

Exercise and cancer-related lymphedema (CRL): Prevention and treatment

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Body & Cancer



- RCT 2003 (n=269) , implemented 2007
- Cancer patients in chemotherapy (app. 50% breast cancer)
- Six-week, 9-hours weekly; Team training
- Multimodal, high- and low-intensity components

Monday	Tuesday	Wednesday	Thursday	Friday
Resistance and Cardio exercise	Body awareness	Resistance and Cardio exercise	Free	Resistance and Cardio exercise
Relaxation	Relaxation	Relaxation		Relaxation
Massage				Massage

Adamsen et al., 2009



Cancer-related lymphedema

- A result of acquired interruption or damage to the axillary lymphatic system due to cancer treatment or cancer itself
 - = lymphatic load exceeds transport capacity

Too simplistic! Does not explain variations in lymphedema presentation!

- A likely predisposition
 - Inherent variations in lymph flow
 - Higher lymphatic flow; transport capacity already near maximum
 - Additional insult (e.g., surgery) further predisposes

Cintolesi et al. 2016, Rockson et al. 2019



Incidence estimates of lymphedema in various cancers

Breast (2013)

Sentinel Node	6%
Axillary dissection	20%

Gynaecological (2017)

24 months postop.	37%
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Melanoma (2017)

Sentinel node axilla	5%
Axillary dissection	31%
Sentine node inguinal	35%
Inguinal dissection	83%

Head & Neck (2016)

External	7%
Internal	30%
Ext. & Int.	38%

Rockson et al., 2019



Challenges in quantifying CRL: examples from breast cancer

No standardized measurement method or cutoff criteria

- 5% lymphoscintigraphy vs. 28% more than one measure

Timing

- ↑ incidence up to two years post surgery (up to 80%)
- Transient swelling (60% dissipated within the first year)

Treatment burden

- Prevalence range of 13% - 65% depending on treatments received

*Kilbreath et al., 2013; Disipio et al., 2013;
Gartner et al., 2010; McLaughlin, Brunelle & Taghian, 2020*



BCRL risk factors: strong* or moderate levels of evidence

Demographic	Treatment related	Lifestyle
	<p>Axillary surgery</p> <ul style="list-style-type: none"> -Number of metastatic lymph nodes -Number of lymph nodes removed* -Four fold ↑ incidence ALND vs. SNB* <p>Mastectomy*</p> <p>Adjuvant treatments</p> <ul style="list-style-type: none"> - Radiotherapy - Chemotherapy 	<p>BMI ≥ 25 at diagnosis*</p> <p>Physical inactivity</p>

Similar considerations apply to CRL in the upper and lower extremities, but the evidence is not equally robust because fewer studies have been performed.

Disipio et al., 2013; Rockson et al., 2019



Risk reduction recommendations



Historically, risk reduction recommendations included avoidance of exercise as exercise, especially “vigorous” exercise or exercise that included heavy lifting, was considered unsafe and controversial.

K. Johansson & S. Hayes, 2020



Abreast in a boat



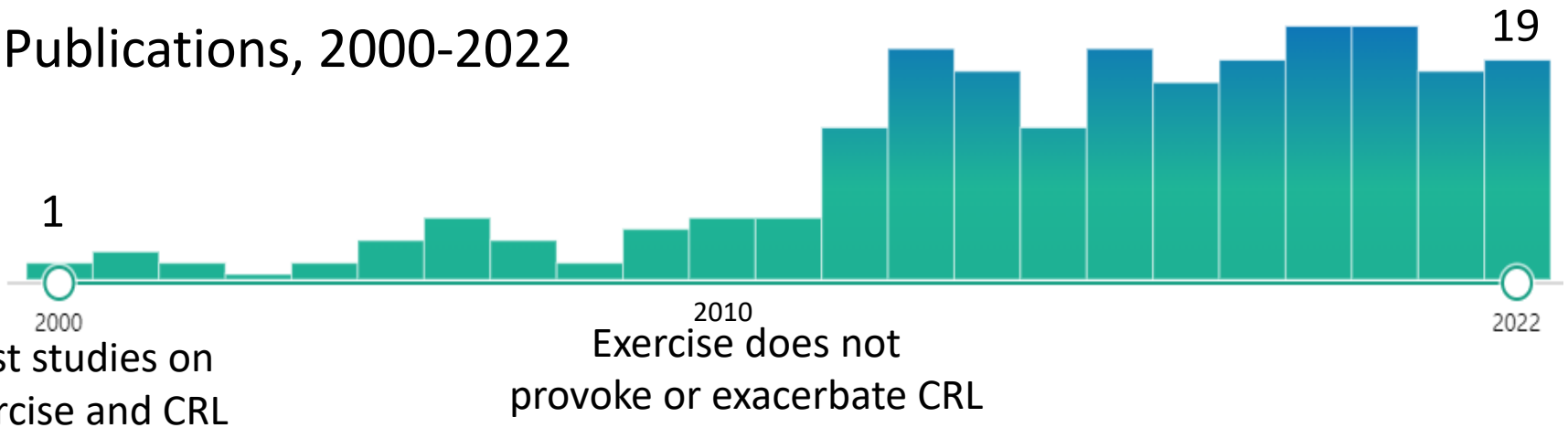
Fig. 1: The Abreast in a Boat team braving the rough waters of Wellington Harbour, New Zealand, at the World Club Crew Championships.

