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Effectiveness and equity in community-based rehabilitation on pain, physical function, and quality of life following unilateral lower limb amputation: A systematic review

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Running head: Community-based amputation rehabilitation

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ABSTRACT

Objectives: To synthesise evidence for 1) the effectiveness of exercise-based rehabilitation interventions in the community and/or at home following transfemoral (TFA) and transtibial (TTA) 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, PsycINFOOpenGrey, and ClinicalTrials.gov were systematically searched from inception to August 12th 2021, for published, unpublished, and registered ongoing randomized controlled trials (RCTs).

Study Selection: Three review authors completed screening and quality appraisal in Covidence using the Cochrane Risk of Bias Tool. Included were RCTs of exercise-based rehabilitation interventions based in the community or at home for adults with TFA or TTA, which assessed effectiveness on pain, physical function, or quality of life.

Data Extraction: Effectiveness data were extracted to templates defined a priori and 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 behavioural 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 (65%) of potential participants were inequitably excluded from identified trials limiting the generalizability of interventions to the underlying population.

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

KEYWORDS

Amputation, Lower extremity, Community-based rehabilitation, Exercise, Inequity

Systematic Review Registration Number: PROSPERO - CRD42020171140

List of abbreviations

PRISMA Preferred Reporting Items for Systematic Review and Meta-analysis

RCTs Randomized Controlled Trials

TFA Transfemoral

TTA Transtibial

TUG Timed-Up-and-Go

Transfemoral (TFA) and transtibial (TTA) amputation are life-changing events with substantial associated disability and give rise to numerous long-term secondary complications [1–3]. For adults following 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 life [10–12]. Therefore, rehabilitation following 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.

There is reported high adherence rates for randomized controlled trials (RCTs) of rehabilitation interventions for adults following TFA or TTA [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 programmes offered by the clinics 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 who are less likely to adhere to rehabilitation following TFA or TTA and who 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]. Healthcare services are commissioned based on evidence of clinical efficacy and cost effectiveness, often from randomised controlled trials 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 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 following 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 reported the review in adherence to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement [30] and the Equity extension to the PRISMA statement [31, 32].

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 which contained at least one physical exercise component of any frequency, intensity, type, or timing, performed individually or in a group, and in any mode e.g., face-to-face or remote. We included RCTs which selected pain, physical function, and/or quality of life as an outcome of interest. We excluded studies which were not RCTs, non-English language RCTs, those of inpatient rehabilitation, paediatric population, and 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 (e.g., active, passive, wait-list), geographical 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). We searched the electronic databases Embase, MEDLINE, PEDro, Cinahl, Global Health, and PsycINFO for published trials, Open Grey for unpublished trials, and ClinicalTrials.gov for registered ongoing trials from inception to the 12th August 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 (CENTRAL).

Selection

We imported citations into Covidence for the removal of duplicates and screening [36]. Three review authors (KS, AW, KC) independently screened titles, abstracts, and full texts to determine trial eligibility against pre-defined criteria. Conflicts were resolved by consensus (KS, AW, KC).

Data extraction

One author (AW) extracted data onto a pre-defined template comprised of author, year, location, study design, sample size, eligibility criteria, baseline characteristics, cause, type, and time since amputation, intervention, setting, control, outcomes, intervention effect (intergroup), follow-up, and equity factors in eligibility criteria. Data from protocols and registered ongoing trials was 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, 37]. PROGRESS is an acronym for Place of residence, Race/ethnicity/language/culture, Occupation, Gender (sex), Religion, Education, Socioeconomic status and Social Capital [31, 37]. PLUS captures other factors which impact equity namely age, disability and, time-dependent relationships [31, 37]. 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's recommended tool for RCTs – the Cochrane Risk of Bias Tool [38] which considered 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 reported 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 reported results using a narrative review approach [39]. We summarized 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, 40–45], 2 protocols [46, 47], 3 registered ongoing trials [48–50]). Two studies reported different outcomes for the same trial [44, 45].

Completed trial characteristics

All completed trials included in the review were published after 2015. These trials were performed in 5 countries: Turkey (n=3) [40–42], USA (n=2) [21, 43], South Africa (n=1) [17], Canada (n=1) [22], and UK (n=1) [44, 45]. Most participants were male (n=256, 73%), following amputation due to vascular disease (n=223, 63.5%), trauma (n=116, 33.0%), tumour (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 (25.9%) participants and less than 6 months for 192 (54.7%) participants.

