery disease. This will be a beneficial step for future trials of rehabilitation interventions after TFA and TTA. There may be a need to consider additional outcomes that may be relevant to all-cause amputation and long-term recovery compared to outcomes relevant to amputations caused by peripheral artery disease and for short- and medium-term recovery.

All trials excluded potential participants based on 4 or more PROGRESS-Plus equity factors. The most common reasons for exclusion were place of residence, time-dependent relationships, and disability. We noted that most of these factors related to disabilities rather than social determinants. There were some notable exceptions. A few trials limited eligibility to men,[39] young and relatively healthy individuals,[39,40] and those within the study catchment area.[21] A further study included mainly participants of African-Caribbean ethnicity without any explanation of the lack of diversity.[42] The exclusion of potential participants from interventions based on these equity factors has several implications. First, it narrows inclusion criteria and reduces sample size, limiting the generalizability of the trial findings to the underlying population and clinical practice. Second, it denies access to additional care through intervention enrollment for those who may benefit. Finally, it may explain the high reported adherence rates (>80% in 6 of the 8 completed trials) because participants were often healthier, having unilateral (compared with bilateral) TTA (compared with TFA), established in their prosthesis use, and local to recruitment sites.

The population with LLA is a very heterogenous group (ie, cause, type, level of amputation, time since amputation, and functional level). Limiting RCT participation to larger population subgroups may be to provide some level of homogeneity and greater probability of determining effectiveness (with subsequent limited generalizability) or because of the safety profile of an intervention (eg, excluding participants with TFA and/or bilateral amputation from interventions targeting advanced balance training because of the high falling risk) and/or feasibility of intervention delivery (eg, excluding nonprosthesis users from interventions targeting walking training). These justifications do not necessarily imply inequity. However, populations that experience disadvantages in opportunities for care experience health inequities, and this is often reflected in poor health outcomes.[27] These interventions may contribute to relative discrimination whereby access is denied to additional rehabilitation for those with higher needs. Exclusion of these groups systematically leads to a dearth of evidence required to support health care funding for these individuals and creates challenges for decision makers who have to consider the effects of interventions among groups of people excluded from these trials.

Limitations

Although we searched several databases for published trials, excluding the Cochrane Central Register of Controlled Trials may have resulted in an underestimation of relevant studies for inclusion in the review. We limited our search of unpublished literature to 1 database and excluded trials not published in English, which may have led to publication bias. The exclusion of non-English-language studies may also have led to an underestimation of the extent to which inequities in access to interventions were captured by the current review. We included RCTs to enable determination of the cause and effect of rehabilitation interventions on outcomes. However, exclusion of observational studies may have limited the number of eligible studies for the review. We focused on exercise-based rehabilitation in the community or at home after unilateral LLA, and the findings are not generalizable to the nonexercise interventions, inpatient rehabilitation settings, or bilateral amputations. Finally, we focused on pain, physical function, and quality of life as outcomes of interest for this review. Future research may wish to evaluate other outcomes such as psychological well-being and prosthetic function/fit and the associated inpatient and outpatient services related to prosthetic fitting.

Conclusion

Policymakers and service planners require evidence of effectiveness to inform future funding and structure of services. However, there was inconclusive evidence for an effect of community- and home-based rehabilitation interventions that incorporate exercise on pain and quality of life after TFA and TTA. These interventions have the potential to support recovery of specific physical function measures depending on the intensity, time of delivery, and whether they are supervised or unsupervised, which needs to be confirmed with future high-quality trials. In addition, potential participants were excluded based on equity factors, limiting the generalizability of interventions to the underlying population. Future research should determine the effectiveness of these interventions among a representative sample of participants in different health care contexts.

Supplier

a. Covidence; Veritas Health Innovation Ltd, Melbourne, Australia.

Keywords

Amputation; Community; Exercise; Lower extremity; Rehabilitation; Quality of life

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