# Systematic review and meta-analysis of exercise therapy for venous leg ulcer healing and recurrence

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## ABSTRACT

**Objective:** National guidelines in the United Kingdom have recommended regular exercise for individuals with venous leg ulceration. However, data on the effects of exercise on ulcer healing and recurrence are sparse. In the present study, we aimed to quantify the evidence for exercise regarding venous ulcer healing with respect to the primary outcomes of the proportion of healed ulcers and rate of ulcer recurrence. The secondary outcomes were improvement in ulcer symptoms, ulcer healing time, quality of life, compliance, and adverse events reported.

**Methods:** The review followed PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines using a registered protocol (CRD42021220925). The MEDLINE and Embase databases and Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, European Union Clinical Trials, and International Standard Randomised Controlled Trial Number registries were searched up to April 6, 2022 and included studies comparing exercise therapy and compression vs compression alone. Data for the proportion of healed ulcers were pooled using a fixed effects meta-analysis.

**Results:** After screening 1046 reports, 7 were included, with 121 participants allocated to exercise therapy and 125 to compression alone. All the reports were of randomized controlled trials and had reported ulcer healing at 12 weeks, with a pooled relative risk of ulcer healing of 1.38 for exercise vs compression (95% confidence interval, 1.11-1.71). Only one study had reported on recurrence; thus, data pooling was not performed. No differences between exercise and usual care were demonstrated. Compliance with exercise ranged from 33% to 81%. The included studies demonstrated low enrollment and a high risk of bias. Also, most of the trials had failed to demonstrate any differences in activity completed between the intervention and control arms.

**Conclusions:** A paucity of studies has examined leg ulcer recurrence after exercise programs, with no evidence to show that exercise is beneficial. Furthermore, the quality of evidence supporting exercise as an adjunct to ulcer healing is very low, and the trials demonstrated serious methodologic flaws, chiefly in recording the activity undertaken by the participants in the intervention arm. Future randomized controlled trials should implement activity monitoring and standardize the reporting of key patient, ulcer, and reflux characteristics to enable future meaningful meta-analyses to determine the role of exercise as an adjunct to venous leg ulceration healing. (J Vasc Surg Venous Lymphat Disord 2023;11:219-26.)

**Keywords:** Exercise; Ulcer healing; Ulcer recurrence; Venous leg ulceration

Venous leg ulceration (VLU) has been defined as an epithelial defect in the lower limb that will not heal within 2 weeks because of an underlying venous etiology.[1] VLU accounts for 60% to 80% of all leg ulcers, with an estimated global prevalence of 0.42% for active ulcers and 1% for healed ulcers.[2,3] Such ulcers also result in a serious economic burden, with 4.6 million practice nurse visits and 2.1 million district nurse visits, costing £941 million per annum in the United Kingdom.[4]

The treatment of VLU requires endovenous ablation of superficial venous reflux, combined with compression therapy using stockings, inelastic garments, or multilayer bandaging. The use of compression therapy will not cure the underlying venous disease but can improve symptoms via the following mechanisms: facilitation of the unidirectional flow of blood, improvement in calf muscle pump function, reduction of proinflammatory cytokines, and an increase in limb tissue oxygenation.[5-10]

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However, compression therapy has often been prescribed in the community clinic setting without a proper ankle brachial pressure index assessment, compliance will often be poor, and the therapy has been ineffective for approximately one third of compliant patients.[4,10] Even with ablation of superficial venous reflux and adequate compression therapy, a proportion of patients will continue to experience nonhealing ulcers and ulcer recurrence.[11,12] Therefore, consideration has been given to the role of other interventions such as exercise therapy.