Don McKenzie, 1998



Cancer-related lymphedema AND exercise

Publications, 2000-2022



Pubmed, September 2022



Breast Cancer Res Treat (2014) 148:249–268
DOI 10.1007/s10549-014-3162-9

REVIEW

Safety and efficacy of progressive resistance training in breast cancer: a systematic review and meta-analysis

Birinder S. Cheema · Sharon L. Kilbreath · Paul P. Fahey · Geoffrey P. Delaney · Evan Atlantis

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© Springer Science+Business Media New York 2014

Abstract The purpose of this study was to assess the safety and efficacy of progressive resistance training (PRT) in breast cancer. Randomized controlled trials (RCTs) published to November 2013 that reported on the effects of PRT (>6 weeks) on breast cancer-related lymphedema (BCRL) (incidence/exacerbation, arm volume, and symptom severity), physical functioning (upper and lower body muscular strength), and health-related quality of life (HRQoL) in breast cancer patients were included. Of 446 citations retrieved, 15 RCTs in 1,652 patients were included and yielded five studies on BCRL incidence/exacerbation ($N = 647$), four studies on arm volume ($N = 384$) and BCRL symptom severity ($N = 479$), 11 studies on upper body muscular strength ($N = 1,252$), nine studies on

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Archives of Physical Medicine and Rehabilitation 2016;97:302-15



REVIEW ARTICLE (META-ANALYSIS)

Systematic Review and Meta-Analysis of the Effects of Exercise for Those With Cancer-Related Lymphedema



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lymphedema and related symptoms, and to determine the need for those with

Med, ProQuest Health and Medical Complete, ProQuest Nursing and Allied searched for trials published before January 1, 2015.

als and single-group pre-post studies published in English were included. redefined data fields by 1 reviewer and assessed for accuracy by a second health Practice Project Quality Assessment Tool.

to assess the effects of acute and long-term exercise on lymphedema and reise mode and intervention length. There was no effect of exercise (acute or lardized mean differences from all analyses ranging between -0.2 and 0.1 node (aerobic, resistance, mixed, other) and intervention duration (>12wk + lymphedema or associated symptoms. There were too few studies evaluating a-analysis.

participate in progressive, regular exercise without experiencing a worsening of evidence to support or refute the current clinical recommendation to wear

Lymphedema is a pathologic swelling of limbs or other body parts associated with pain, heaviness, tightness, and other symptoms.¹ Lymphedema may progress in severity over time from mild pitting edema to severe edema, which may be accompanied by fibrosis and other complications such as cellulitis.^{2,3} Cancer-related lymphedema occurs because of obstructed or disrupted lymph flow, which may result from the presence of a tumor, or from trauma or damage to the lymphatic system as a consequence of cancer treatment.^{4,5} Lymphedema risk factors related to cancer and its treatment include more extensive surgery (eg, mastectomy vs lumpectomy), more extensive lymph node dissection (eg, axillary lymph node dissection vs sentinel lymph node biopsy), a greater number of positive lymph nodes, a higher stage of cancer, and treatment with chemotherapy or

of Rehabilitation Medicine

Journal of Physiotherapy 60 (2014) 136-143

Journal homepage: www.elsevier.com/locate/jphys

Research

Weight training is not harmful for women with breast cancer-related lymphoedema: a systematic review

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KEYWORDS
Breast neoplasm
Lymphoedema
Weight training
Exercise

ABSTRACT

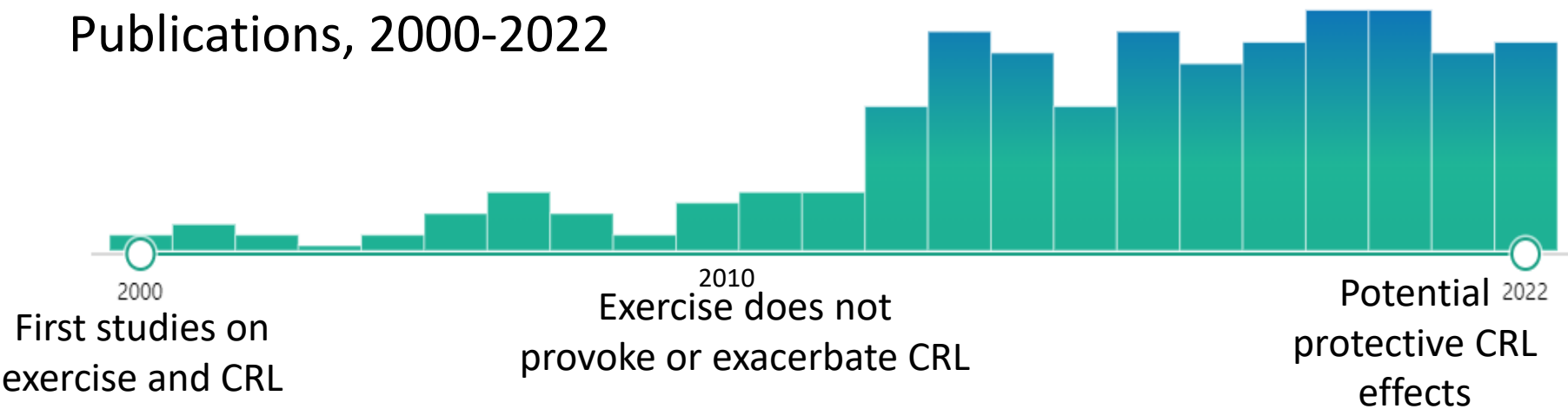
Question: Is weight-training exercise intervention harmful to women with or at risk of breast cancer-related lymphoedema? **Design:** Systematic review with meta-analysis of randomised trials. **Participants:** Women with or at risk of breast cancer-related lymphoedema. **Intervention:** Progressive weight-training exercise. **Outcome measures:** The primary outcomes were severity (volume difference) and incidence of arm lymphoedema. Secondary outcomes included muscle strength of the upper and lower limbs, quality of life and body mass index. **Results:** Eleven studies from eight trials involving 1091 women were included. Weight-training exercise of low to moderate intensity with relatively slow progression significantly improved the upper limb strength (SMD 0.93, 95% CI 0.73 to 1.12) and lower limb strength (SMD 0.75, 95% CI 0.47 to 1.04) without increasing the arm volume (SMD -0.09, 95% CI -0.23 to 0.05) or incidence of breast cancer-related lymphoedema (RR 0.77, 95% CI 0.52 to 1.15). No significant effects were noted for body mass index (SMD -0.10, 95% -0.31 to 0.11). Some aspects of quality of life may improve with weight training. Participants in all trials used pressure garments and received supervision; no trials used high-intensity weight training. **Conclusions:** Weight training appears to be safe and beneficial in improving limb strength and physical components of quality of life in women with or at risk of lymphoedema. Pressure garments, supervision and limiting the intensity of the weight training may each be important, but this could not be confirmed with this review. **Registration:** PROSPERO CRD42012002737. [Paramanandam VS, Roberts D (2014) Weight training is not harmful for women with breast cancer-related lymphoedema: a systematic review. *Journal of Physiotherapy* 60: 136-143]

