

APPENDIX

Conservative intervention strategies for adult cancer-related lymphedema: a systematic review and network meta-analysis of randomized controlled trials

Lyubov Lytvyn, Dena Zeraatkar, Allison Anbari, Pamela Ginex, Michael J Zoratti, Kacper Niburski, Behnam Sadeghirad, Madelin Siedler, Lehana Thabane, Rebecca L. Morgan

Table of Contents

APPENDIX 1. PRISMA NMA CHECKLIST OF ITEMS TO INCLUDE WHEN REPORTING A SYSTEMATIC REVIEW INVOLVING A NETWORK META-ANALYSIS.	2
APPENDIX 2. SEARCH STRATEGY.....	6
APPENDIX TABLE 3. SECONDARY OUTCOMES HIERARCHY.	10
APPENDIX TABLE 4. DESCRIPTIONS AND CLASSIFICATIONS OF INTERVENTION ARMS.	11
APPENDIX TABLE 5. STUDIES EXCLUDED AT FULL TEXT SCREENING, WITH REASONS.	14
APPENDIX TABLE 6. STUDY FUNDING AND AUTHOR DECLARATIONS OF INTEREST.....	20
APPENDIX TABLE 7. RISK OF BIAS AMONG INCLUDED STUDIES.	22
APPENDIX TABLE 8. NARRATIVE SUMMARY INCLUDED INTERVENTIONS ON LYMPHEDEMA VOLUME.	24
APPENDIX TABLE 9. NETWORK META-ANALYSIS OF LYMPHEDEMA VOLUME LEAGUE TABLE.	26
APPENDIX TABLE 10. INCONSISTENCY TEST BETWEEN DIRECT AND INDIRECT TREATMENT COMPARISONS.	27
APPENDIX TABLE 11. NARRATIVE SUMMARY OF INCLUDED INTERVENTIONS ON PAIRWISE COMPARISONS.....	28
APPENDIX TABLE 12. NARRATIVE SUMMARY OF ADVERSE EVENTS OF INCLUDED INTERVENTIONS.	31
APPENDIX FIGURE 1. NETWORK META-ANALYSIS OF CONSERVATIVE INTERVENTIONS COMPARED TO STANDARD CARE ON LYMPHEDEMA VOLUME CHANGE	33

Appendix 1. PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis.

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review <i>incorporating a network meta-analysis (or related form of meta-analysis)</i> .	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: Background: main objectives Methods: data sources; study eligibility criteria, participants, and interventions; study appraisal; and <i>synthesis methods, such as network meta-analysis</i> . Results: number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; <i>treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.</i> Discussion/Conclusions: limitations; conclusions and implications of findings. Other: primary source of funding; systematic review registration number with registry name.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, <i>including mention of why a network meta-analysis has been conducted</i> .	4-5
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-5
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. <i>Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification)</i> .	6-7

Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6-7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7-9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-9
Geometry of the network	S1	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	NA
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8-9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). <i>Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.</i>	9
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: <ul style="list-style-type: none"> • <i>Handling of multi-arm trials;</i> • <i>Selection of variance structure;</i> • <i>Selection of prior distributions in Bayesian analyses; and</i> • <i>Assessment of model fit.</i> 	9
Assessment of Inconsistency	S2	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	9
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8-9
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: <ul style="list-style-type: none"> • Sensitivity or subgroup analyses; 	NA

- Meta-regression analyses;
- *Alternative formulations of the treatment network; and*
- *Use of alternative prior distributions for Bayesian analyses (if applicable).*

RESULTS†

Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10, 22
Presentation of network structure	S3	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	23
Summary of network geometry	S4	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	NA
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10, 24-26
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	10-11
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. <i>Modified approaches may be needed to deal with information from larger networks.</i>	NA
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. <i>In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.</i> If additional summary measures were explored (such as treatment rankings), these should also be presented.	11-12
Exploration for inconsistency	S5	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, <i>P</i> values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	Appendix X
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, <i>alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses, and so forth</i>).	NA

DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). <i>Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).</i>	14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	1

Appendix 2. Search strategy.

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date searched: October 31 2019

Records identified: 890

#	Term
1.	exp LYMPHEDEMA/
2.	lymph?edema.tw.
3.	lymph* edema.tw.
4.	lymph* oedema.tw.
5.	exp EXERCISE/
6.	exercis*.tw.
7.	training.tw.
8.	exp Physical Therapy Modalities/
9.	physiotherap*.tw.
10.	exp Drainage/
11.	lymph* drain*.tw.
12.	lymph* therap*.tw.
13.	manual lymph*.tw.
14.	massag*.tw.
15.	decongesti* therap*.tw.
16.	decongesti* treatment*.tw.
17.	decongesti* physiotherap*.tw.
18.	laser therap*.tw.
19.	exp Compression Bandages/
20.	compression.tw.
21.	bandag*.tw.
22.	dressing*.tw.
23.	garment*.tw.
24.	clinical trial.mp.