The U.K. National Institute for Health and Care Excellence guidelines have recommended regular walking as a part of the lifestyle advice for treating VLU.[2] Regular walking is thought to augment calf muscle pump function.[2] The action of the calf is responsible for the return of 60% of the blood from the deep venous system to the heart, and patients with chronic venous disease can have impaired calf muscle pump function.[13,14] Calf function has been seen to improve after exercise.[15] However, whether this will translate into improved VLU healing has not yet been determined. Theoretically, a strong calf muscle pump, combined with competent valves, will reduce the venous hydrostatic pressure when walking by fragmenting the column of blood between the right atrium and the leg. However, for patients with venous insufficiency, the decrease in venous hydrostatic pressure during activity will be much less, or will even increase, owing to the valvular incompetence. Valvular incompetence allows for pooling of the blood into one continuous column, resulting in venous hypertension, which, in time, can evolve into VLU.[16] The adjunct of exercise to compression therapy might act to mimic the normal venous physiology, with compression to simulate intact valves plus exercise to increase the power of the calf muscle pump to prevent venous stasis and fractionate the blood, decreasing the venous hydrostatic pressure.[16,17]

A previous systematic review and meta-analysis of exercise with compression for VLU in 2017 concluded that the evidence base might be sufficiently large for clinicians to recommend resistance (weight) training for patients.[18] However, they did not report on the rate of ulcer recurrence, a key VLU healing parameter, and did not document patient compliance with exercise. Furthermore, the study was performed 5 years earlier; thus, a reevaluation of the reported data is justified. In the present systematic review and meta-analysis, we aimed to quantify the effect of exercise programs on VLU. The primary outcomes were the proportion of healed ulcers and rate of ulcer recurrence. The secondary outcomes were the time to ulcer healing, improvement in ulcer symptoms, quality of life, adverse events and compliance with intervention.

## METHODS

The PRISMA (preferred reporting items for systematic reviews and meta-analysis) guidelines were followed in conducting the database searches.[19,20] The study protocol was preregistered and is freely accessible (PROSPERO no. CRD42021220925).

**Search strategy.** The Cochrane Library, Embase, and MEDLINE databases were accessed up to April 6, 2022, without limitations imposed regarding the date, study design, or language. Unpublished data were screened by searching for trials on ClinicalTrials.gov, European Union Clinical Trials, and the International Standard Randomised Controlled Trial Number. The searches included 14 different terms for venous leg ulcers, 23 different terms for exercise, and appropriate MeSH (medical subject heading) terms (Supplementary Table I, online only). The references of the included studies were screened for further eligible studies.

**Eligibility criteria.** The participants of the included studies had had the following characteristics:

1. Venous leg ulceration
2. Ankle brachial pressure index >0.8
3. Exercise intervention compared with the current standard of care, compression therapy, or control

The excluded criteria were as follows:

1. Nonvenous leg ulceration (eg, arterial, diabetic, vasculitic, gravitational, traumatic, and malignant ulcers)
2. No primary outcomes reported
3. No follow-up data
4. No assessment of differences in activity between the trial arms
5. Nonoriginal research, full text not available in English, case reports, conference abstracts, duplicate reports. and nonhuman studies

**Study screening.** The reports were screened independently against the eligibility criteria by two authors (B.R.H.T., S.J.). Any discrepancies were mediated by a third reviewer (M.M.). The screening process was conducted using EndNote X9 (Clarivate, London, UK) and Covidence (Melbourne, Australia), with the titles and abstracts screened before the full-text review.[17]

**Data extraction.** Two authors (B.R.H.T., S.J.) extracted the data using a template in Microsoft Excel (Microsoft Corp, Redmond, WA). Any discrepancies in the data were mediated by a third reviewer (M.M.).

**Quality assessment.** The GRADE (grading of recommendations assessment, development and evaluation) assessment was performed using the online platform GradePro (available at: https://www.gradepro.org/) to assess the quality of the included data. The platform permits the summation of outcomes and rates the strength of the evidence according to the directness, consistency, precision, study design, and risk of bias.