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Cancer-related lymphedema AND exercise

Publications, 2000-2022



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Lymphology 53 (2020) 55-62

A HISTORICAL ACCOUNT OF THE ROLE OF EXERCISE IN THE PREVENTION AND TREATMENT OF CANCER-RELATED LYMPHEDEMA

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ABSTRACT

In the absence of guidance from scientific evidence, a range of lymphedema prevention and management, guidelines were developed by relevant organizations around the world. These became publicly available, promoted and endorsed, particularly to women with breast cancer. The recommendations advised avoidance of any activity that could overload or restrict the lymphatic system and need for caution when participating in specific physical activities. However, over the past 20 years evidence has accumulated which has significantly challenged the safety of these recommendations, in particular for those with cancer. There now exists consistent and compelling evidence in support of exercise following a diagnosis of cancer. Participating in exercise during and following cancer treatment improves function and quality of life, reduces treatment-related morbidity, and may improve survival. Further, exercise, including resistance exercise at moderate or high load, is considered safe for those at risk- or with lymphedema. That is, exercise has not been shown to cause or worsen cancer-related lymphedema. This article provides a historical account of the advice given to patients in the prevention and management of lymphedema and how this advice has evolved.

Keywords: lymphedema, physical activity, exercise, cancer, prevention, treatment

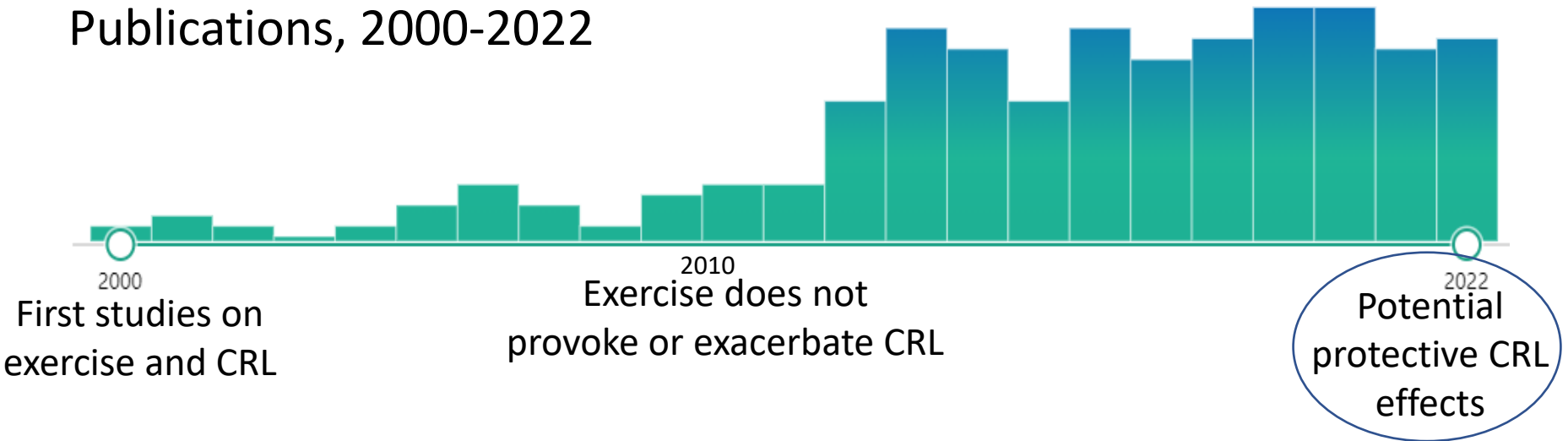
Lymphedema manifests as a consequence of lymphatic system insufficiency where lymph transport capacity is lower than lymph load (1). It is a debilitating condition of worldwide concern and is prevalent in developing and developed countries (2). The major contributing factors to its development differ between countries. In developed nations, it is largely associated with the presence of chronic diseases, including obesity, type II diabetes, and cardiovascular disease, although is most well-known as a consequence of treatment for cancer (2).