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, 42–45] (Figure 2). There was insufficient information to assess allocation concealment for five

trials [40–45]. Lack of blinding of personnel and participants was the only reason for high bias assignment for six trials [17, 21, 40, 42–45]. The RCT by Anaforoglu et al 2016 was assigned high risk of bias for lack of blinding of personnel and participants as well as lack of blinding of outcome assessors [40]. The RCT by Anaforoglu et al 2019 was not assigned high bias for any domain, however there was insufficient information to assess four of six domains of bias in this RCT [41].

Completed trial intervention characteristics

Interventions comprised stretching and strengthening of lower limb and/or trunk muscles [17, 21, 22, 40, 43], cycle ergometery [43–45], aerobic exercises [22, 43–45], balance and gait training [17, 22, 42–45], Cognitive Behavioural Therapy [21]. The frequency of rehabilitation interventions ranged from daily [41] to once a week [21]. The length of the interventions ranged from 2 weeks [40] to 12 weeks [17, 21, 44, 45]. Session duration (where specified) ranged from 15 minutes [41] to 60 minutes [40, 42, 43]. Mode of intervention delivery was face to face in all the trials. Where reported, methods used to encourage participant adherence during the intervention and follow-up included consultations via telephone [17, 22, 41], in-person at weekly meetings [21], or were under direct supervision by a physiotherapist [42–45]. Dropout rates of participants during the follow-up period of completed trials ranged from 0% [40, 41] to 33% [43] with adverse events/complications reported in four trials (all were attributed to pre-existing medical conditions) [17, 22, 43, 44].

Five trials compared the intervention to active controls (dual task vs single task [42], health education programme [40], cognitive games [22], attention control [21], and mirror therapy [41]), and 3 trials compared the intervention to passive controls (usual care [17, 44, 45]), and waitlist control [43]. Follow-up evaluation of the intervention was reported in 6 out of the 8

trials and ranged from 3 weeks [22] to 12 months [44, 45]. Further details may be found in Table 1.

Pain

Two trials employed pain (back pain [40], phantom limb pain [41], and back pain-related disability [40]) as an outcome. Of the 2 trials, one reported an improvement in back pain and related disability following a 2-week supervised exercise programme and education compared with education alone at 1-month and 3-month follow-up ($p<0.05$) [40]. The other trial favoured mirror therapy compared to exercises in reducing phantom limb pain at 1-month, 3-month, and 6-month follow-up ($p<0.001$) [41] (Table 1).

Physical function

Seven trials assessed the effectiveness of exercise-based rehabilitation in the community or home on physical function. We reported 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 [43] and 2-minute walk test [22]) following 1) an 8-week evidence-based amputation rehabilitation exercise intervention compared to waitlist control at intervention end ($p<0.05$) [43] and 2) a 4-week Wii Fit balance board intervention compared to a seated cognition improving programme (cognitive games) at intervention end and 3-week follow-up ($p<0.05$) [22]. In contrast, no effect on endurance (2-minute walk test) was observed following a 3-month behaviour change intervention comprised of cognitive behavioural therapy and home-based exercises compared to an attention control at intervention end and 12-week follow-up ($p>0.05$) [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]) following 1) a 3-month behaviour change intervention comprised of cognitive behavioural therapy and home-based exercises compared to an attention control at intervention end and 12-week follow-up ($p<0.05$) [21] and 2) a 4-week Wii Fit balance board intervention compared to a seated cognitive game at ($p<0.05$) [22]. However, the latter trial also reported no change in physical activity level when measured by Physical Activity Scale for Elderly ($p>0.05$).

Gait parameters

Two trials reported a beneficial effect of the intervention on gait speed following 1) a 4-week dual-task balance training intervention compared to single-task balance training at intervention end ($p<0.05$) [42], and 2) a 12-week supervised and personalized exercise programme compared to usual care control at 12-month follow-up ($p<0.05$) [44]. In contrast Christiansen et al. [21] reported no change in gait speed following a 3-month behaviour change intervention comprised of cognitive behavioural therapy and home-based exercises compared to an attention control at intervention end and 12-week follow-up ($p>0.05$).

Schafer et al. (2018) [44] 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 following their 12-week supervised and personalized exercise programme 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 two trials reported no effect. A beneficial effect was observed following 1) an 8-week evidence-based

amputation rehabilitation exercise intervention compared to waitlist control at intervention end ($p<0.05$, Amputee Mobility Predictor with and without prosthesis) [43] and 2) a 3-month education and exercise intervention compared to usual care at intervention end ($p<0.05$, Locomotor Capability Index) [17]. No effect was observed following 1) a 3-month behaviour change intervention comprised of cognitive behavioural therapy and home-based exercises compared to an attention control at intervention end and 12-week follow-up ($p>0.05$, 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 ($p>0.05$, 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]) following 1) a 3-month behaviour change intervention comprised of cognitive behavioural therapy and home-based exercises compared to an attention control at intervention end and 12-week follow-up ($p>0.05$) [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 ($p>0.05$) [22], and 3) a 3-month education and exercise intervention compared to usual care at intervention end and 3-month follow-up ($p>0.05$) [17]. In contrast Demirdel et al. [42] reported a beneficial effect of the intervention on lower extremity functioning (TUG test) under cognitive dual task following a 4-week dual-task balance training intervention compared to single-task balance training at intervention end ($p<0.05$).