25.	clinical trial.pt.
26.	random:.mp.
27.	tu.xs.
28.	OR/1-4
29.	OR/5-23
30.	OR/24-27
31.	28 and 29 and 30

Database: OVID Embase 1974 to 2018 December 14

Date searched: October 31 2019

Records identified: 1664

#	Term
1.	exp lymphedema/
2.	lymph?edema.tw.
3.	lymph* edema.tw.
4.	lymph* oedema.tw.
5.	exp exercise/
6.	exercis*.tw.
7.	training.tw.
8.	exp physiotherapy/
9.	physiotherap*.tw.
10.	exp lymphatic drainage/
11.	exp manual lymphatic drainage/
12.	lymph* drain*.tw.
13.	lymph* therap*.tw.
14.	manual lymph*.tw.
15.	massag*.tw.
16.	decongesti* therap*.tw.
17.	decongesti* treatment*.tw.
18.	decongesti* physiotherap*.tw.
19.	laser therap*.tw.

20.	exp compression bandage/
21.	exp compression therapy/
22.	exp compression garment/
23.	compression.tw.
24.	bandag*.tw.
25.	dressings*.tw.
26.	garment*.tw.
27.	random:.tw.
28.	clinical trial:.mp.
29.	exp health care quality/
30.	or/1-4
31.	or/5-26
32.	or/27-29
33.	30 and 31 and 32

Database: CINAHL

Date searched: October 31 2019

Records identified: 787

#	Term
1.	MH "Lymphedema+"
2.	lymphedema
3.	lymphoedema
4.	"lymph* edema"
5.	"lymph* oedema"
6.	MH "Exercise+"
7.	exercis*
8.	training
9.	MH "Physical Therapy+"
10.	physiotherap*
11.	MH "Drainage+"
12.	"lymph* drain*"

13.	“lymph* therap*”
14.	“manual lymph*”
15.	massag*
16.	“decongesti* therap*”
17.	“decongesti* treatment*”
18.	“decongesti* physiotherap*”
19.	“laser therap*”
20.	MH "Elastic Bandages"
21.	compression
22.	bandag*
23.	dressing*
24.	garment*
25.	S1 OR S2 OR S3 OR S4 OR S5
26.	S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24
27.	TX allocat* random* OR (MH "Quantitative Studies") OR (MH "Placebos") OR TX placebo* OR TX random* allocat* OR (MH "Random Assignment") OR TX randomi* control* trial* OR TX ((singl* n1 blind*) OR (singl* n1 mask*)) OR TX ((doubl* n1 blind*) OR (doubl* n1 mask*)) OR TX ((tripl* n1 blind*) OR (tripl* n1 mask*)) OR TX ((trebl* n1 blind*) OR (trebl* n1 mask*)) OR TX clinic* n1 trial* OR PT Clinical trial OR (MH "Clinical Trials+")
28.	S25 AND S26 AND S27

Appendix Table 3. Secondary outcomes hierarchy.

Lymphedema swelling and symptoms	Return to work and usual activities of daily living & Decrease in physical activity	Fatigue	Function	Quality of life	Pain
1. Heaviness	1. Social reclusion	1. Fatigue	1. Disabilities of the Arm, Shoulder, and Hand questionnaire (DASH)	1. Lymphoedema Quality of Life Questionnaire (LYMQOL)	1. Pain - VAS
2. Lymphedema-related limb symptoms			2. Quick Disability of the Arm, Shoulder and Hand questionnaire (Quick DASH)	2. Functional Assessment of Cancer Therapy Questionnaire for Breast Cancer - for patients with lymphedema (FACT-B+4)	2. Pain - Other
3. Self-reported questionnaire			3. Grip strength	3. Lymphedema Symptom and Intensity Survey - Arm (LSIDS-A)	3. Brief Pain Inventory Questionnaire (BPI)
4. Subjective symptom questionnaire			4. Loss of shoulder mobility	4. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 (EORTC QLQ-C30)	4. Short-form McGill Pain Questionnaire (MPQ)
5. Sensations			5. Arm function	5. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Breast Cancer 23 (EORTC QLQ-BR23)	
			6. Limb range of motion	6. Short-Form 36 Questionnaire (SF-36)	
			7. Shoulder range of motion	7. American Shoulder and Elbow Surgeons Standardized Shoulder Assessment Form (ASES)	
			8. Shoulder abduction	8. Quality of Life Lymphedema Questionnaire	
				9. Beck Depression Inventory (BDI)	

Appendix Table 4. Descriptions and classifications of intervention arms.