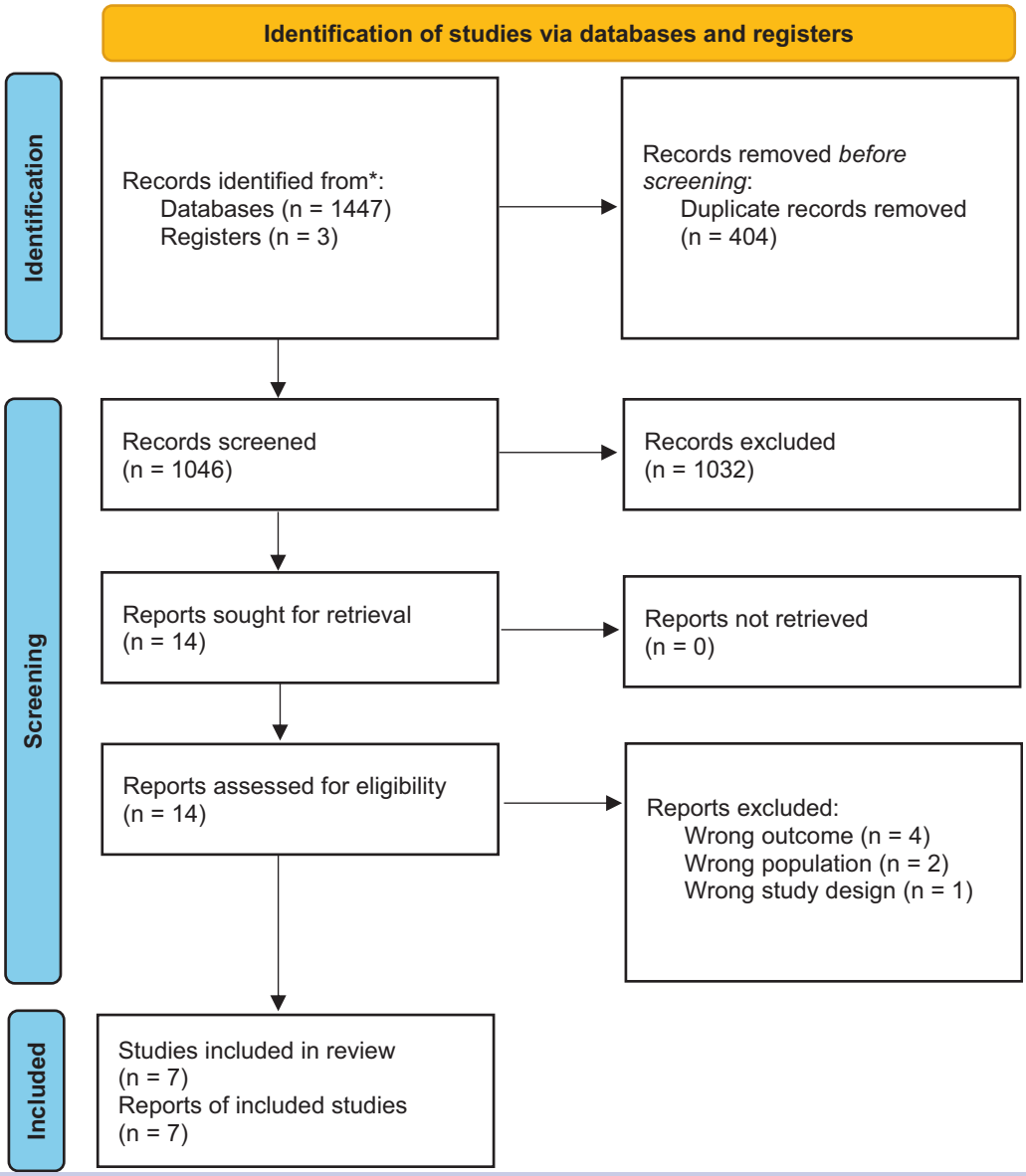


**Fig 1.** PRISMA (preferred reporting items for systematic reviews and meta-analyses) flow diagram of included studies showing study identification, stage at which they were excluded, and the reasons for exclusion.

**Data synthesis.** To assess the heterogeneity, the outcomes data were imported into RevMan 5, version 5.4 (The Cochrane Collaboration; available at: https://training.cochrane.org/online-learning/core-software/revman/revman-5-download). Given the substantial differences in outcomes reporting between studies, it was only possible to perform a meta-analysis for the proportion of healed ulcers at 12 weeks. For missing data or inappropriately excluded data, an intention-to-treat analysis was performed. A narrative synthesis was conducted for data that were not suitable for meta-analysis. A fixed effects model was used in the meta-analysis to pool the data for the primary outcome.

