

## REVIEW ARTICLE

# Effects of exercise in treating patients with venous leg ulcers: A systematic review and meta-analysis

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**Abstract**

To determine the effects of exercise on VLU healing and exercise adherence, and to provide evidence for clinical practice and scientific investigation. PubMed, Embase and Scopus were searched from inception to 31st March, 2022. Pooled relative risks (RRs), standardised mean differences (SMDs), adherence rate with respective 95% confidence intervals (CIs) were calculated. Quality assessment of included studies were performed using the Cochrane Collaboration risk of bias evaluation. Heterogeneity between enrolled studies was evaluated. We identified eight randomised control studies (RCTs) that met the inclusion criteria. The pooled RR for healing rate was 1.38 (95% CI: 1.14 to 1.66;  $P = 0.0008$ ) with no significant heterogeneity between component studies ( $I^2 = 0\%$ ,  $P = 0.96$ ). SMD for differences of total range of ankle joint motion (ROAM) at the end and at the initiation of follow-up in the intervention and control groups was 0.87 (95% CI: 0.22, 1.52;  $P = 0.0091$ ), no significant heterogeneity was detected ( $I^2 = 59\%$ ,  $P = 0.0622$ ). Pooled adherence rate was 64% (95% CI: 53%, 75%) with no significant heterogeneity. Exercise manifested positive effects on VLU healing, range of ankle mobility compared with the control group. Patients' adherence to the exercise regimens was favourable.

**KEYWORDS**

adherence rate, exercise, meta-analysis, therapy, venous leg ulcer

## 1 | INTRODUCTION

Venous leg ulcer (VLU) is the most common type of leg ulcers, accounting for 80% to 90% of lower extremity ulcers.<sup>1</sup> VLU impacts a great number of patients around the world and may impose a significant socio-economic burden on the health system and pose significantly psychological and physical affections on the affected individuals.<sup>2</sup> Moreover, it is estimated that the VLU cost burden would be on a dramatical rise owing to the aging of

population, increased prevalence of diabetes mellitus, and other associated conditions including venous circulation dysfunction, elevated body mass index, family history of chronic venous insufficiency, history of pulmonary embolism or venous thrombosis, local osseous or joint diseases.<sup>3-9</sup> The main cause of VLU is that the calf muscle pump cannot properly return blood from the legs to the heart due to venous reflux and obstruction.<sup>10</sup>

Venous leg ulcers are usually irregular in shape with well-defined borders.<sup>11</sup> Heavy limbs, itching, pain and

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edema are commonly presented symptoms of VLU, which are exacerbated during the day and improved with elevation of affected limbs.<sup>6,10,12</sup> Diagnostic strategy comprised of ultrasonography, arterial pulse examination and measurement of ankle-brachial index is recommended for individuals suspected of VLU.<sup>13,14</sup> The primary goals for treating patients with VLU include alleviation of pain and edema, ulcer healing and prophylaxis of ulcer recurrence.<sup>2,10,15</sup> Elevation of lower extremities is regarded as the simplest approach to reverse the effects of venous insufficiency, Abu-Own et al. recommended that elevation of the legs above the heart level for 3 to 4 times daily, 30 minutes per time, along with leg elevation throughout the night could improve venous circulation.<sup>16</sup> Nonetheless, a majority of patients cannot tolerate the frequency of leg elevation. Compression remains the mainstay of treatment for patients with VLU.<sup>17,18</sup> Multilayer elastic bandages are considered as the gold standard with the most powerful evidence in favour of increased healing rates and decreased recurrence as compared with no compression.<sup>19,20</sup> Of note, compression should be employed with caution in patients who suffered from congestive heart failure and arterial insufficiency.<sup>21</sup> Exercise is another approach for the therapy of VLU. During exercise, the calf muscles contraction propels the compression of the intramuscular and deep veins, which increase the venous pressure and promote the blood in the deep vein back to the heart.<sup>22</sup> In addition, increased number of studies investigated the role of exercises on the treatment of VLU by improving calf muscle function and ankle joint range of motion in patients with VLU.<sup>23-25</sup> The results are conflicting and varied based on the characteristics of study design and conduction. The aim of this meta-analysis was to determine the effects of exercise on the clinical outcome measurement of VLU healing and adherence, and to provide evidence for clinical practice and scientific investigation.

## 2 | MATERIALS AND METHODS

### 2.1 | Statements

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines.<sup>26-28</sup> Dataset in this study was generated from published articles, thus the informed consent was not required.