Falls and Balance

Two trials reported a beneficial effect on balance outcomes. Schafer et al. (2018 & 2021) [44, 45] reported a reduction in falls incidence [44] and improvement in postural control

(equilibrium, strategy score, and vestibular ratio) [45] following a 12-week supervised and personalized exercise programme compared to usual care control at 12-month follow-up ($p<0.05$). Demirdel et al. [42] reported improvement in static and dynamic balance (one-leg stance time and four-square step test, respectively) under cognitive and/or motor dual tasks following a 4-week dual-task balance training intervention compared to single-task balance training at intervention end ($p<0.05$). 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. (2021) [45] ($p>0.05$). This is in keeping with findings from Imam et al. [22] where no effect on balance confidence (Activity-specific Balance Confidence scale) was reported following a 4-week Wii Fit balance board intervention compared to a seated cognitive game at intervention end and 3-week follow-up ($p>0.05$).

Other measures of physical function

Improved flexibility was observed (change in distance between two anatomical reference points before and after the movement) following a 2-week supervised exercise programme and education compared with education alone at 1-month (trunk lateral flexion to right, $p<0.05$) and 3-month (trunk flexion, lateral flexion to right, and rotation to right, $p<0.05$) follow-up [40]. Activities of daily living (Barthel index) was not improved following 3-month education and exercise intervention compared to usual care at intervention end and 3-month follow-up ($p>0.05$) [17].

Quality of life

Quality of life was employed as an outcome in 2 trials [17, 41]. One trial reported improvement in quality of life following a 3-month education and exercise intervention compared with usual care at intervention end ($p<0.05$) but not at 3-month follow-up ($p>0.05$)

[17]. The other trial favoured mirror therapy compared to exercises in improving quality of life of adults with TTA suffering from phantom limb pain ($p<0.05$) [41] (Table 1).

Protocols and registered ongoing trials

Two protocols [46, 47] and 3 registered ongoing trials [48–50] were included. Proposed interventions of these trials include strengthening exercises [47–50], cycle ergometry [49], aerobic exercises [49], and virtual reality games [46] (Table 1). In contrast to other studies which propose face-to-face delivery, one registered ongoing trial plans for telerehabilitation [50]. These trials will measure back pain [47], physical function [46–50], and quality of life [47, 50] 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, 41, 43–45, 48–50] to 7 [22, 47] across trials (Table 2 and 3). All the completed trials excluded participants based on the PROGRESS factor - place of residence (not registered in selected hospital/prosthetic centre/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 gender (sex) [40]. 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 (65%) potential participants due to equity related factors [21, 22, 40, 42, 44]. The remaining 3 trials did not specify either the criteria for exclusions [40] or the number and criteria of potential participants excluded [17, 41].

DISCUSSION

Main findings

Fourteen studies for 13 RCTs (8 completed trials, 2 protocols, and 3 registered ongoing trials) of exercise-based rehabilitation in the community or at home for adults following unilateral LLA were identified. All the participants included in the completed trials were prosthetic users with comparatively higher functional status. Interventions comprised mostly of comprehensive exercise programs with a few trials incorporating strategies such as cognitive behavioural 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 two pain types (back pain [40] and phantom limb pain [41]) which are different in terms of underlying pathophysiology, clinical presentation, management, and outcomes. Of the two 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 one 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 which were tailored, supervised, of higher intensity, and not in the immediate post-acute 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 two RCTs, and there was heterogeneity in interventions and outcomes limiting the ability to determine optimal rehabilitation parameters. Moreover, where reported, 423 (65%) potential participants were excluded from trials due to equity related factors the most frequent of which were age, place of residence and disability.

Interpretation

Similar to the present review, two 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 two RCTs (with methodological concerns) reporting beneficial effect of interventions on gait speed at intervention end [42] and 12-month follow up [44], and one RCT which identified a beneficial effect of additional gait parameters at 12-month follow-up [44]. However, we also noted one RCT reporting no significant effect on gait speed [21]. Those which demonstrated a beneficial effect included supervised exercise programmes with higher proportion of functional tasks while 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 which included higher intensity exercise components (e.g. ergometry, squats, step-ups) more often saw a beneficial effect than lower intensity exercise interventions (e.g. stump positioning, transfer techniques, stretching). This is consistent with the findings of a recent systematic review which 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 [51]. Therefore, we suggest tailoring exercise prescription to baseline physical function in future trials. In contrast to the above evidence, one study included in the present review favoured mirror therapy (which is less physically demanding compared to exercises) over phantom exercises for phantom limb pain and quality of life [41]. However, there was insufficient information to assess the methodological quality of this study, which reduced the validity of the results. Similarly, two previous systematic reviews found that there is a lack of high quality evidence to support the positive effects of mirror therapy on outcomes following LLA [52, 53].