Study Label (Author, Y)	Treatment duration (weeks)	Arm	Classification	MLD	SLD	Remedial exercise	Skin and nail care	Compression bandages	Compression garments	Compression pumps	Resistance/weight training exercise	Aerobic exercise	Water-based/yoga exercise
Anderson 2000	2	Arm 1	CDT	X	X	X	X		X				
	NR	Arm 2	Standard care			X	x		X				
Bergmann 2014	3-4	Arm 1	CDT	X		X	X	X	X				
	NR	Arm 2	Standard care			X	X	X	X				
Bok 2016	8	Arm 1	CDT + Resistance exercise	X			X	X			X		
	8	Arm 2	CDT	X			X	X					
Buchan 2016	12	Arm 1	Aerobic exercise									X	
	12	Arm 2	Resistance exercise								X		
Buragadda 2015	6	Arm 1	CDT	X		X			X				
	6	Arm 2	CDT	X	X	X	X		X				
Chmielewska 2016	4	Arm 1	Compression pumps							X			
	4	Arm 2	Compression pumps + Resistance exercise							X	X		
Cormie 2013	21	Arm 1	Resistance exercise								X		
	21	Arm 2	Standard care										
Dayes 2013	4 + 2*	Arm 1	CDT	X		X	X	X	X				
	6	Arm 2	Standard care			X	X		X				
Didem 2005	4	Arm 1	CDT	X	X	X	X	X					
	4	Arm 2	Standard care		X	X	X	X					
Do 2015	1-2 + 8**	Arm 1	CDT + Resistance exercise	X		X	X		X		X		
	1-2	Arm 2	CDT	X		X	X		X				
Do 2017	4	Arm 1	CDT + Compression pumps + Aerobic and resistance exercise	X	X	X	X	X	X	X	X	X	
	4	Arm 2	CDT + Compression pumps	X	X	X	X	X	X	X			
Gradalski 2015	2	Arm 1	CDT	X		X	X	X	X				
	2	Arm 2	Standard care			X	X	X	X				

Study Label (Author, Y)	Treatment duration (weeks)	Arm	Classification	MLD	SLD	Remedial exercise	Skin and nail care	Compression bandages	Compression garments	Compression pumps	Resistance/weight training exercise	Aerobic exercise	Water-based/yoga exercise
Gurdal 2012	6	Arm 1	CDT	X		X	X	X	X				
	6	Arm 2	Compression pumps		X	X	X		X	X			
Haghighat 2010	2-3	Arm 1	CDT + Compression pumps	X	X	X	X	X	X	X			
	2-3	Arm 2	CDT	X	X	X	X	X	X				
Hayes 2009	12	Arm 1	Aerobic and resistance exercise								X	X	
	12	Arm 2	Standard care										
Jeffs 2013	26	Arm 1	Resistance exercise			X	X		X		X		
	26	Arm 2	Standard care			X	X		X				
Johansson 1998	2	Arm 1	Compression pumps						X	X			
	2	Arm 2	MLD	X					X				
Johansson 2013	8	Arm 1	Water-based/yoga exercise			X							X
	NR	Arm 2	Standard care			X							
Letellier 2014	12	Arm 1	Water-based/yoga exercise			X	X		X				X
	12	Arm 2	Standard care			X	X		X				
Ligabue 2019	24	Arm 1	CDT	X	X		X	X	X				
	24	Arm 2	CDT	X			X		X				
Loudon 2014	8	Arm 1	Water-based/yoga exercise		X		X		X				X
	NR	Arm 2	Standard care		X		X		X				
Luz 2018	8	Arm 1	CDT	X		X	X	X			X		
	8	Arm 2	CDT + Resistance exercise	X		X	X	X					
McClure 2010	17	Arm 1	Water-based/yoga exercise										X
	17	Arm 2	Standard care										
McKenzie 2003	8	Arm 1	Aerobic and resistance exercise						X		X	X	
	8	Arm 2	Standard care										
McNeely 2004	4	Arm 1	MLD	X			X	X					
	4	Arm 2	Standard care				X	X					