Removal of lymph nodes and receipt of adjuvant therapy, such as radiotherapy and chemotherapy have been identified as the primary treatment-related risk factors for the development of cancer-related lymphedema (3). These represent common treatment options for the most prevalent cancers, including breast, prostate, colorectal, and melanoma, but also for the treatment of other solid cancers, such as gynecological, genitourinary, and head and neck cancers. Following a meta-analysis, the incidence of upper-limb lymphedema associated with breast cancer has been estimated to be 21% (3), however with more invasive treatment the



Cancer-related lymphedema AND exercise

Publications, 2000-2022



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The Effect of Exercise for the Prevention and Treatment of Cancer-Related Lymphedema: A Systematic Review with Meta-analysis

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ABSTRACT

HAYES, S. C., B. SINGH, H. REUL-HIRCHE, K. BLOOMQUIST, K. JOHANSSON, C. JÖNSSON, and M. L. PLINSINGA. The Effect of Exercise for the Prevention and Treatment of Cancer-Related Lymphedema: A Systematic Review with Meta-analysis. *Med. Sci. Sports Exerc.*, Vol. 54, No. 8, pp. 1389–1399, 2022. **Introduction:** The purpose of this systematic review and meta-analysis was to evaluate the effects of exercise on (i) the prevention of cancer-related lymphedema (CRL) and (ii) the treatment of CRL, lymphedema-associated symptoms, and other health outcomes among individuals with CRL. **Methods:** An electronic search was undertaken for exercise studies measuring lymphedema and involving individuals at risk of developing or with CRL. The Effective Public Health Practice Project Quality scale was used to assess study quality, and overall quality of evidence was assessed using the Grading of Recommendation, Assessment, Development and Evaluation approach. Meta-analyses were performed to evaluate effects of exercise on CRL incidence, existing CRL status, lymphedema-associated symptoms, and health outcomes. **Results:** Twelve studies ($n = 1955$; 75% moderate-high quality) and 36 studies ($n = 1741$; 58% moderate-high quality) were included in the prevention and treatment aim, respectively. Relative risk of developing CRL for those in the exercise group compared with the nonexercise group was 0.90 (95% confidence interval (CI), 0.72 to 1.13) overall and 0.49 (95% CI, 0.28 to 0.85) for those with five or more lymph nodes removed. For those with CRL in the exercise group, the standardized mean difference (SMD) before to after exercise of CRL was -0.11 (95% CI, -0.22 to 0.01), and compared with usual care postintervention, the SMD was -0.10 (95% CI, -0.24 to 0.04). Improvements after intervention were observed for pain, upper-body function and strength, lower-body strength, fatigue, and quality of life for those in the exercise group (SMD, 0.3–0.8; $P < 0.05$). **Conclusions:** Findings support the application of exercise guidelines for the wider cancer population to those with or at risk of CRL. This includes promotion of aerobic and resistance exercise, and not just resistance exercise alone, as well as unsupervised exercise guided by symptom response. **Key Words:** LYMPHEDEMA, CANCER, AEROBIC EXERCISE, RESISTANCE EXERCISE, EXERCISE ONCOLOGY

Lymphedema is a pathological swelling that affects the limbs or other body segments. In developed countries, lymphedema is most commonly associated with cancer treatment that causes obstruction or disruption of lymph flow (1), including surgical removal of lymph nodes or damage to lymphatics through radiation therapy, and/or increases in lymphatic load, such as through chemotherapy (2,3). Consequently,

cancer-related lymphedema (CRL) has been reported among individuals treated for a range of cancers including melanoma, breast, genitourinary, gynecological, and head and neck (4).

Approximately 20% of breast cancer survivors will develop lymphedema within the first 2 yrs after diagnosis (2), and although less well understood, incidence of lymphedema associated with treatment for other solid tumors ranges between 7% and 38%, depending on the cancer type, and method and timing of lymphedema assessment (4). More extensive lymph node dissection represents the most consistent and strongest risk factor for the development of lymphedema (2). The severity of lymphedema may progress over time from mild edema to severe, chronic edema, and is associated with pain, heaviness, and tightness in the affected region (5,6). The societal cost of the condition is significant. Those with CRL are more likely to experience physical impairments, depression, anxiety, social avoidance, disturbances in relationships, higher financial toxicity, and significantly lower quality of life compared with cancer survivors without lymphedema (7,8).

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APPLIED SCIENCES

Hayes et al., 2022



Main objectives

Evaluate effects of exercise on:

1. The prevention of CRL in at-risk populations
2. Treatment; swelling, lymphedema-related symptoms, and other health outcomes in individuals with CRL

The Effect of Exercise for the Prevention and Treatment of Cancer-Related Lymphedema: A Systematic Review with Meta-analysis

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ABSTRACT
 OBJECTIVE: To evaluate the effect of exercise on the prevention and treatment of cancer-related lymphedema (CRL).
 DESIGN: Systematic review with meta-analysis.
 SETTING: PubMed, Embase, and Cochrane.
 PARTICIPANTS: 19 studies involving 1,100 participants.
 MEASUREMENTS AND MAIN RESULTS: Exercise significantly reduced the risk of CRL in at-risk populations (OR 0.45, 95% CI 0.25-0.85) and improved lymphedema-related symptoms in individuals with CRL (OR 0.45, 95% CI 0.25-0.85).
 CONCLUSIONS: Exercise is an effective intervention for the prevention and treatment of CRL.

KEY WORDS: exercise, lymphedema, cancer, prevention, treatment, meta-analysis.

INTRODUCTION
 Lymphedema is a pathological swelling that affects the limbs or other body segments. In developed countries, lymphedema is most commonly associated with breast cancer, but it can also occur in individuals with other types of cancer. The condition is caused by damage to lymphatic vessels, which results in impaired lymphatic drainage. This leads to the accumulation of fluid in the interstitial space, which causes swelling and discomfort. Lymphedema is a chronic condition that can significantly impact quality of life. It is important to identify effective interventions for the prevention and treatment of lymphedema.