For the two RCTs which 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 which included participants with a long-standing history of amputation (at least 6 months) saw beneficial effects of their interventions on these outcomes (TUG test [42], endurance [22, 43], and gait speed [42, 44]). The difference in observed benefit may be due to differences in the quality of the underlying evidence, indeed those trials which 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 lower limb amputation, which reduces thereafter [54, 55]. Moreover, the psychological impact of TFA and TTA may be greater in the early postoperative phase which may inhibit engagement in an early postoperative exercise programme [56]. Therefore, the optimal components of an intervention may vary depending on the timing of its delivery."

For the current review, two RCTs [17, 21] focused exclusively on participants following vascular LLA noting a potential benefit of rehabilitation on walking activity and quality of life, while two RCTs [40, 41] focused exclusively on participants following traumatic amputation noting 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 one trial, often with some methodological concerns therefore requiring replication by future research. It was more common for RCTs to enrol participants after LLA irrespective of underlying mechanism – vascular or trauma (n = 4) [22, 42–45], 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: lower gait speed [57] and balance outcomes [58] 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 was analysed together. This is again despite the known difference in functional levels between

these two groups [59, 60]. 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 as follow-up times were short (≤ 3 months) in most of the trials (n = 6) [17, 21, 22, 40, 42, 43]. For the two trials which included longer term follow-up (6-months [41] and 12-months [44, 45]) retention of intervention effect was reported. Of the two trials, one favoured mirror therapy over exercise and the other one exercise over usual care which hinders the ability to build a conclusion. Reporting on follow-up effect 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 [42] and n = 38 [21]) used five and six outcomes, respectively, to test the effect of the intervention, which might have resulted in false positive results [61]. 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 [62, 63]. We also observed the effect of an intervention on physical activity when measured 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 following TFA or TTA. Ambler et al. [64] are developing a core outcome set for trials involving patients undergoing major lower limb amputation 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 as compared to those following peripheral artery disease and for the short- and medium-term recovery.

All the trials excluded potential participants based on four 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 [40], young and relatively healthy individuals [40, 41], 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 [43]. 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 enrolment for those who may benefit. Finally, it may explain the high reported adherence rates (> 80% in 6 of the 8 completed trials) as 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 (i.e. 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 generalisability), due to the safety profile of an intervention (e.g. excluding participants with TFA and/or bilateral amputation from interventions targeting advanced balance training due to the high falling risk), and/or feasibility of intervention delivery (e.g. excluding non-prosthesis 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 healthcare funding for these individuals and creates challenges for decision-makers who have to consider the effects of interventions among groups of people excluded in these trials.

Limitations

Although we searched several databases for published trials, excluding Cochrane Central Register of Controlled Trials (CENTRAL) may have resulted in an underestimation of relevant studies for including in the review. We limited our search of unpublished literature to one 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 following unilateral lower limb amputation and the findings are not generalizable to the non-exercise interventions, inpatient rehabilitation setting, 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 in-patient and out-patient 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 which incorporate exercise on pain and quality of life following 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 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 healthcare contexts.

Supplementary data: Details on search strategies can be found in the supplementary file A.