## RESULTS

Our searches of online databases revealed 1046 results. Screening of the article titles and abstracts excluded 1032 reports, with 14 proceeding to full-text review. Another seven studies were excluded for the following reasons: no primary outcomes reported (n = 4), a nonvenous study population (n = 2), and an inappropriate study design (n = 1). Two unpublished trials were identified; however, one was currently recruiting and the other had not yet collected any interim results.[21,22] In addition, a trial included in a previous systematic review was excluded because it had not reported the proportion of healed ulcers or ulcer recurrence.[23] The PRISMA flow diagram is shown in Fig 1.

**Study characteristics.** All included studies were prospective, randomized, controlled trials that had directly compared exercise plus compression to compression alone. The studies had been reported between 2009 and 2020, with centers in the United Kingdom,[24,25] Australia,[26,27] New Zealand,[28] Ireland,[29] and Thailand.[30] The studies were all small, with a range of 13 to 63 participants,[26,27] for a total of 121 participants randomized to an exercise intervention and 125 participants randomized to standard care. Of the 246 participants, 41% were men. The average age ranged from a median of 54 years to a mean of 75 years.[24,28] Patient age was significantly different between the intervention and control groups in two trials, with younger participants in the exercise group, who had also been walking a greater number of steps at baseline.[29,30] The average ulcer area ranged from 2.4 to 7.5 $cm^2$.[27,29] The ulcer area was not significantly different between the groups in any trial but was smaller, on average, in the exercise group in four trials.[24,25,29,30] The average ulcer duration ranged from 11.8 to 34.2 weeks.[25,29] The ulcer duration had varied greatly within the groups, and the difference was significant in one study, with a mean ulcer duration of 42 weeks for the exercise group vs 20 weeks for the compression group.[24] An additional intergroup difference in ulcer was reported in two other studies.[29,30] Venous intervention was an exclusion criterion for one trial[25] and had been performed after the study period in another trial.[30] However, the remaining reports had not documented the use of previous venous intervention. No study had documented the VLU etiology, distribution of venous reflux on duplex ultrasound scanning, or the use of venoactive pharmacologic agents.

**Exercise interventions.** All the studies had reported the use of an active exercise program plus compression therapy and compared that to the use of compression alone. The exercise arm in each trial had performed a greater level of activity compared with the compression alone group,[24-30] although this had only been quantitatively demonstrated in the trial of prescribed walking.[26] Six studies had used unsupervised home-based exercise programs.[24,26-30] Exercise had been performed with a variable frequency, from daily to three times per week. The specific details of each exercise intervention are included in Supplementary Table II (online only).

**Quality of evidence.** The GRADE assessment was performed for the proportion of healed ulcers and revealed very low certainty in the outcome owing to the serious risk of bias and serious risk of imprecision. The assessment was not performed for the remaining outcomes because the combinable data were insufficient.

**Risk of bias assessment.** The studies were appraised using the Cochrane Risk of Bias tool (Supplementary Table III, online only). We found a low risk of selection bias from random sequence generation and allocation concealment. Six trials had used computerized sequences and one had used sealed, randomized envelopes.[29] All included studies had had a high risk of performance bias from the inclusion of unblinded participants and personnel. Two trials had demonstrated a low risk of detection bias because the outcome assessors were blinded.[25,30] However, in general, the outcomes assessment was unblinded. An intention-to-treat analysis had been performed in four studies,[24,25,27,28] two studies had reported no attrition,[29,30] and one study had excluded patients who had been lost to follow-up from the statistical analysis.[26] These patients were included in the meta-analysis as treatment failure; therefore, the risk of attrition was low. Four studies had had a low risk of reporting bias because they had followed their registered protocols.[25,27,28,30] The other studies had deviated from the registered protocol in terms of outcomes reporting[24,26,29]; however, reporting of the prespecified ulcer healing outcomes was not affected.

**Proportion of healed ulcers.** The data were pooled for the proportion of ulcers that had healed within 12 weeks, and a fixed effects meta-analysis was conducted (Fig 2). The pooled risk difference was 18 extra healed ulcers per 100 patients for the exercise group (95% confidence interval, 7-30). Heterogeneity was not significant ($I^2 = 25\%$; $P = .24$). The relative risk of ulcer healing was 1.38 in favor of exercise (95% confidence interval, 1.11-1.71) with nonsignificant heterogeneity ($I^2 = 29\%$; $P = .21$). The outcome was downgraded from high to low certainty owing to the serious risk of bias in all seven trials.

