

BMJ Open Effects of different types of exercise intervention for alleviating breast cancer-related lymphedema: a systematic review protocol and network meta-analysis

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ABSTRACT

Introduction Exercise is the main treatment for patients with breast cancer-related lymphedema (BCRL) and different types of exercises were performed in these patients. However, it is unclear which type of exercise or combination of these is the most effective in reducing arm swelling and lymphedema-related symptoms, and quality of life in patients with BCRL.

Aims This study aimed to compare the relative efficacy of different types of exercise in treating BCRL and determine the most effective exercise therapy for patients with BCRL.

Methods and analysis This review will search English-language databases (Cochran Library, Cumulative Index to Nursing and Allied Health Literature, EBSCO, EMBASE, PubMed/Medline and Web of Science). The following Chinese-language databases will also be searched: Chinese Biomedical Literature Database (SinoMed), China National Knowledge Infrastructure, Wanfang Data and China Science and Technology Journal Database. The search was conducted up to 31 December 2024. Randomised controlled trials comparing different types of exercise on BCRL will be eligible. Data will be extracted from eligible trials by two independent researchers based on the selection criteria. Two reviewers will ascertain the risk of bias of the selected studies using a modified version of the Cochrane Risk of Bias Tool. The study's characteristics (study type, characteristics of the patients, intervention prescriptions) and primary outcomes (limb volume, physical function, physical and psychological symptoms) will be summarised in a narrative format. Meta-analyses (ie, network and pairwise) will be used to assess the indirect and direct effects of the exercise interventions. The relative effects of different types of exercise in treating BCRL will be examined by the surface under the cumulative ranking curve to calculate the ranking of treatments and determine the most effective intervention.

Ethics and dissemination This review does not require ethical approval. The findings will be submitted for peer-reviewed publication.

PROSPERO registration number The systematic review protocol has been registered in the International

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This review will address the need to establish best practices for treating breast-cancer related lymphedema (BCRL) by comparing and ranking the effectiveness of different categories of exercise interventions.
- ⇒ The review's results will promote evidence-based decision-making in prevention strategies and provide reliable recommendations for exercise interventions in the treatment of BCRL.
- ⇒ A limitation of the review relates to the methodological heterogeneity given the variation in exercise protocols and participants' baseline characteristics (severity of lymphedema, age, comorbidities and general physical condition), which may limit the ability to pool treatment effect.
- ⇒ The language of the articles included in the review will be restricted to English and Chinese, and grey literature will not be included in the review. To minimise the risk of publication bias, manually screen the reference lists of all included articles and relevant systematic reviews, and attempt to contact study authors to retrieve additional information or unpublished data when necessary.

Prospective Register for Systematic Reviews
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INTRODUCTION

Breast cancer-related lymphedema (BCRL) is a chronic complication related to the side effects of treatments for breast cancer (eg, mastectomy, axillary lymph node dissection, radiotherapy).^{1 2} Lymphedema is mainly characterised by swelling of the affected body part, accompanied by a feeling of swelling, heaviness, tightness and/or weakness in the affected limb.^{3 4} Approximately 20% of breast cancer survivors develop BCRL.⁵ Lymphedema has many negative effects on patients,

including psychosocial symptoms (anxiety, distress, disturbances in relationships and social avoidance), and impaired emotional, social, functional and quality of life.⁶ Dealing with lymphedema is a new challenge for cancer survivors.⁷

Lymphedema is incurable and treated with physical therapy, such as complex decongestive therapy (CDT), which is currently considered the most successful intervention. The treatment consists of manual lymphatic drainage, compression therapy (eg, multi-layer bandaging), exercise and skin care.^{8,9} The aim of CDT is to prevent disease progression while improving lymphedema-related symptoms, functioning and recovery of the affected limbs.¹⁰ Other physical therapy interventions include laser therapy and kinesio-taping. According to current evidence and clinical guidelines, these modalities are often recommended to be used in combination rather than as stand-alone treatments.¹¹