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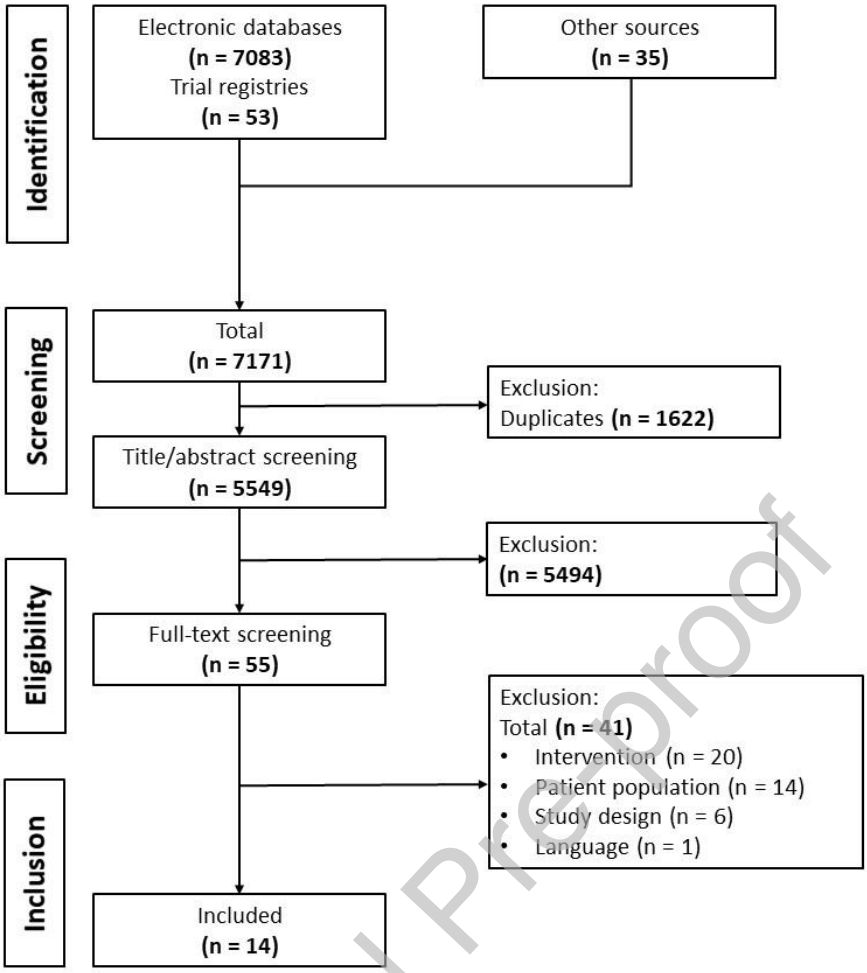