**Rate of ulcer recurrence.** One trial had reported on ulcer recurrence, therefore, it was not possible to pool the data. In this study, the recurrence rate for VLU was low in both trial arms, with two cases in the exercise group and one case in the compression group.[25]

**Time to ulcer healing.** Most of the trials had assessed ulcer healing at 0 and 12 weeks, with only one study measuring ulcer healing at fixed 4-week intervals.[29] The change in ulcer area over time was reported by multiple studies.[24,25,27-30] However, the heterogeneous reporting precluded a pooled analysis of these outcomes.

**Adverse events.** Four trials had reported on adverse events.[24-28,30] One trial had demonstrated high rates of adverse events compared with the others in the following categories: ulcer deterioration (n = 10), skin deterioration (n = 20), new ulcer (n = 6), pain related to ulcer (n = 10), infection in ulcer (n = 7), hospitalization (n = 1), and other (n = 10).[28] Other studies had reported either increased wound exudate or no adverse events or had not defined the types of events within the trial or protocol.

**Compression.** The numbers of participants were insufficient to perform subgroup analyses for the different

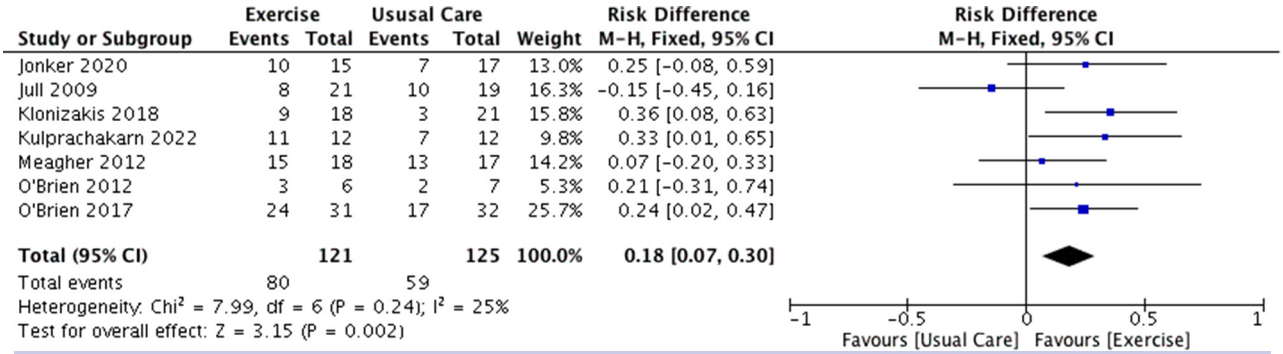


**Fig 2.** Proportion of ulcers healed within 12 weeks in the exercise plus compression vs compression alone groups. Forest plot demonstrating a pooled risk ratio of 1.35 in favor of the exercise group (95% confidence interval [CI],1.07-1.71). *M-H,* Mantel-Haenszel.

types of compression therapy. Compliance with the exercise protocol was measured using self-reported diaries in four studies and objective measures in two studies.[25,29] The methods of reporting varied: where documented, the total rates were 71% to 81%.[25,28,30] In studies in which compliance thresholds had been used, 50% to 60% of the participants had been compliant with 75% to 80% of the sessions.[26,27] In the daily walking study, 33% of the participants had achieved 10,000 steps.[29] Given the heterogeneity in compliance reporting for the exercise protocols, a meta-analysis was precluded. All the trials had reported 100% compliance with compression therapy.