Study Label (Author, Y)	Treatment duration (weeks)	Arm	Classification	MLD	SLD	Remedial exercise	Skin and nail care	Compression bandages	Compression garments	Compression pumps	Resistance/weight training exercise	Aerobic exercise	Water-based/yoga exercise
Park 2017	4	Arm 1	Aerobic and resistance exercise								X	X	
	4	Arm 2	CDT	X			X	X		X			
Pasyar 2019	8	Arm 1	Water-based/yoga exercise										X
	NR	Arm 2	Standard care										
Sanal Toprak 2019	5	Arm 1	Compression pumps			X		X		X			
	5	Arm 2	CDT	X		X		X					
Schmitz 2009	13 + 39***	Arm 1	Resistance exercise			X	X		X		X		
	NR	Arm 2	Standard care			X	X		X				
Schmitz 2019	52	Arm 1	Aerobic and resistance exercise						X		X	X	
	NR	Arm 2	Standard care						X				
Sitzia 2002	5	Arm 1	CDT	X		X	X	X					
	5	Arm 2	CDT	X		X	X	X					
Szolnok 2009	2	Arm 1	CDT + Compression pumps	X		X	X	X		X			
	2	Arm 2	CDT	X		X	X	X					
Szuba 2002	2	Arm 1	CDT + Compression pumps	X	X			X	X	X			
	NR	Arm 2	CDT	X	X			X	X				
Tambour 2018	4	Arm 1	CDT	X		X	X	X					
	4	Arm 2	SC			X	X	X					
Uzkeser 2015	3	Arm 1	CDT + Compression pumps	X			X	X		X			
	3	Arm 2	CDT	X			X	X					
Wigg 2009	2	Arm 1	Compression pumps			X	X	X		X			
	2	Arm 2	CDT	X		X	X	X					

* = 4 weeks CDT + 2 weeks standard care. ** = 1-2 weeks CDT + 8 weeks exercise. *** 13 weeks supervised exercise, 39 weeks unsupervised.

CDT = Complete Decongestive Therapy, MLD = Manual Lymphatic Drainage, NR = Not Reported, SLD = Self Lymphatic Drainage.

Appendix Table 5. Studies excluded at full text screening, with reasons.

#	Author	Year	Title	Reason for exclusion
1	Arinaga	2016	A 10 Minute Self-Care Program May Reduce Breast Cancer-Related Lymphedema: A Six-Month Prospective Longitudinal Comparative Study	Wrong study design - Not RCT
2	Badger	2001	Multilayer bandaging plus compression hosiery was better than hosiery alone for unilateral lymphedema of a limb	Wrong study design - Not RCT
3	Carvalho	2016	Association of elastic stockings and mechanical lymphatic therapy	Wrong study design - Not RCT
4	Cooper	2013	Compression therapy in chronic oedema and lymphoedema	Wrong study design - Not RCT
5	Cooper	2013	Compression therapy in oedema and lymphoedema	Wrong study design - Not RCT
6	Dayes	2008	Lymphedema in women with breast cancer: characteristics of patients screened for a randomized trial	Wrong study design - Not RCT
7	De Godoy	2010	Intensive treatment of leg lymphedema	Wrong study design - Not RCT
8	Deltombe	2013	Manual drainage versus Lymphassist at 40 mm Hg: Comparative plethysmographic study on upper limb lymphoedema	Wrong study design - Not RCT
9	Dhinakaran	2014	Effect of Complete Decongestive Therapy (CDT) in Upper Limb Lymphedema in Breast Cancer Patients	Wrong study design - Not RCT
10	Douglass	2012	Yoga for women with breast cancer-related lymphoedema: A preliminary month study	Wrong study design - Not RCT
11	Fiaschi	1998	Manual lymphatic drainage for chronic post-mastectomy lymphoedema treatment	Wrong study design - Not RCT
12	Fillon	2018	Combined physiologic and excisional therapies improve cancer-related lymphedema outcomes	Wrong study design - Not RCT
13	Fisher	2014	Effects of yoga on arm volume among women with breast cancer related lymphedema: A pilot study	Wrong study design - Not RCT
14	Fong	2014	Effects of qigong exercise on upper limb lymphedema and blood flow in survivors of breast cancer: a pilot study	Wrong study design - Not RCT
15	Franks	2015	Intermittent pneumatic compression devices in the management of lymphedema	Wrong study design - Not RCT
16	Galantino	2013	Exercise interventions for upper limb dysfunction due to breast cancer treatment	Wrong study design - Not RCT
17	Guerreiro Godoy Mde	2010	Active exercises utilizing a facilitating device in the treatment of lymphedema resulting from breast cancer therapy	Wrong study design - Not RCT
18	Imamoglu	2016	The Effect of Education on Upper Extremity Function in Patients with Lymphedema after Breast Cancer Treatments	Wrong study design - Not RCT
19	Kang	2012	Pressure monitoring of multilayer inelastic bandaging and the effect of padding in breast cancer-related lymphedema patients	Wrong study design - Not RCT
20	Karadibak	2009	Effect of complex decongestive therapy on upper extremity lymphedema	Wrong study design - Not RCT
21	Kraft	2010	Weak benefit of aqua lymphatic therapy for mild lymphoedema after breast cancer	Wrong study design - Not RCT
22	Lindquist	2015	Water Exercise Compared to Land Exercise or Standard Care in Female Cancer Survivors with Secondary Lymphedema	Wrong study design - Not RCT