Figure 1: PRISMA flowchart of study selection

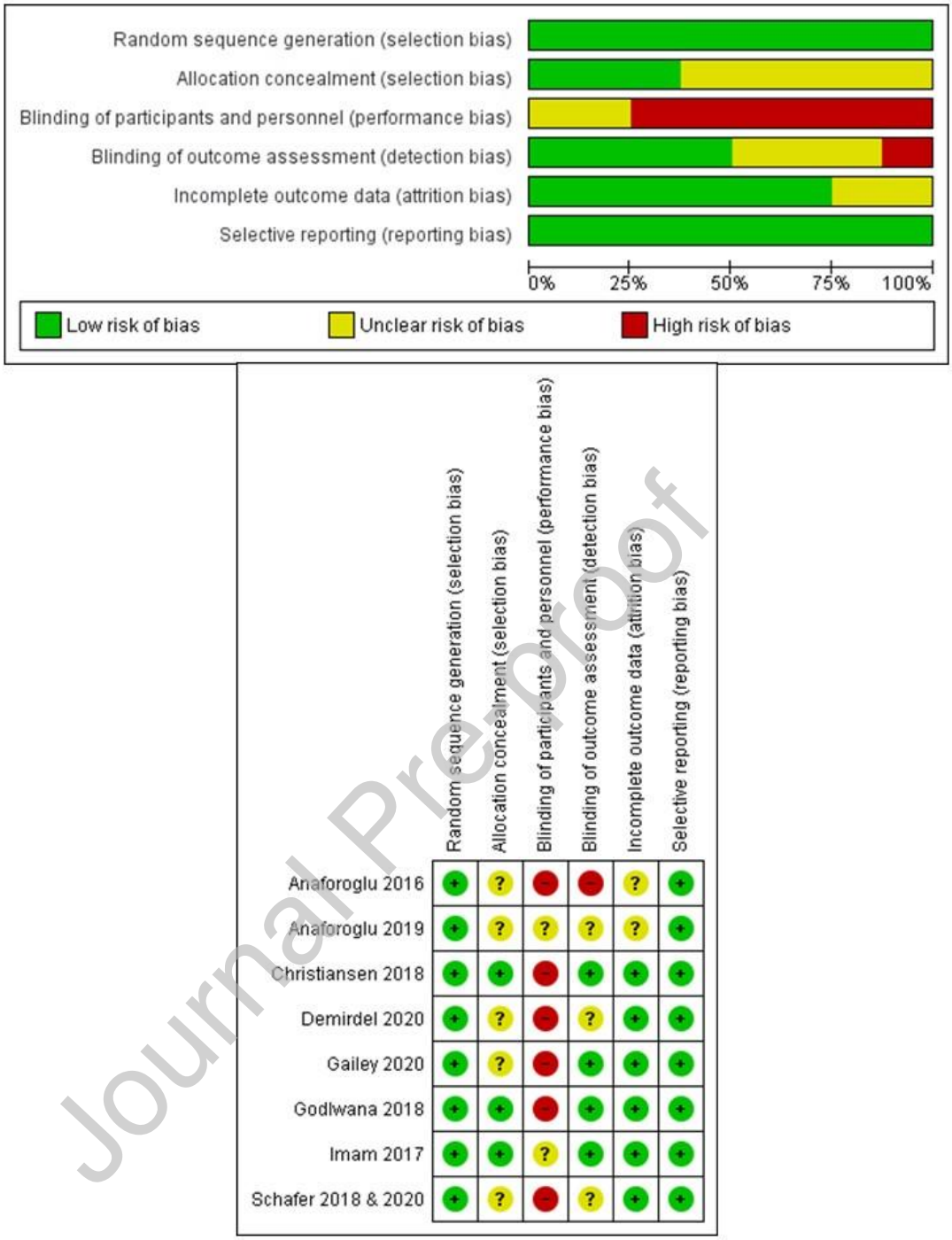

Figure 2: Risk of bias

Table 1: Effectiveness of exercise-based rehabilitation in the community and/or at home on pain. physical function, and quality of life following transfemoral/transtibial amputation.

Author and year / Identifier	**Location**	**Sample size**	**Population**	**Intervention**	**Control**	**Outcomes**	**Effect**
Completed trials							
Anaforoglu 2016 [40]	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 (1h/day, 5days/week) supervised back health education (anatomy, biomechanics, spinal ergonomics) and exercise (ergonomics during activities, strengthening, stretching, spinal stabilization, dynamic stump) programme.	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 ($p<0.05$). No intergroup change in trunk flexion, extension, lateral flexion to left, rotation ($p>0.05$).

							3-month follow-up: VAS, ODI scores, and trunk flexion, lateral flexion to right and rotation to right improved for intervention vs. control ($p<0.05$). No intergroup change in extension, flexion to left, and rotation to left ($p>0.05$).
Anaforoglu 2019 [41]	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	†Phantom Exercises (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	Mirror Therapy (MT).	**Pain** - PLP (VAS) **Quality of life** - SF-36	**IAI:** VAS and SF-36 scores improved for MT group vs. PE group ($p<0.05$). **3-month follow-up:** VAS and SF-36 scores

			average intensity of at least 40 on VAS).	relaxation/PLP disappeared (whichever is earlier) I1 session daily for 4 weeks).			improved for MT group vs. PE group ($p<0.05$). **6-month follow-up:** VAS and SF-36 scores improved for MT group vs. PE group ($p<0.05$).
Christiansen 2018 [21]	USA	38	Male (n=35) and female (n=3) age 62 (59, 65) (intervention) and 65 (60, 71) (control) unilateral TTA < six months with type II DM and/or PAD, household ambulators (or better), prosthetic users, living within 45 min of a	3-month behaviour-change intervention (30-minute weekly sessions), based on Social Cognitive and Control Theories of behaviour 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-	**IAI:** Daily step count increased for intervention vs. control ($p<0.05$). No intergroup change in other outcomes ($p>0.05$). **12-week follow-up:** Time spent in sedentary activity

			participating clinic.			MWT) - Ability to perform functional tasks (PEQ-MS)	decreased for intervention vs. control ($p<0.05$). No intergroup change in other outcomes ($p>0.05$).
Demirdel 2020 [42]	Turkey	20	Male (n=14) and female (n=6) age 18 - 65 years, unilateral TFA, prosthesis > 1 year, able to walk 10m 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 minutes 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 ($p<0.05$). No intergroup change in any of the outcomes under single task ($p>0.05$). **No follow-up**

Gailey 2020 [43]	USA	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 post-amputation rehabilitation and prosthetic training.	8-week EBAR program (60 minutes, 3 times/week) 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 6MWT distance improved for intervention vs. control ($p<0.05$). **No follow-up**
Godlwana 2018 [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), 1st time major unilateral lower limb	Usual care + Home education and exercise programme for 3 months which includes stump positioning, safe transfer techniques, stretching and strengthening exercises, and balance re-education.	Usual care	**Physical function** - Functional independence (Barthel Index) - Basic mobility (TUG test)	**IAI:** Modified LCI-5 and Euroqol-5D improved for intervention vs. control ($p<0.05$). No intergroup change in other outcomes

			amputees			- Ability to perform locomotor activities (Modified LCI-5) **Quality of life** - Euroqol-5D	(p>0.05). **3-month follow-up:** No intergroup change in any of the outcomes (p>0.05).
Imam 2017 [22]	Canada	28	Male (n=18) and female (n=10) age ≥ 50 years, unilateral TTA or TFA ≥ 1 year, prosthesis ≥ 2 hours/day for past 6 months, not participating in formal exercise/training programmes.	4-week Wii.n.Walk programme (40 minutes, 3 times/week) 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	**IAI:** 2-MWT distance and daily step count increased for intervention vs. control (p<0.05). No intergroup change in other outcomes (p>0.05). **3-week follow-up:** 2-MWT distance and daily step count