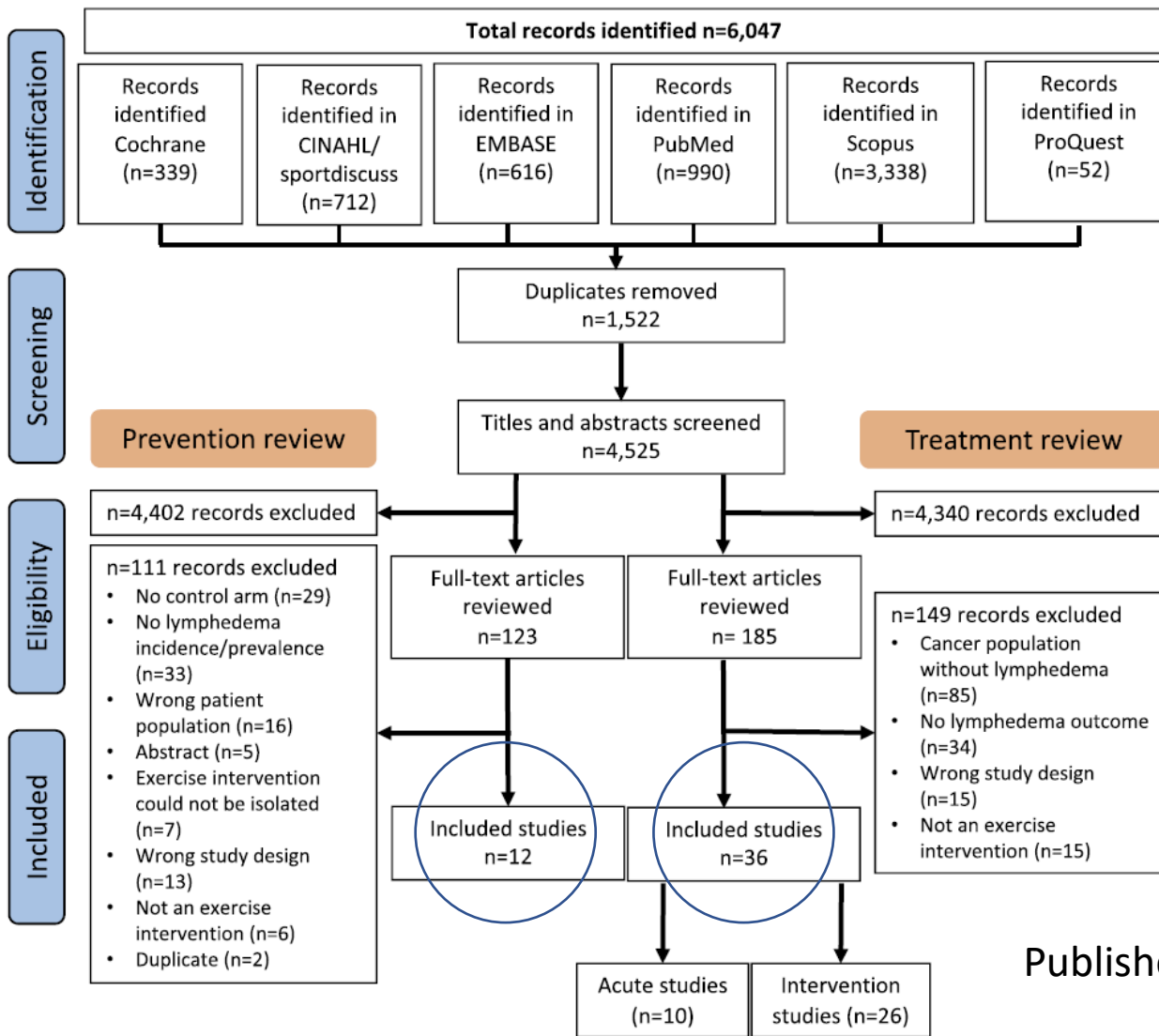
OBJECTIVES
 The primary objective of this systematic review was to evaluate the effect of exercise on the prevention and treatment of CRL. The secondary objectives were to evaluate the effect of exercise on lymphedema-related symptoms and other health outcomes in individuals with CRL.

RESULTS
 The review included 19 studies involving 1,100 participants. Exercise significantly reduced the risk of CRL in at-risk populations (OR 0.45, 95% CI 0.25-0.85) and improved lymphedema-related symptoms in individuals with CRL (OR 0.45, 95% CI 0.25-0.85). The most commonly used exercise interventions were aerobic and resistance training. The most commonly used outcome measures were lymphedema-related symptoms and quality of life.

CONCLUSIONS
 Exercise is an effective intervention for the prevention and treatment of CRL. It is important to encourage individuals at risk of CRL to engage in regular exercise. For individuals with CRL, exercise can help to improve lymphedema-related symptoms and quality of life.



Literature search



The Effect of Exercise for the Prevention and Treatment of Cancer-Related Lymphedema: A Systematic Review with Meta-analysis

KAREN A. LEBERSON, DAVID R. BEN, BENJAMIN H. HARRIS, JESSICA L. HARRIS, KAREN CHANDRAN, CHARLOTTE DUNN, and MELANIE LARSEN FLEMMING

ABSTRACT

OBJECTIVE: To evaluate the effect of exercise on the prevention and treatment of cancer-related lymphedema. DESIGN: Systematic review with meta-analysis. SETTING: Not applicable. PARTICIPANTS: 10,000 patients with breast cancer. MEASUREMENTS AND MAIN RESULTS: The meta-analysis included 10 studies with 10,000 patients. The overall effect size was 0.15 (95% CI 0.05 to 0.25). The meta-analysis included 10 studies with 10,000 patients. The overall effect size was 0.15 (95% CI 0.05 to 0.25). The meta-analysis included 10 studies with 10,000 patients. The overall effect size was 0.15 (95% CI 0.05 to 0.25).

CONCLUSIONS

Exercise is a promising intervention for the prevention and treatment of cancer-related lymphedema. Further research is needed to evaluate the effect of exercise on the prevention and treatment of cancer-related lymphedema.

Published prior to March 1, 2021

FIGURE 1—PRISMA flow diagram.