### 2.2 | Literature search

Potential eligible studies were identified through comprehensive search of several electronic databases, including

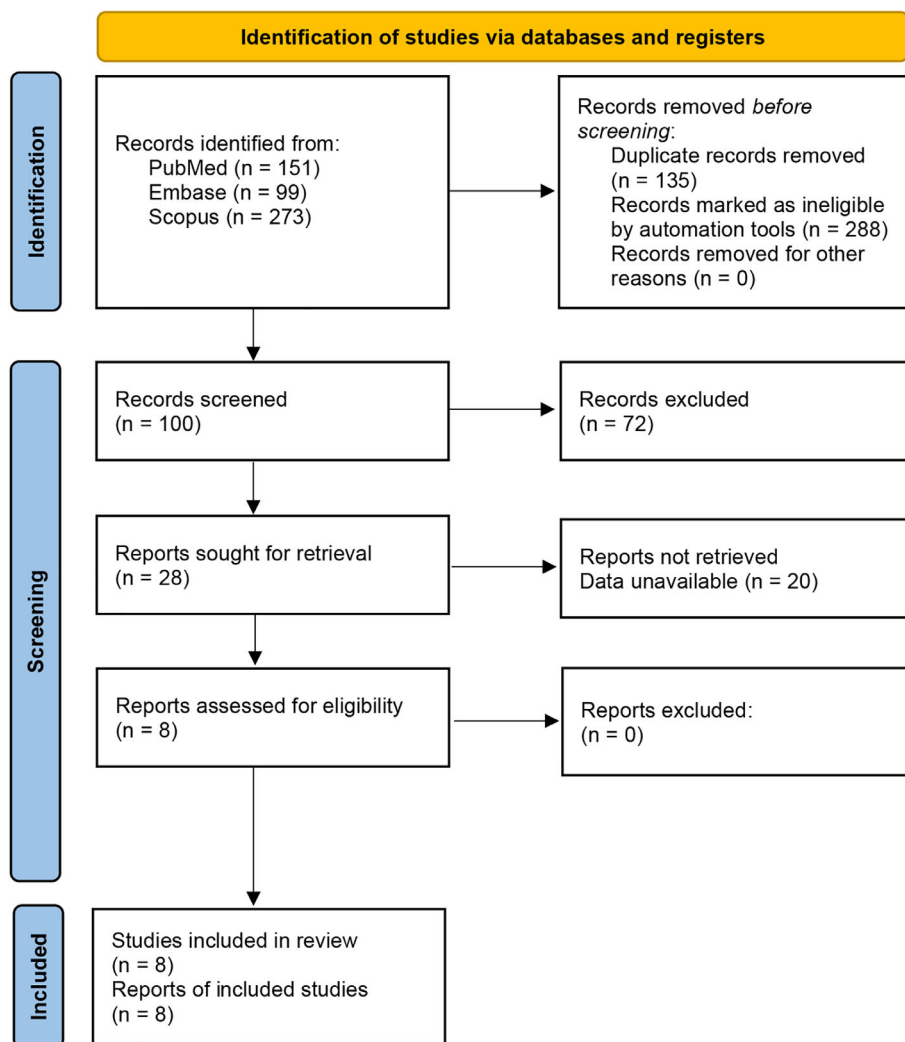
the PubMed, Embase and Scopus databases. Search terms included a strategic combination of “leg ulcer” and “exercise.” The term “leg ulcer” was used instead of “venous leg ulcer” to retrieve as many eligible studies as we could. All papers published from inception to 31st March, 2022 with the English language were included. Based on the results of the initial literature search. The titles and abstracts of each record searched were screened to exclude duplicates and any obviously irrelevant researches. Afterwards, full texts of the remaining articles were reviewed to determine for final inclusion. The bibliographies of the identified studies or review articles were manually searched for further eligible records. The article search and screening were performed by two authors, any disagreement was addressed through discussion.

### 2.3 | Study selection, data extraction and quality assessment

The inclusive selection criteria were as follows: (1) Randomised control trials or cohort studies used exercise regardless of any form for the treatment of diagnosed venous leg ulcers; (2) Outcomes including healing rates, total range of ankle joint motion and adherence rates were reported in the enrolled studies. Conference abstracts, reviews, case reports, animal studies were excluded. Name of first author, year of publication, country, study design, number of participants, age of participants (in year), details on intervention, details on control, follow-up duration (in week) and outcomes aforementioned were extracted into a predefined form. Two independent reviewers conducted the entire process of study selection and data extraction, any discrepancy was solved through discussion by the two authors. Two authors then independently assessed the quality of included studies using the Cochrane Collaboration risk of bias evaluation,<sup>29</sup> with discordance resolved by discussion. As the blind of intervention exercises were impossible to the patients, performance bias for blinding was not evaluated.