						scale) - Daily step count (activity monitor) - Ability to perform locomotor activities (LCI-5)	increased for intervention vs. control ($p<0.05$). No intergroup change in other outcomes ($p>0.05$).
Schafer 2018 [44] **Schafer 2020 [45]**	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	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)	**12-month follow-up:** Number of falls reduced and strategy score, equilibrium score, and vestibular ratio improved for intervention vs. control ($p<0.05$). Increased walking speed, cadence (intact limb), terminal stance

	deemed at risk of falling	- 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)	peak hip extension angle (bilaterally), ankle plantarflexion in pre-swing (intact limb), concentric powers at the hip (bilaterally), eccentric powers at the hip (affected limb), ankle joint power (intact limb), peak vertical GRF in pre-swing (intact limb), peak propulsive GRF during push-off (affected limb), and decreased peak hip flexion angle in pre-swing (affected limb),

							power absorption and generation (intact and affected hip joint, and intact ankle joint) for intervention vs. control ($p<0.05$). No intergroup change in step length, stance, double support durations, somatosensory ratio, visual sensory ratio, latency scores, and ABC scale ($p>0.05$).
Protocols and registered ongoing trials							
Bourque 2019 [46]	USA	60	Male and female age ≥ 18 years, unilateral TTA, prosthesis ≥ 6 months,	8-week (1.5h/session, 1 session/week) training sessions with a virtual reality active gaming component (i.e., PT	Sham control	**Physical function** - Functional ability	Protocol

			balance confidence (ABC scale) < 80.	component), and CBT strategies.		(BBS and L-test) - Balance confidence (ABC scale) - Community integration (Activity monitor and FAI) **Quality of life** - SF-36 - PEQ	
Wasser 2017 [47]	USA	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	12-week exercise programme 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 (1st phase -	Waitlist control	**Pain** Back pain severity (NPS) **Physical function**	Protocol

			episodes per week), having regular access to a computer for Skype®, or a mobile phone or iPAD, prosthesis K-level of K2 or greater.	2 days/week, other 5 phases - 3 days/week)		- 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** - Impact of pain on QoL (pain medications used,SF-36, ODI, RMDQ	
NCT04114175 [48]	Turkey	22	Male and female, age 18 – 65 years, unilateral	Usual care + Spinal (core) stabilization exercises for 8 weeks	Usual care	**Physical function** - Energy	Registered ongoing trial

			TTA ≥ 6 months, prosthetic users, quadriceps and hamstring strength of the residual limb (Lovett's manual muscle test) ≥ 4			expenditure and exercise capacity (6-minute step test) - Fatigue (Modified Borg scale) - Strength of deep spinal muscles (Stabilizer) - Mobility (PEQ)	
NCT04165434 [49]	Brazil	26	Male and female age 18 - 50 years, unilateral TTA, prosthesis > 3 months, discharge of the rehabilitation programme	8-week 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	Registered ongoing trial

						Test) - Muscular Strength (Isokinetic Dynamometry) - Cardiopulmonary Capacity (VO2max) - Dynamic and static balance (Balance Master System version 8.1 - Dual force platform system)	
NCT04968691 [50]	Turkey	40	Male and female age 30 - 60 years, unilateral TTA, using active vacuum system	A structured exercise program supported by telerehabilitation (online supervision through mobile telecommunication applications and videos) 3 days per week	Sham control	**Physical function** - Mobility (TUG test) - Leg strength and	Registered ongoing trial

	prosthesis and carbon foot > 1 year, mobility level K2-K3, Montreal Cognitive Assessment Score ≥ 21	for 6 weeks + home exercise programme for remaining days of the week.	endurance (Sit-to-stand test) - Balance confidence (ABC scale) **Quality of life** - TAPES

1-RM = 1 - repletion 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 confidence; AMPPro/AMPnopro = amputee mobility predictor with prosthesis/without prosthesis; BBS = berg balance scale; CBT = cognitive behavioural therapy DM = diabetes mellitus; EBAR = evidence-based amputee rehabilitation; FAI = Frenchay activity index; FSST = Four 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 = One 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; TFA = transfemoral amputation; TTA = transtibial amputation; TUG = timed-up-and-go; VAS = visual analogue scale

†superiority trial

Table 2: Contribution of PROGRESS-Plus equity factors to eligibility criteria in randomized controlled trials of exercise-based rehabilitation in the community and/or at home after transfemoral/transtibial amputation.