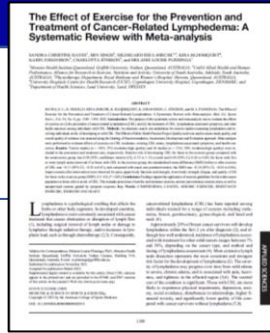




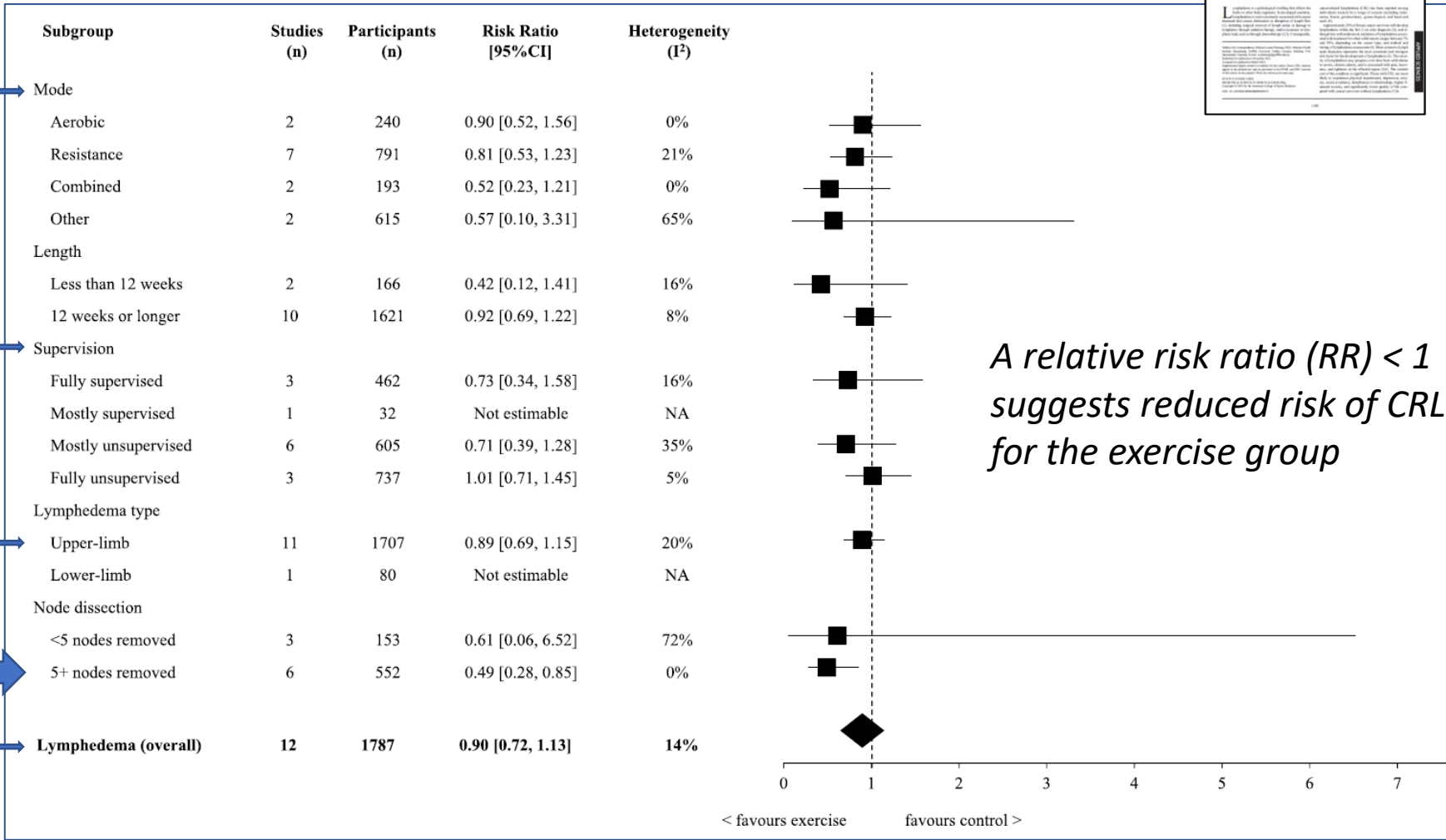
Eligibility criteria: Prevention

- Population: “at risk” of developing CRL and treated for cancer (of any type)
- Intervention: regular exercise with CRL assessed before and after intervention
 - Excluded:
 - **acute** studies that assessed the effects after a single bout of exercise
 - exercise + **other interventions if effects of exercise could not be isolated**
- Comparator: no exercise, usual care, CRL prevention intervention **without exercise**
- Outcomes: CRL (swelling) via any method (e.g., self-reported, BIS, circumference) with or without CRL-related symptoms





Results: Prevention (n = 12)