### 2.4 | Statistical analysis

Data synthesis for each outcome was performed using R software (Version 4.0.3, Comprehensive R Archive Network) using the random effects model.<sup>30</sup> Standardised mean differences (SMDs) (for continuous variables in intervention and control groups), relative risks (RRs) (for dichotomous outcomes in intervention and control groups), pooled adherence rate and their respective 95% confidence intervals (CIs) were calculated. Heterogeneity



**FIGURE 1** Flow chart of literature search

between component studies was tested by the  $Q$  test and  $I^2$  statistic.  $I^2$  values  $\geq 25\%$ ,  $\geq 50\%$  and  $\geq 75\%$  were regarded as low, moderate and high degree of heterogeneity, respectively.<sup>31</sup> Linear regression test of funnel plot asymmetry was utilised to determine publication bias. A  $P$  value  $< 0.05$  was considered as statistical significance.

### 3 | RESULTS

#### 3.1 | Baseline characteristics of included studies

A total of 523 records were initially retrieved. After excluding 135 duplicate studies and ineligible studies (77 reviews, 18 case reports, 3 animal studies, 18 conference abstracts, 172 irrelevant records), a total of 100 studies were evaluated for eligibility in the next step of screening. After full-text review of 28 articles, we finally identified eight randomised control studies that met the inclusion criteria, including a total of 270 patients with

diagnosed VLU.<sup>32-39</sup> Details on literature search is depicted in Figure 1. The year of publication for included studies ranged from 2010 to 2022. Mean (median) age of participants in each study was more than 60 years old. More information on the baseline characteristics of the included studies is shown in Table 1. All studies were considered to have low-risk selection bias in sequence generation. Three trials were judged to be at high risk of bias on blinding of outcome assessment due to the open-label design of these trials. Overall results of quality assessment for the enrolled records are shown in Figure 2.

#### 3.2 | Effects on ulcer healing

Seven studies reported the outcomes on ulcer healing at 12 weeks except that one study revealed proportion of patients healed at 9 weeks. The pooled RR for healing rate of the seven included studies was 1.38 (95% CI: 1.14 to 1.66;  $P = 0.0008$ ), no significant heterogeneity between

TABLE 1 Baseline characteristics of included studies

Name of First Author	Year of Publication	Country	Study Design	No. of Participants	Age of Participants (years)	Intervention	Control	Follow-up duration (weeks)
Szewczyk	2010	Poland	Randomised control study	32	73.3 ± 9.7	The supervised exercises were performed 3 times a day, in series of 15 repetitions; walking 3 km daily; exercising on training bikes.	Performing exercises by themselves	9
Meagher	2011	Ireland	Randomised control study	35	71 (32–91)	Taking 10 000 steps per day. Participants were fully educated on the use of the pedometer and regular contact was maintained to address any queries, as necessary.	The control group were not asked to alter their walking activity at any point in the study, and no specific advice regarding exercise was given.	12
O'Brien	2013	Australia	Randomised control study	11	64.9 ± 13	An individualised exercise programme	Usual care	12
O'Brien	2017	Australia	Randomised control study	59	71.5 ± 14.6	A home-based progressive resistance exercise programme	Usual care	12
Klonizakis	2018a	United Kingdom	Randomised control study	38	66.9 ± 13.9	Usual care plus a supervised exercise programme	Usual care	12
Klonizakis	2018b	United Kingdom	Randomised control study	39	63.5 ± 12.8	Three sessions of supervised exercise each week for 12 weeks	Usual care	12
Jonker	2020	United Kingdom	Randomised control study	32	73 ± 4	StepIt exercise programme	Standard care	12
Kulprachakarn	2022	Thailand	Randomised control study	24	NR	Conventional treatment plus tailored exercise training	Conventional treatment	12

Abbreviation: NR, not reported.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Szewczyk 2010	+	+	+	?	+
Meagher 2011	+	+	-	+	+
O'Brien 2013	+	?	-	+	+
O'Brien 2017	+	+	-	+	+
Klonizakis 2018a	+	+	+	+	?
Klonizakis 2018b	+	+	?	+	+
Jonker 2020	+	+	?	+	+
Kulprachakarn 2022	+	+	+	+	+

+ Low risk of bias    
 ? Unclear risk of bias    
 - High risk of bias

FIGURE 2 Risk of bias summary for each included study

component studies was detected ( $I^2 = 0\%$ ,  $P = 0.96$ ) (Figure 3). The overall healing rate at 12 weeks was 1.39 (95% CI: 1.15 to 1.68;  $P = 0.0007$ ), statistical heterogeneity was considered as not significant ( $I^2 = 0\%$ ,  $P = 0.96$ ).