23	Loudon	2012	The effect of yoga on women with secondary arm lymphoedema from breast cancer treatment	Wrong study design - Not RCT
24	Martin	2011	Manual lymphatic drainage therapy in patients with breast cancer related lymphoedema	Wrong study design - Not RCT
25	McNeely	2011	Conservative and dietary interventions for cancer-related lymphedema	Wrong study design - Not RCT
26	Swedish Council on Health Technology	2005	Manual Lymph Drainage Combined With Compression Therapy for Arm Lymph- edema Following Breast Cancer Treatment	Wrong study design - Not RCT
27	Szuba	2005	Literature watch. The addition of manual lymph drainage to compression therapy for breast cancer related lymphedema: a randomized controlled trial	Wrong study design - Not RCT
28	Anonymous	2012	Effects of complex decongestive physiotherapy on physical function and depression level of subjects with secondary lymphedema after modified radical mastectomy	Wrong study design - Not RCT
29	Ergin	2017	Effects of Aqua-Lymphatic Therapy on Lower Extremity Lymphedema: A Randomized Controlled Study	Wrong population – Not secondary cancer-related lymphedema
30	Cho	2016	Effects of a physical therapy program combined with manual lymphatic drainage on shoulder function, quality of life, lymphedema incidence, and pain in breast cancer patients with axillary web syndrome following axillary dissection	Wrong population - Not cancer-related lymphedema
31	de Godoy	2014	Synergistic effect of adjustments of elastic stockings to maintain reduction in leg volume after mechanical lymph drainage	Wrong population - Not cancer-related lymphedema
32	Mariana	2011	The effect of mechanical lymph drainage accompanied with heat on lymphedema	Wrong population - Not cancer-related lymphedema
33	Anderson	2012	A randomized trial of exercise on well-being and function following breast cancer surgery: the RESTORE trial	Wrong population - Not baseline lymphedema/prevention intervention
34	Basen-Engquist	2006	Randomized pilot test of a lifestyle physical activity intervention for breast cancer survivors	Wrong population - Not baseline lymphedema/prevention intervention
35	Brown	2015	Weight-lifting and appendicular skeletal muscle mass among breast cancer survivors: a randomized controlled trial	Wrong population - Not baseline lymphedema/prevention intervention
36	Brown	2012	Safety of weightlifting among women with or at risk for breast cancer-related lymphedema: musculoskeletal injuries and health care use in a weightlifting rehabilitation trial	Wrong population - Not baseline lymphedema/prevention intervention
37	Campbell	2012	Five year follow up of an exercise intervention during breast cancer treatment	Wrong population - Not baseline lymphedema/prevention intervention
38	Cases	2016	Detailed methods of two home-based vegetable gardening intervention trials to improve diet, physical activity, and quality of life in two different populations of cancer survivors	Wrong population - Not baseline lymphedema/prevention intervention
39	Fernandez-Lao	2013	Water versus land-based multimodal exercise program effects on body composition in breast cancer survivors: a controlled clinical trial	Wrong population - Not baseline lymphedema/prevention intervention
40	Forchuk	2004	Postoperative arm massage: a support for women with lymph node dissection...previously published in Cancer Nursing, Volume 27, Issue No. 1, pp. 233 (2004). Reprinted with permission	Wrong population - Not baseline lymphedema/prevention intervention