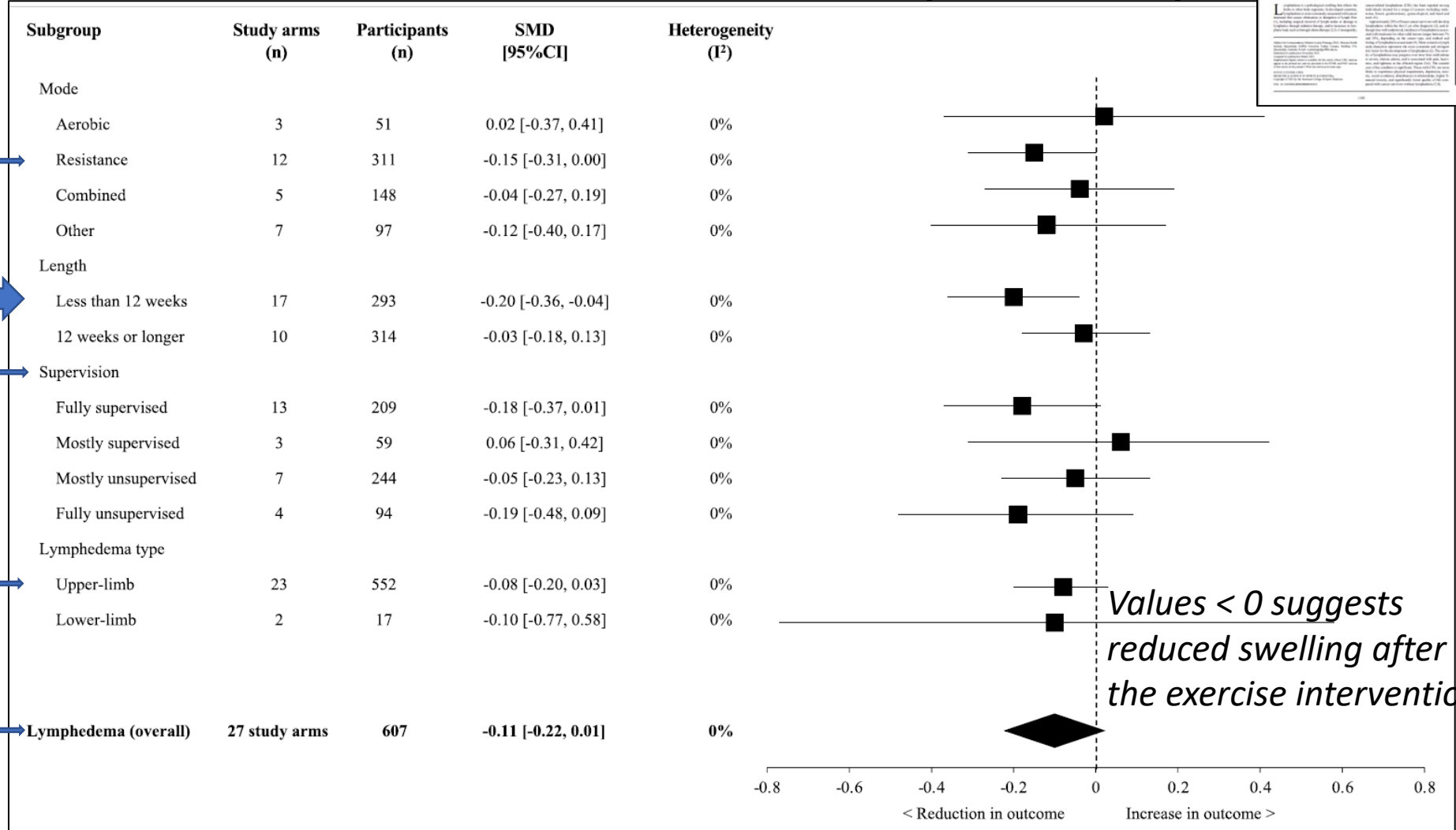
Eligibility criteria: Treatment

Population: with CRL.

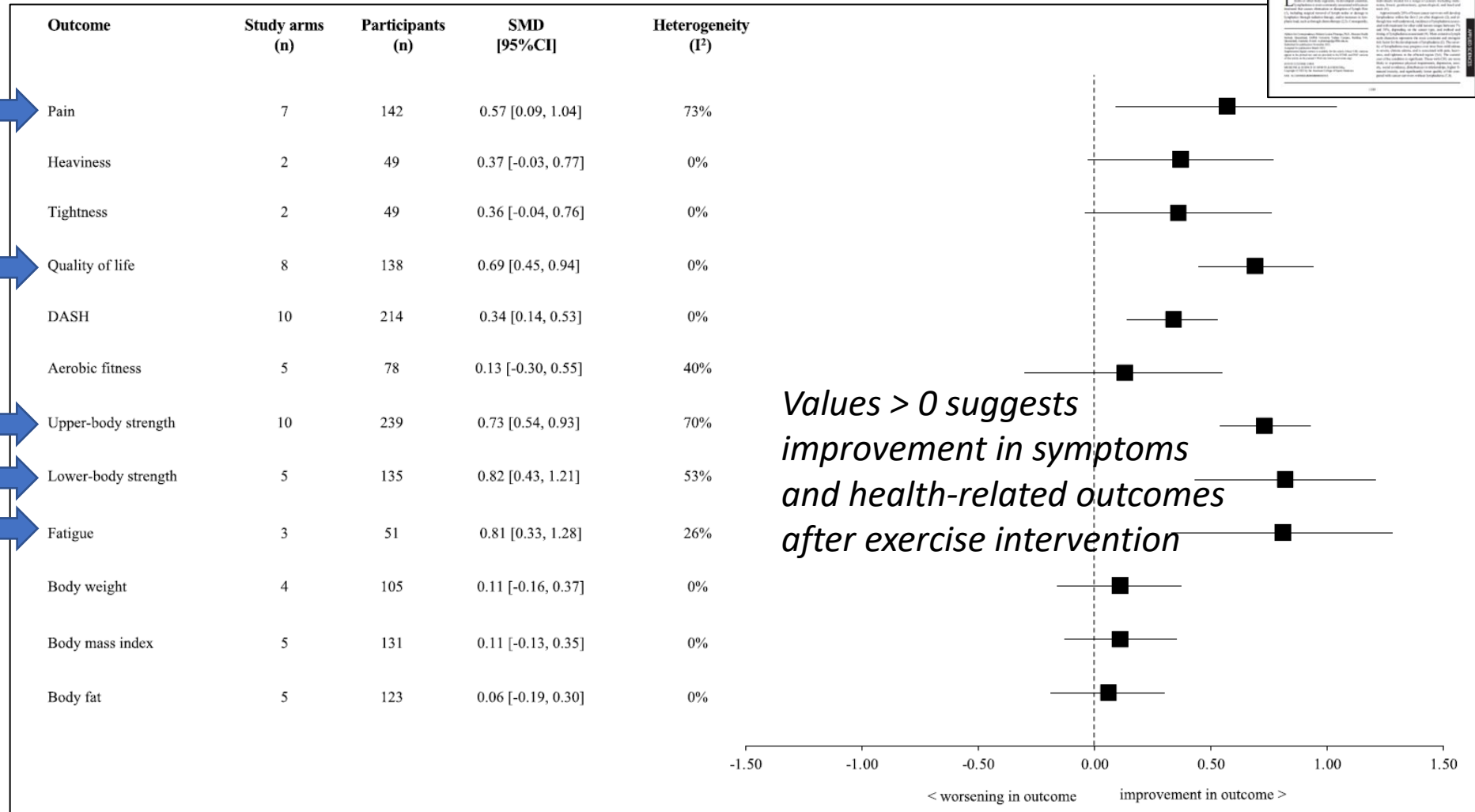
- **Intervention:** regular exercise with CRL assessed before and after intervention and **acute** studies that assessed the effects after a single bout of exercise
 - Excluded:
 - exercise + **other interventions if effects of exercise could not be isolated**
 - exercise as **component of complete decongestive therapy**
- **Comparator:** no exercise, usual care, a different mode of exercise (including different dose or intensity), other intervention, or single-group studies with no comparator
- **Outcomes:** CRL (swelling) via any method (e.g., self-reported, BIS, circumference) with or without CRL-related symptoms