**Improvement in ulcer symptoms.** Two studies had reported on improvement in any ulcer-related symptoms.[24,29] One did not show a significant difference between the intervention and control groups,[24] and the other had not directly compared the exercise and compression groups after the intervention.[29]

**Quality of life.** Three trials had reported on quality of life. However, quality of life was not compared between the intervention and control arms in one trial,[25] only the baseline measurement of quality of life at week 0 had occurred in another trial,[24] and no difference was found in the quality of life when remeasured at 12 weeks in the third trial.[27]

## DISCUSSION

In the present review, we considered the evidence for the additional benefit of exercise on VLU healing. To our knowledge, this study is the first to consider the effect of exercise programs on the recurrence of VLU. The recurrence of VLU has significant morbidity, with 12-month recurrence rates of 28% after compression therapy in large randomized trials,[31,32] increasing to 38% to 44% within 3 years[32,33] and 56% within 4 years.[11] Despite this, only one trial had reported on 12-month recurrence of VLU after an exercise intervention and failed to show any significant differences between the groups.[25] The records of the physical function indexes during follow-up did not show any statistically significant differences between the trial arms, suggesting that the activity rates were not maintained after the exercise program. It is, therefore, important to distinguish that that study had presented data for the 1-year ulcer recurrence rate after a 12-week exercise program, rather than the effect of regular exercise. Also, it is difficult to extrapolate the effectiveness of any 12-week intervention to the 1-year ulcer healing and/or recurrence outcomes. Considering these issues, no recommendation can be made regarding the role of exercise with compression for preventing VLU recurrence.

Regarding VLU healing, the absolute risk difference had increased to 18 extra healed ulcers per 100 participants from 14 ulcers in the previous systematic review, with two additional studies reported and a 30% increase in patient numbers. Precision was also improved, with a narrower 95% confidence interval of 7 to 30 healed ulcers. However, the presence of small, low-quality studies with a high risk of bias meant that the certainty of the outcome is very low. When the landmark trials for VLU such as the EVRA (early venous reflux ablation) or ESCHAR (effect of surgery and compression on healing and recurrence) trials are considered, along with the number of participants enrolled, it is highly likely that the included studies, which ranged from 13 to 63 participants recruited, were significantly underpowered to detect a smaller effect size.[12,31] Furthermore, the 12-week period to assess ulcer healing outcomes was relatively short compared with the landmark trials, both of which documented 24-week outcomes for the proportion of healed ulcers and might explain the lower rates of healing observed across the included trials. This makes the evidence for exercise as an adjunctive intervention for VLU difficult to compare to the present reference

standard management. Thus, future trials should enroll a greater number of patients and observe the healing outcomes for a longer period.

The two registered, unreported controlled trials will be larger studies (380 participants and 224 participants) of exercise interventions with blinded outcome assessments that will assess the healing outcomes at both 12 and 24 weeks, which should greatly improve the quality of available data. Furthermore, both trials have planned to measure the change in ulcer area, time to ulcer healing, adverse events, and quality of life metrics. However, objective measures of adherence to the exercise intervention will only be used in the Active Legs trial, and neither protocol will address the distribution of venous incompetence.[22] VLU recurrence will be addressed only by the Active Legs trial during a 6-month period; thus, further trials of exercise interventions will be necessary to demonstrate any role of exercise in preventing VLU recurrence.

Several studies have analyzed the factors affecting VLU healing, including ulcer size, ulcer duration, body mass index, distance walked daily, reduced ankle range of motion, previous ulceration, venous reflux pattern, and a lack of high compression.[34,35] The VenUS IV (venous leg ulcer study IV) was the first to quantify the effect of ulcer size and duration on ulcer healing and recurrence. For a 1-$cm^2$ ulcer that had been present for 1 month, the healing and recurrence probabilities were 97.6% and 25.1%, respectively, at 12 months.[36] For a 25-$cm^2$ ulcer that had been present for 16 months, the healing and recurrence likelihood was 61.3% and 74.9%, respectively.[36] Despite randomization, the critical ulcer healing characteristics were not always equally balanced between the groups. In the context of small numbers of trial participants, it is critical that stratified randomization of ulcer characteristics is undertaken.