Lymphatic fluid is primarily pushed by negative pressure in the chest generated by spontaneous muscle contractions and inspiration.⁸ Among the various physical therapy approaches, exercise interventions have received increasing attention because of their safety, feasibility and broad health benefits, and they have become a key component in the treatment and management of BCRL.^{9,12,13} Exercise can activate the musculoskeletal pump and enhance lymph flow but also enhances cardiovascular function, muscle strength and mental well-being.¹⁴

Current exercise interventions can be divided into three main types: aerobic, resistance and flexibility exercise.^{8,9} However, no evaluation studies have been published on the degree to which some types of exercise are more successful than others in alleviating lymphedema and its associated symptoms, thereby enhancing patients' quality of life. Meta-analyses of networks have gained more attention in recent years because they are quantitative methodologies used to simultaneously compare multiple interventions across different trials, which makes it possible to provide rankings of treatment options based on their effectiveness.^{15,16}

Previous systematic reviews, such as the protocol by Aguilera-Eguía's *et al*,¹⁷ have explored a wide range of physical therapy interventions for BCRL, including manual lymphatic drainage, compression therapies, laser therapy, exercise, yoga and other complementary techniques. This study proposes a systematic review and network meta-analysis focused exclusively on exercise interventions for BCRL. By narrowing the scope, this study aims to provide greater specificity and clinical relevance for healthcare professionals seeking exercise-based recommendations and enables deeper analysis of exercise variables such as frequency, intensity and duration, providing insights into differential effects and offering more precise clinical guidance for optimising exercise-based management of BCRL, which were not addressed in Aguilera-Eguía's protocol. Given the current gaps in the literature, the implementation of this study holds significant clinical value.

METHODS AND ANALYSIS

Design

The protocol of this review follows the Preferred Reporting Items for Systematic reviews and Meta-Analysis Protocols (PRISMA-P) to design our systematic review protocol.¹⁸ The protocol for the review was registered in the International Prospective Register for Systematic Reviews (registration number: CRD42022370817).

Information sources and search strategy

A systematic search will be conducted using the following English-language electronic databases: Cochrane Library, Cumulative Index to Nursing and Allied Health Literature, EBSCO, EMBASE, PubMed/Medline and Web of Science. The Chinese-language databases to be searched will include the Chinese Biomedical Literature Database (SinoMed), China National Knowledge Infrastructure, Wanfang Data and China Science and Technology Journal Database. Our anticipated search dates will end on 31 December 2024. No restrictions on publication date will be required. All reference lists will be searched for relevant articles, including trials and systematic reviews. The search strategy is provided in online supplemental file 1).

The search terms will consist of medical subject headings (MeSH) and entry terms (eg, a PubMed query): 'Breast Neoplasms' (Mesh) OR 'breast cancer' (Title/Abstract) OR 'breast neoplasm' (Title/Abstract) OR 'breast carcinoma' (Title/Abstract) OR 'breast tumour' (Title/Abstract) OR 'breast malignancy' (Title/Abstract) AND 'lymphedema' (Mesh) OR 'lymphedema' (Title/Abstract) OR 'swelling' (Title/Abstract) OR 'oedema' (Title/Abstract) OR 'lymphoedema' (Title/Abstract) OR 'BCRL' (Title/Abstract) AND 'weight lifting' (Mesh) OR 'exercise' (Mesh) OR 'exercise' (Title/Abstract) OR 'training' (Title/Abstract) OR 'physical activity' (Title/Abstract) OR 'resistance training' (Mesh) OR 'resistance training' (Title/Abstract) OR 'resistance exercise' (Title/Abstract) OR 'weight training' (Title/Abstract) OR 'weight lifting' (Title/Abstract) OR 'strength training' (Title/Abstract) OR 'endurance training' (Title/Abstract) OR 'Yoga' (Mesh) OR 'Yoga' (Title/Abstract) OR 'Pilates Training' (Mesh) OR 'Pilates Training' (Title/Abstract) OR 'aerobic training' (Mesh) OR 'aerobic training' (Title/Abstract) OR 'Aquatic Therapy' (Mesh) OR 'Aquatic Therapy' (Title/Abstract) OR 'water based therapy' (Title/Abstract).

Eligibility criteria

The participants will be women aged ≥ 18 years who have secondary lymphedema related to breast cancer in their upper extremities.