Results: Treatment (n = 23)



Results: Treatment



Aerobic

Resistance

Other

Prevention studies

Mode	Exercises on cycle ergometer, treadmill, or elliptical; step aerobics; brisk walking; water-based exercises; individual or group-based (classes)	Upper- and lower-body, machine, free-weight, and Theraband resistance exercises; individual or group-based (classes)	Football fitness, deep breathing, stretches; individual or group-based (classes)
Intensity	Low-high	Low-high	Low-high
Duration of session	15-40 min per session; weekly total of 150 min	45-90 min	45-60 min
Frequency	3-4 sessions per week	2-4 sessions per week; daily (P9, P15)	2-4 sessions per week; daily (43)
Intervention duration	8 wk-6 months; duration of chemotherapy (39)	8 wk-24 months; duration of chemotherapy (39)	6 wk-24 months
Progression	When specified: aerobic intensity progression weeks 1-6 at 60% $\dot{V}O_{2max}$, weeks 7-12 at 70%, >week 12 at 80% (39). Duration progression week 1 to 3 for 15 min, 5-min increase every 3 wk up to 45 min (39). Resistance: progressed individually per week or increase resistance weight by 5%-10%		

Treatment studies

Acute studies

Mode	Nordic (pole) walking; treadmill walking	Upper body, machine and free-weight resistance exercises	Tai chi, repetitive active arm exercises with/ out equipment
Intensity	Low-high	Low-high	Low-moderate
Session duration	≤60 min	≤60 min	≤60 min

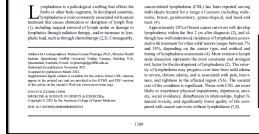
Intervention studies

Mode	Walking, jogging, cycling, swimming, aerobics, Nordic (pole) walking, arm ergometry, floor-based aerobic exercise to music, water-based aerobics; individual or group-based (classes)	Upper- and lower-body, machine, free-weight and Theraband resistance exercises; individual or group-based (classes)	Yoga, Pilates, Tai chi, water-based exercises; individual or group-based (classes)
Intensity	Low-high	Low-high	Low-high
Session duration	10-60 min per session, performed as continuous aerobic exercise or 1-6 bouts of 1-20 min; weekly total of 150-180 min	35-90 min per sessions; weekly total of 150-180 min	30-90 min
Frequency	2-7 sessions per week	1-7 sessions per week; twice daily for ≤10 min of bouts	2-3 sessions per week
Intervention duration	4 wk-12 months	4 wk-12 months	6-12 wk
Progression	When specified: Aerobic: increase in 1-2 metabolic equivalents per week; or progressive increase in exercise time and/or intensity to maintain prescribed total exercise dose if there was no worsening in lymphedema. Resistance: individualized exercise progression involving adding 1-2 new exercises per week or increase resistance weight by 5%-10%. Generally, exercise was progressed if (i) no changes in swelling or lymphedema-related symptoms, (ii) a given level of resistance could be performed with proper form, and/or (iii) individuals were able to perform more repetitions than the prescribed amount during a set without changes in lymphedema or symptoms		
Indications to stop or reduce exercise	Excessive fatigue, postexercise muscle soreness >48 h, or a worsening of swelling or symptoms during or after exercise		



In summary

- Overall CRL prevention and treatment favored participation in exercise, although this was only **supported statistically for the effect of exercise on CRL prevention for women with breast cancer with 5 + nodes removed.**
- In individuals with CRL; **benefits observed in pain, fatigue, upper-body function, strength, and quality of life** underscore the importance of regular exercise.
- **Findings reflect breast cancer survivors.** However, consistent trends favoring exercise suggest that the **physical activity and exercise guidelines promoted to the wider cancer population are likely applicable to those at risk or with CRL.**



In summary



- Findings support that exercise, no matter the type, should be encouraged and promoted. This importantly **allows for patient exercise preferences** to be considered.
- Findings also support that **patients with or at risk of CRL should be encouraged and empowered to exercise, even in the absence of supervision.**
- Importantly, **an individualized approach** should be taken to exercise prescription letting **lymphedema symptom response guide** pace and increments of progression in exercise duration, intensity and frequency.



Tak!