41	Kawada	2017	Influence of exercise or educational programs on long-term physical activity by patients after surgery for primary breast cancer: A randomized trial	Wrong population - Not baseline lymphedema/prevention intervention
42	Kilbreath	2012	Upper limb progressive resistance training and stretching exercises following surgery for early breast cancer: a randomized controlled trial	Wrong population - Not baseline lymphedema/prevention intervention
43	Kilbreath	2006	Resistance and stretching shoulder exercises early following axillary surgery for breast cancer	Wrong population - Not baseline lymphedema/prevention intervention
44	Ochalek	2018	Do Compression Sleeves Reduce the Incidence of Arm Lymphedema and Improve Quality of Life? Two-Year Results from a Prospective Randomized Trial in Breast Cancer Survivors	Wrong population - Not baseline lymphedema/prevention intervention
45	Oliveira	2018	Long term effects of manual lymphatic drainage and active exercises on physical morbidities, lymphoscintigraphy parameters and lymphedema formation in patients operated due to breast cancer: A clinical trial	Wrong population - Not baseline lymphedema/prevention intervention
46	Sawan	2009	Lower-limb lymphedema and vulval cancer: feasibility of prophylactic compression garments and validation of leg volume measurement	Wrong population - Not baseline lymphedema/prevention intervention
47	Ahmed	2006	Randomized controlled trial of weight training and lymphedema in breast cancer survivors	Wrong population - Not baseline lymphedema/prevention intervention
48	Dini	1998	The role of pneumatic compression in the treatment of postmastectomy lymphedema. A randomized phase III study	Wrong population - Not baseline lymphedema/prevention intervention
49	Kim	2010	Effect of Active Resistive Exercise on Breast Cancer-Related Lymphedema: A Randomized Controlled Trial	Wrong population - Not baseline lymphedema/prevention intervention
50	Sandel	2005	Dance and movement program improves quality-of-life measures in breast cancer survivors	Wrong population - Not baseline lymphedema/prevention intervention
51	Sener	2017	Effects of Clinical Pilates Exercises on Patients Developing Lymphedema after Breast Cancer Treatment: A Randomized Clinical Trial	Wrong population - Not baseline lymphedema/prevention intervention
52	Bergan	1998	A comparison of compression pumps in the treatment of lymphedema	Wrong outcome - Less than 2-week follow-up
53	Abe	2017	Difference between immediate effects of active exercise with compression therapy on lower-limb lymphedema while seated and supine	Wrong intervention - Less than 2 weeks treatment
54	Bok	2018	Evaluation of Stiffness in Postmastectomy Lymphedema Using Acoustic Radiation Force Impulse Imaging: A Prospective Randomized Controlled Study for Identifying the Optimal Pneumatic Compression Pressure to Reduce Stiffness	Wrong intervention - Less than 2 weeks treatment
55	Cormie	2016	Acute Inflammatory Response to Low-, Moderate-, and High-Load Resistance Exercise in Women With Breast Cancer-Related Lymphedema	Wrong intervention - Less than 2 weeks treatment
56	Damstra	2010	Comparative prospective study between volume and low and high interface pressure under short-stretch compression bandages in the treatment of breast cancer lymphedema	Wrong intervention - Less than 2 weeks treatment
57	Damstra	2009	Compression therapy in breast cancer-related lymphedema: A randomized, controlled comparative study of relation between volume and interface pressure changes	Wrong intervention - Less than 2 weeks treatment