Studies involving any form of physical activity or exercise will be included. Three major types of exercise for managing lymphedema effectively will be evaluated: aerobic exercise is aerobic conditioning, also called cardiovascular exercise, includes activities that involve large muscle groups and raise the heart rate to around 60–70% of one's maximum potential; Resistance exercises,

commonly associated with weight-lifting, can include activities such as push-ups that use body weight or the use of equipment like dumbbells and weight machines; Flexibility exercises involve numerous activities designed to stretch muscle and connective tissues, thereby increasing or preserving range of motion.⁹ The main types of exercise: (1) Aerobic or cardiopulmonary exercise: nordic walking, dragon boating, aerobic exercise/training, water-based/aquatic exercise. (2) Resistance or weight-lifting exercise: resistance exercise/training, weight lifting, strength exercise/training, pilates training. (3) Flexibility or stretching exercises: yoga, stretching exercises or any combination of them. (4) Resistance exercise plus aerobic exercise or any combination of the above exercise. (5) Mind-body exercises: tai Chi, Baduanjin. The control groups will receive usual care, no intervention, no exercise, or health education.

The main outcome(s) include: (1) Limb volume, as measured by water displacement volumetry, arm circumference, bio-impedance spectroscopy, dual X-ray absorptiometry and perometry. (2) Physical Symptoms associated with lymphedema, such as heaviness, pain, swelling, tightness and other symptoms, should also be measured using self-report scales (eg, the Lymphedema and Breast Cancer Questionnaire and the Visual Analogue Scale). (3) Physical function: muscle strength, cardiopulmonary fitness (eg, Maximal Oxygen Uptake (VO₂ max), target heart rate), shoulder range of motion and body composition (eg, bone mineral density, percentage body fat and lean body mass). (4) Psychological symptoms: anxiety, depressive, fatigue, health-related quality of life.

The studies included in this review will be restricted to randomised controlled trials published in English or Chinese.

Selection process

We will first use Endnote to remove duplicates from the retrieved studies. When all duplications are removed, we will screen the abstracts and titles of the retrieved studies to remove irrelevant articles. Two trained reviewers will independently evaluate the full texts of the relevant articles, using our inclusion and exclusion criteria. Discrepancies will be resolved through discussion, and, if necessary, final decisions will be made by a third reviewer.

Data extraction

Two reviewers will independently review each of the selected articles. Any disagreements will be settled by a third researcher. The following information will be extracted: (1) Publication information: authors, title, institution and country where the study was conducted, year published and study design. (2) Participants' information: the number of patients and their characteristics (age, type of disease and treatment). (3) Intervention information: type of exercise intervention, prescription for the exercise programme (type, frequency, intensity, session and total duration, setting and supervision or not). (4) Outcome data: measurements and results (limb

circumference and volume, symptoms, and additional primary and secondary outcomes, as well as appropriate statistics, (eg, means, SD, P values and 95% CI). (5) Main conclusions.

Risk of bias assessment of individual studies

Two authors will evaluate the risk of bias of the included studies using the Cochrane Risk of Bias Assessment Tool. Differences between the authors will be resolved through discussion or by a third evaluator. This assessment will consist of checks on the generation of randomised sequences to allocate study participants, concealment of allocation, blinding of participants or personnel, data integrity, possibility of reporting bias and other sources of bias (eg, biases related to funding and other conflicts of interest).¹⁹ The level of risk assessed in each study will be categorised as low, unclear, or high.

Data synthesis

We will summarise the study's characteristics in a narrative format (study type, patients' characteristics, intervention prescriptions and outcomes), and the findings from the included studies. After data extraction is complete, the reviewers will determine whether a network meta-analysis is feasible. If a network meta-analysis is conducted, STATA V.15 statistical software will be used to compare the indirect and direct effects of exercise interventions. Surface under the cumulative ranking curve (SUCRA) is employed to calculate the ranking of treatments. In this study, the average area under the cumulative ranking curve will be used to rank the exercise interventions according to their efficacy. A higher SUCRA value indicates treatment with a higher efficacy rating. The SUCRA value can approach 100% among the top ranked treatments.²⁰