	Exclusion criteria		
	N	(%)	References
Total	13	(100)	
PROGRESS-Plus factors*			
Place of residence			
Not registered in selected hospital/prosthetic centre/clinic/amputee support group	11	(84.6)	[17, 21, 22, 40-44, 46-48]
outside trial catchment area	3	(23.1)	[21, 22, 40]
Race/Ethnicity/Language/Culture			
Language barrier	1	(7.7)	[22]
Gender			
Gender	1	(7.7)	[40]

Education			
low technology literacy	1	(7.7)	[47]
inability to understand instructions/provide consent	2	(15.4)	[17, 22]
Socioeconomic status			
No internet and communication technology at home	1	(7.7)	[47]
Social capital			
use of rehabilitation services	6	(46.2)	[22, 41, 44, 46, 47, 50]
type of prosthesis	2	(15.4)	[42, 50]
Plus: time dependent relationships			
time since amputation	5	(38.5)	[21, 22, 43, 47, 48]
time using prosthesis	9	(69.2)	[22, 40, 42, 43, 44, 46, 47, 49, 50]
Plus: age			

minimum age	12	(92.3)	[17, 21, 22, 40-50]
maximum age	9	(69.2)	[21, 37-40, 47-50]
Plus: disability			
Disability (See Table 3 for details)			

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

	Exclusion criteria		
	N	(%)	References
Total	13	(100)	
Plus: Disability			
Patient-related			
Cognitive impairment	5	(38.5)	[41, 42, 44, 50]
Using a walking aid/assistive device	4	(30.8)	[40-42, 47]
Ill-fitting/ill-functioning prosthesis	4	(30.8)	[22, 43, 46, 48]
Pregnancy	1	(7.7)	[47]

Mobility/functional impairment	8	(61.5)	[17, 21, 42, 44, 46-48, 50]
Medical/surgical condition limiting exercise	7	(53.8)	[22, 42, 46, 47-50]
Higher functional/mobility level	1	(7.7)	[43]
Higher balance confidence	1	(7.7)	[46]
Not a prosthetic user	11	(84.6)	[21, 22, 40, 42-44, 46-50]
Not completed traditional/conventional prosthetic training	2	(15.4)	[43, 49]
Comorbidities			
Systemic disease	5	(38.5)	[40-42, 49, 50]
Radiating pain	1	(7.7)	[40]
Lumbar disc herniation	2	(15.4)	[40, 47]
Inflammatory back pain	1	(7.7)	[40]
History of spinal surgery	2	(15.4)	[40, 47]

Structural spinal deformities	1	(7.7)	[40]
Neuropathic pains except PLP	1	(7.7)	[41]
History of surgery due to pain	1	(7.7)	[41]
Chronic diseases	2	(15.4)	[44, 49]
Uncontrolled asthma	1	(7.7)	[44]
Uncontrolled diabetes	1	(7.7)	[44]
High blood pressure	1	(7.7)	[49]
Severe osteoporosis	1	(7.7)	[44]
Severe pulmonary disease	1	(7.7)	[43]
Severe cardiac disease	1	(7.7)	[43]
Poorly controlled metabolic disease	1	(7.7)	[43]
Neurological disorders	6	(46.2)	[42, 43, 47-50]

Unstable heart condition	1	(7.7)	[43]
Acute back injury	1	(7.7)	[47]
Chronic back pathologies	1	(7.7)	[47]
History of neurodegenerative disease	1	(7.7)	[47]
History of stroke	1	(7.7)	[47]
Musculoskeletal conditions	3	(23.1)	[43, 49, 50]
Hearing, vision, & speech impairments	1	(7.7)	[50]
Not having low back pain	2	(15.4)	[40, 47]
Not having PLP	1	(7.7)	[40]
Not having type II diabetes and/or PAD	1	(7.7)	[21]
Not satisfying a pre-defined outcome	7	(53.8)	[42, 43, 46-50]
Not sustained a fall/no risk of fall	1	(7.7)	[44]

Injury-related			
Trauma-related amputation	2	(15.4)	[17, 21]
Cancer-related amputation	4	(30.8)	[17, 21, 40, 41]
Vascular-related amputation	4	(30.8)	[17, 40, 41, 47]
Bilateral amputation	13	(100)	[17, 21, 22, 40-44, 46-50]
Complications			
Non-healing wounds	1	(7.7)	[43]
Open wounds on weight bearing surfaces	1	(7.7)	[47]
Stump pain and/or oedema	2	(15.4)	[41, 48]
Cardiac complications	1	(7.7)	[44]

PAD = peripheral arterial disease; PLP = phantom limb pain