58	Damstra	2013	Prospective, randomized, controlled trial comparing the effectiveness of adjustable compression Velcro wraps versus inelastic multicomponent compression bandages in the initial treatment of leg lymphedema	Wrong intervention - Less than 2 weeks treatment
59	Fukushima	2017	Immediate effects of active exercise with compression therapy on lower-limb lymphedema	Wrong intervention - Less than 2 weeks treatment
60	Fukushima	2015	Immediate effects of active exercise with compression therapy on lower-limb lymphedema	Wrong intervention - Less than 2 weeks treatment
61	Godoy Mde	2012	Synergic effect of compression therapy and controlled active exercises using a facilitating device in the treatment of arm lymphedema	Wrong intervention - Less than 2 weeks treatment
62	Jonas	2016	Efficacy of the Stendo Pulsating suit in patients with leg lymphedema: a pilot randomized study	Wrong intervention - Less than 2 weeks treatment
63	Radakovk	1998	A comparative pilot study of the treatment of arm lymphedema by manual drainage and sequential external pneumatic compression (SEPC) after mastectomy	Wrong intervention - Less than 2 weeks treatment
64	Rezende	2017	Blood Flow Velocity in Brachial and Subclavian Vessels Immediately After Compressive Procedures for Treatment of Postcancer Therapy Lymphedema in Breast Cancer: A Randomized Blind Clinical Trial	Wrong intervention - Less than 2 weeks treatment
65	Theys	2015	Milking effect on lymphoedema forearm: Manual versus pneumatic drainages	Wrong intervention - Less than 2 weeks treatment
66	Vale	2011	Synergistic effect of low elastic compression sleeves in the treatment of lymphedema after breast cancer treatment	Wrong intervention - Less than 2 weeks treatment
67	Zanolla	1984	Evaluation of the results of three different methods of postmastectomy lymphedema treatment	Wrong intervention - Less than 2 weeks treatment
68	Odebiyi	2014	Effects of exercise and oedema massage on fatigue level and quality of life of female breast cancer patients	Patients still receiving cancer treatment
69	Biffaud	2013	[Lymphedema after breast cancer surgery and research in physiotherapy]	Non-English study
70	Castro-Sanchez	2011	Preventing lymphoedema after breast cancer surgery by elastic restraint orthotic and manual lymphatic drainage: A randomized clinical trial. [Spanish]	Non-English study
71	da Silva Leal	2011	Lymphedema after breast cancer: comparison between two physical therapy techniques -- a pilot study	Non-English study
72	Damstra	2009	The treatment of arm lymphedema in breast cancer. Randomized, controlled comparative study of changes of the arm volume with short stretch bandages with low and high compression pressure. [German]	Non-English study
73	Damstra	2011	Referat zu: Compression therapy in breast cancer-related lymphedema: A randomized controlled study of relation between volume and interface pressure changes. [German]	Non-English study
74	Daubert		Efficacy of Manual Lymphatic Drainage in the Maintenance-Phase Treatment of Unilateral, Secondary Arm Lymphedema - A Pilot Study. [German]	Non-English study
75	Feiskhanov	2016	Comprehensive physical antiedematous therapy in treatment of patients with lymphedema. [Russian]	Non-English study

76	Gerasimenko	2015	The application of the method of kinesio-taping technique for the combined non-pharmacological rehabilitation of the patients presenting with lymphedema of the lower extremities. [Russian]	Non-English study
77	Gómez-Sadornil	2014	Effectiveness of physiotherapy in postmastectomy lymphedema	Non-English study
78	Ahmed	2006	Randomized controlled trial of weight training and lymphedema in breast cancer survivors	Duplicate
79	Anonymous	2018	Correction to: Effects of aqua-lymphatic therapy on lower extremity lymphedema: A randomized controlled study	Duplicate
80	Bracha	2012	The immediate effect of upper arm exercise compared with lower or combined upper and lower arms exercise on arm volume reduction in women with breasts cancer related lymphedema: a randomize preliminary study	Duplicate
81	Brown	2015	Weight-lifting and physical function among breast cancer survivors: A post hoc analysis of a randomized controlled trial	Duplicate
82	Castro-Sanchez	2011	[Preventing lymphoedema after breast cancer surgery by elastic restraint orthotic and manual lymphatic drainage: a randomized clinical trial]	Duplicate
83	Johansson	2013	Water-Based Exercise for Patients with Chronic Arm Lymphedema	Duplicate
84	Ridner	2011	A randomized clinical trial comparing advanced pneumatic truncal, chest, and arm treatment to arm treatment only in self-care of arm lymphedema	Duplicate
85	Sitzia	2002	Manual lymphatic drainage compared with simple lymphatic drainage in the treatment of post-mastectomy lymphoedema	Duplicate
86	Tidhar	2010	Aqua lymphatic therapy in women who suffer from breast cancer treatment-related lymphedema: A randomized controlled study	Duplicate
87	Ahemed	2006	Erratum: Randomized controlled trial of weight training and lymphedema in breast cancer survivors (<i>Journal of Clinical Oncology</i> (2006) 24, (2765-2772))	Duplicate
88	Anonymous	2018	Erratum: Correction to: "Effects of Aqua-Lymphatic Therapy on Lower Extremity Lymphedema: A Randomized Controlled Study"	Duplicate
89	Moattari	2013	The effect of combined decongestive therapy and pneumatic compression pump on lymphedema indicators in patients with lymphedema secondary to breast cancer treatment	Duplicate
90	Moattari	2015	Improving quality of life, lymphedema and range of motion in patients with breast cancer	Duplicate
91	Moattari	2013	The effect of combined decongestive therapy and pneumatic compression pump on lymphedema indicators in patients with lymphedema secondary to breast cancer treatment: a randomized clinical control trial	Duplicate
92	Sener	2015	The effect of clinical pilates exercises on lymphedema secondary to breast cancer treatments	Duplicate
93	Tidhar	2010	Erratum: Aqua lymphatic therapy in women who suffer from breast cancer treatment-related lymphedema: A randomized controlled study	Duplicate
94	Wilburn	2006	A pilot, prospective evaluation of a novel alternative for maintenance therapy of breast cancer-associated lymphedema	Don't report results before cross-over