The protocol for the present review had stated that venous reflux or occlusion should have been confirmed by venous duplex ultrasound to verify the ulcer etiology (eg, post-thrombotic or primary venous insufficiency). The anatomic distribution of reflux is known to differ between these two ulcer groups, with the deep venous reflux the most common pattern in post-thrombotic ulcers vs superficial venous reflux in primary chronic venous insufficiency.[37] Deep venous reflux and obstruction have been demonstrated in multiple studies to significantly affect ulcer healing. Thus, without proper quantification of these characteristics, it will be very difficult to understand the value of the exercise intervention.[1,31,38] However, no studies have documented these data, and, hence, none could have been included in the present review. The ulcer healing outcomes were not reported separately for men and women in the included trials. Although chronic venous disease has been more common in women,[3] recent population data have demonstrated a significant link between male gender and the diagnosis of VLU and increased mortality due to VLU, which could lead to gender differences in outcomes.[39] Future trials must record all baseline data known to affect ulcer healing and perform stratified randomization by ulcer duration, size and pattern of venous reflux, and ulcer etiology.

The EVRA trial definitively showed that endovenous therapies to treat superficial venous reflux were superior to compression therapy alone in terms of healing and recurrence of VLU with superficial reflux.[12] To the best of our knowledge, no trials have documented a history of surgical intervention, patterns of venous reflux, nor patient eligibility for surgery. Only two had been reported after the EVRA trial, and the most recent had specified that superficial venous incompetence was treated later.[30] Given that no trials had considered exercise as an adjunct to the current standard of care, it was difficult to generalize their results further than those patients for whom surgery is unsuitable, not tolerated, or declined. Furthermore, none of the studies had considered whether the etiology of the venous reflux was primary or secondary disease from post-thrombotic syndrome, in which patients' ability to engage in exercise will be significantly affected by the pain from venous claudication. The reporting of key baseline characteristics is crucial for future venous leg ulcer trials.

**Study limitations.** The activity performed by the exercise groups across the trials ranged from three sessions per week to three per day. Without objective monitoring, it was difficulty to directly compare the efficacy of the individual exercise regimens on VLU healing. Just one of the included studies had demonstrated any difference between the exercise and control groups with an objective measurement tool, a pedometer; However, the issues included the ability to fool the pedometer and whether the demonstrated difference in step count between the intervention and control groups would have been considered clinically significant. These measurement problems were compounded by the variable adherence to the exercise protocols throughout the included studies and explains the very low certainty in the outcomes. Furthermore, some studies demonstrated differences between the intervention and control arms in critical baseline characteristics known to influence ulcer healing, including ulcer size and duration, despite randomization. Other critical mediators of ulcer healing such as deep venous reflux were not addressed at all by the included studies. The trials generally displayed inadequate blinding of the outcome assessors, without the use of objective measurement tools. Therefore, the risk of detection bias, in addition to an unavoidable performance bias owing to the nature of the intervention, was high. For these reasons, the risk of bias was graded as very serious for these outcomes. Moreover, the included studies had had small populations, which

made them unsuitable for detecting meaningful differences in the ulcer healing outcomes.

Improved reporting of ulcer recurrence is essential to assess the safety and benefit of the long-term effects of sustained exercise on VLU disease. The evidence for exercise as an adjunct to ulcer healing demonstrated a benefit from a meta-analysis of the reported data; however, the numerous methodologic issues led to a very low strength recommendation. Fundamentally, most of the trials had not objectively demonstrated a difference in exercise undertaken by the intervention and control arms. Future trials should use activity monitors, which have become common and readily available in the era of the smartphone, to demonstrate that the observed differences in ulcer healing outcomes were related to the exercise intervention. Furthermore, these trials should analyze the role of exercise as an adjunct to the current standard of care (ie, ablation of superficial venous reflux), for which no data are yet available.

## AUTHOR CONTRIBUTIONS

Conception and design: BT, SJ, MM, AJ, AG, JS, SO, AD
Analysis and interpretation: BT, SJ, MM, AJ, AG, JS, SO, AD
Data collection: BT, SJ, MM, AJ
Writing the article: BT, SJ, MM, AJ
Critical revision of the article: BT, SJ, MM, AJ, AG, JS, SO, AD
Final approval of the article: BT, SJ, MM, AJ, AG, JS, SO, AD
Statistical analysis: BT, SJ, MM, AD
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Overall responsibility: AD
BT and SJ contributed equally to this article and share co-first authorship.

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