### 3.3 | Effects on total range of ankle joint motion

Four included studies measured the differences of total range of ankle joint motion (ROAM) at the end (12 weeks in 3 studies, 9 weeks in 1 study) and at the initiation of follow-up in the intervention arm and control arm. Standardised mean difference of differences in the intervention group and control group was 0.87 (95% CI: 0.22, 1.52;  $P = 0.0091$ ), no significant heterogeneity between included studies was detected ( $I^2 = 59\%$ ,  $P = 0.0622$ ) (Figure 4). For the studies with a 12-week follow-up, the estimated overall SMD was 0.74 (95% CI: -0.09, 1.58;  $P = 0.0808$ ) with no significant heterogeneity ( $I^2 = 63\%$ ,  $P = 0.0690$ ).

### 3.4 | Adherence on exercise program

Four records assessed the adherence to exercise programs in the intervention arms. Pooled adherence rate was 64% (95% CI: 53%, 75%). Non-statistical significance for heterogeneity was justified ( $I^2 = 0\%$ ,  $P = 0.54$ ) (Figure 5).

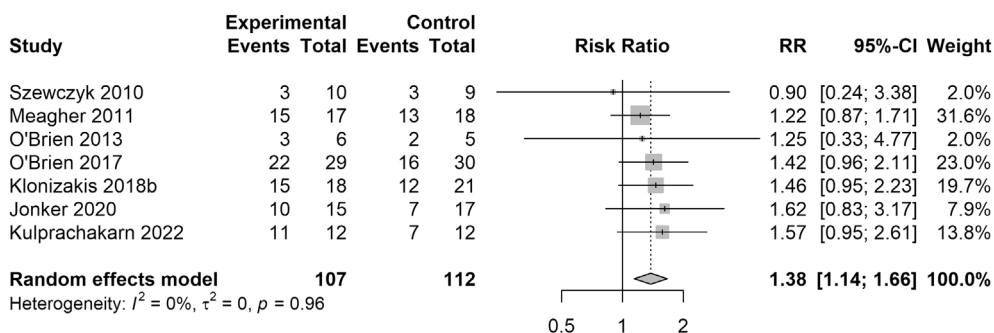


FIGURE 3 Forest plot of healing rates in included studies

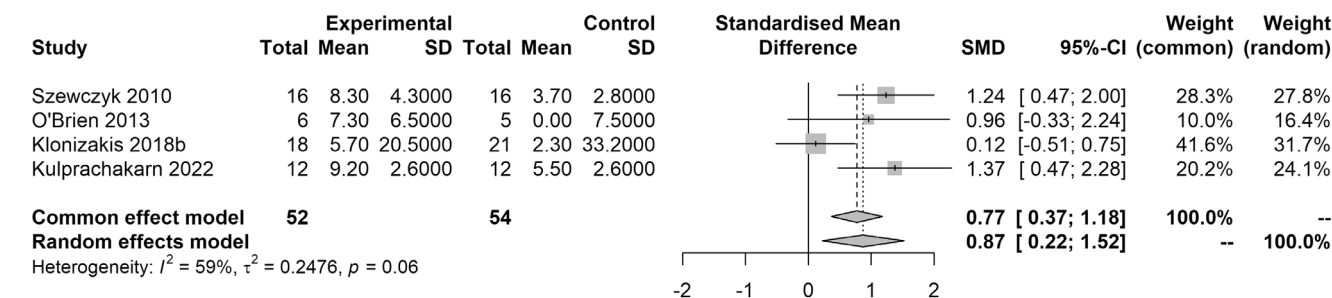


FIGURE 4 Forest plot of total range of ankle joint motion in included studies

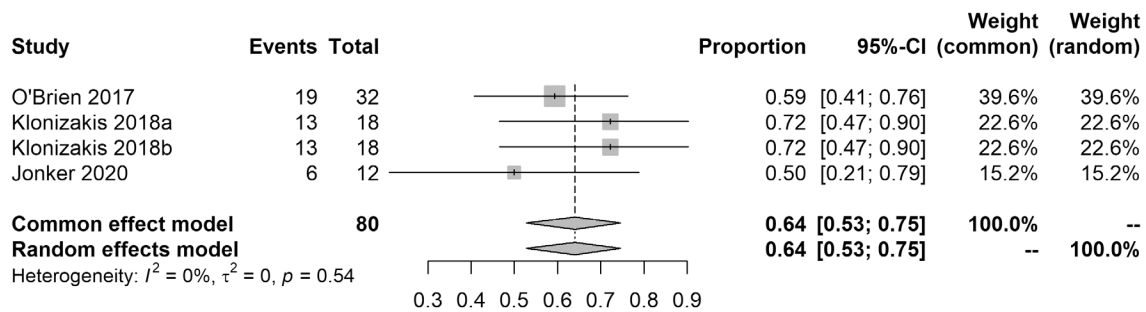


FIGURE 5 Forest plot of adherence rates in included studies

### 3.5 | Publication bias

The Egger's tests yielded  $p$  values of 0.8754, 0.4218 and 0.9810 for the meta-analysis of healing rates, differences of ROAM and adherence rates, respectively (Figures S1–S3).

## 4 | DISCUSSION

The recovery of VLU is one of the comprehensive clinical issues that requires intervention from specialist and multidisciplinary wound care providers.<sup>40</sup> Exercise interventions could improve the outcomes of VLU healing as demonstrated in previous studies.<sup>32,35–37</sup> Moreover, there have been three systematic reviews and meta-analyses of exercise for VLU, nevertheless, one review included quantitative studies up to April 2014 in absence of assessment for risk of bias in enrolled records, and performed a narrative method to synthesising outcomes.<sup>41</sup> The second review was published in 2018 with the literature search up to January 2017, there was no restrictions on ulcer healing outcomes.<sup>40</sup> The third review included electronic databases searched through October 2017, but it assessed the added beneficial effect of exercise when used in addition to compression.<sup>42</sup> Thereby we performed this meta-analysis to quantitatively examine the effects of exercise on healing of VLU along with the assessment of adherence.