The assumptions of heterogeneity, transitivity and consistency will be tested. Heterogeneity will be assessed using the I^2 statistic, with an I^2 value exceeding 50% indicating substantial heterogeneity. The data will be analysed using a random-effects model when I^2 is greater than 50%, and analysed using a fixed-effects model otherwise.¹⁶ Transitivity will be evaluated by comparing clinical and methodological data (eg, patients' diagnoses and assessment scales used).¹⁵ Node splitting will be performed to check for inconsistencies between direct and indirect evidence.²¹ These inconsistencies are likely to result in heterogeneity.²² To determine the extent to which heterogeneity is explained by inconsistencies, models that are consistent and inconsistent will be compared for their degree of heterogeneity.²³

In addition to variations in exercise protocols, heterogeneity may also arise from differences in patient baseline characteristics, such as the severity of lymphedema, age, physical condition and the presence of comorbidities. These factors may influence the effectiveness of interventions and should be taken into account when interpreting the results. Heterogeneity and inconsistency will be analysed if the statistical heterogeneity is greater than 50%.²⁴ If the information is sufficient, we will conduct

subgroup analyses based on the severity of lymphedema, participants' physical condition, with a different level of intervention and a different control group, depending on whether the intervention is administered alone or in combination with other exercises or other physical therapy interventions.

Assessment of evidence certainty

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach for grading the certainty of evidence will be followed, and a Summary of Findings (SoF) will be created using GRADEpro (McMaster University, ON, Canada).²⁵ The SoF will present the following information where appropriate: absolute risks for treatment and control, estimates of relative risk, and a ranking of the quality of the evidence based on the risk of bias, directness, heterogeneity, precision and risk of publication bias of the review results. The outcomes reported in the SoF will be limb volume, symptoms, muscle strength, quality of life, and so on.

Subgroup analysis and sensitivity analysis

To explore potential sources of heterogeneity, subgroup analyses were performed based on factors such as participant baseline characteristics (lymphedema severity, basic physical conditions), exercise type (aerobic vs resistance), exercise intensity (high, moderate, low), exercise intervention duration (<12 weeks or ≥12 weeks), exercise setting (home-based, community-based or hospital-based) and supervision status (supervised or unsupervised).

Sensitivity analyses were conducted to assess the robustness of the results by sequentially removing individual studies and re-analysing the pooled effect estimates.^{26–27} This was done through excluding studies with high risk of bias or removing studies with small sample sizes, missing data or low methodological quality.²⁸

Publication bias

Publication bias was assessed using visual inspection of funnel plots, as well as statistical tests including Egger's test and Begg's test.^{29–31} When publication bias was detected, the trim-and-fill method was applied to adjust the pooled results.

Patient and public involvement

No patient or public was involved in the protocol design.

DISCUSSION

Exercise plays an important role in managing lymphedema. According to a recent clinical practice guideline, patients with BCRL (stages 0–III) should be provided with individualised aerobic and resistance exercise programmes.¹¹ Previous studies indicate that different types of exercise have improved BCRL management.³² However, nurses and other medical professionals may find it difficult to recommend an exercise programme that is appropriate for patients with BCRL. Network meta-analysis will be used to compare the relative efficacies of

the various types of exercise interventions on BCRL. The results of our study will confirm the most beneficial effects of exercise interventions on lymphedema, allowing therapists and patients to make better choices for managing BCRL.

Several mechanisms may be involved in the different effects of various exercise interventions on lymphedema. Despite the lack of clarity about the mechanisms, some researchers suggest that resistance exercise is likely to exert effects not only by improving functional capacity, but also by promoting the contractility and relaxation of the skeletal muscles, thereby providing a primary pump mechanism for lymph flow.³³ In addition, this review aims to explore the importance of including evidence from combined exercise interventions, which may operate differently and be more effective than either intervention alone.

ETHICS AND DISSEMINATION

Ethics approval is not applicable for this review protocol, since it does not involve direct contact with patients. The results of this review will be disseminated through publication in a peer-reviewed journal.

Contributors LW and CY were responsible for the study design. TC and QH contributed to search strategy and data extraction. LW and YD were responsible for the drafting of the manuscript. CY made a critical revision of the manuscript. All authors have reviewed the final draft of the manuscript. CY is the guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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