After a systematic search of the online databases, a total of eight randomised control trials were included in this meta-analysis. The pooled RR for healing rate was 1.38 (95% CI: 1.14 to 1.66), the result is suggestive of the beneficial effect of exercise on VLU healing. Of note, one study reported the proportion of patients healed at 9 weeks while other studies revealed 12-week healing rate. Effect on ulcer healing at 12 weeks remained to be significant with a pooled RR of 1.39 (95% CI: 1.15 to 1.68). Difference on the increase of total range of ankle joint motion in the intervention arm and the control arm was measured to determine the effects of exercise

therapy. Standardised mean difference was 0.87 (95% CI: 0.22, 1.52;  $P = 0.0091$ ) which indicated exercise could significantly improve the range of ankle motion. Nonetheless, the pooled outcome (SMD) showed statistical insignificance with no evidence on heterogeneity after removing the study assessing ROAM at Week 9. The potentially underlying reason for this inconsistency was unclear yet based on the information obtained from the included studies, more evidence is needed to address the contradiction. In the current meta-analysis, the pooled proportion of participants adherent to exercise regimen was 64% (95% CI: 53%, 75%), patients in these studies received clear direction and tutorials on exercise schedule and performance, and were supervised by investigators to improve the compliance with the regimens.<sup>32–34,38</sup> Moreover, results of evaluation for Egger's tests suggested nonsignificant publication bias in enrolled studies.

Although comprehensive approaches in database search, data extraction, quality assessment were used to minimise risk of bias, this meta-analysis remained to be subject to several limitations. Due to limited covariates in this study and insufficient number of in each subgroup, meta-analyses on different forms of exercise (including progressive resistance exercise, walking, ankle exercises), adverse events, quality of life and cost effectiveness were not conducted. More well-designed randomised control trials on the effects of exercise are in need for further evaluation.

In conclusion, in this meta-analysis, exercise manifested positive effects on VLU healing, range of ankle mobility compared with the control group. Patients' adherence to the exercise regimens was favourable. Due to limited information extracted in included studies, further additional systematic review and meta-analyses are needed to provide more reliable and powerful evidence.

### ACKNOWLEDGEMENTS

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## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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