95	Moattari	2012	The effect of combined decongestive therapy and pneumatic compression pump on lymphedema indicators in patients with breast cancer related lymphedema	Don't report data for control arm
96	Williams	2002	A randomized controlled crossover study of manual lymphatic drainage therapy in women with breast cancer-related lymphoedema	Don't report results before cross-over
97	Tidhar	2010	Aqua lymphatic therapy in women who suffer from breast cancer treatment-related lymphedema: a randomized controlled study.[Erratum appears in Support Care Cancer	Data not reported for control arm
98	Forner-Cordero	2012	Effect of decongestive lymphatic therapy in the maintenance phase of lymphedema: Long term results of a randomized, multicenter study	Abstract only
99	Gibbs	2011	High vs low intensity resistance exercise in late stage breast cancer patients with lymphedema: A randomised controlled trial	Abstract only
100	Hanssens	2012	The effect of a varied exercise program (VEP) on shoulder function and lymphedema (LE) in breast cancer survivors (BCs): A pilot study	Abstract only
101	Johansson	2017	Prospective surveillance, early diagnosis and treatment of patients at risk	Abstract only
102	Kaya	2010	Comparison of effectiveness two different physiotherapy approaches in the treatment of upper extremity lymphedema	Abstract only
103	Lanza	2015	Quality of Life and Volume Reduction in Women with Secondary Lymphoedema Related to Breast Cancer	Abstract only
104	Ozesenli	2011	Additional effects of the pneumatic compression treatment associated with the complete decongestive therapy in breast cancer treatment related lymphedema	Abstract only
105	Xin	2017	Trinity interactive transitional care to relieve upper limb lymphedema after breast cancer surgery	Abstract only

Appendix Table 6. Study funding and author declarations of interest.

Study	Funding source	Author declarations of interest
Anderson 2000	University/Hospital/Government	Not reported
Bergmann 2014	Not reported	Not reported
Bok 2016	Not reported	None declared
Buchan 2016	None	None declared
Buragadda 2015	University/Hospital/Government	Not reported
Chmielewska 2016	None	None declared
Cormie 2013	University/Hospital/Government	None declared
Dayes 2013	University/Hospital/Government, Industry donation	None declared
Didem 2005	Not reported	Not reported
Do 2015	Not reported	Not reported
Do 2017	Not reported	None declared
Gradalski 2015	None	None declared
Gurdal 2012	None	None declared
Haghighat 2010	University/Hospital/Government	Not reported
Hayes 2009	University/Hospital/Government	Not reported
Jeffs 2013	University/Hospital/Government, Industry donation	None declared
Johansson 1998	University/Hospital/Government	Not reported
Johansson 2013	University/Hospital/Government	None declared
Letellier 2014	University/Hospital/Government	None declared
Ligabue 2019	Not reported	None declared
Loudon 2014	University/Hospital/Government	None declared
Luz 2018	Not reported	Not reported
McClure 2010	University/Hospital/Government	Not reported
McKenzie 2003	Not reported	Not reported
McNeely 2004	University/Hospital/Government	Not reported
Park 2017	Not reported	None declared
Pasyar 2019	University/Hospital/Government	Not reported
Schmitz 2009	University/Hospital/Government	None declared

Schmitz 2019	University/Hospital/Government	Lead author has patent for lymphedema course; some co-authors have financial compensation, but no major concerns related to this topic
Sitzia 2002	University/Hospital/Government	Not reported
Sanal Toprak 2019	Not reported	None declared
Szolnoky 2009	University/Hospital/Government	None declared
Szuba 2002	University/Hospital/Government	Not reported
Tambour 2018	University/Hospital/Government	None declared
Uzkeser 2011	Not reported	None declared
Wigg 2009	Not reported	Not reported

Appendix Table 7. Risk of bias among included studies.

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel – Objective outcomes	Blinding of participants and personnel – Subjective outcomes	Blinding of outcome assessment – Objective outcomes	Blinding of outcome assessment – Subjective outcomes	Incomplete outcome data	Selective reporting	Other bias
Anderson 2000	Unclear	Unclear	Low	High	Low	High	Low	Unclear	Low
Bergmann 2014	Unclear	Unclear	Low	High	Low	High	Low	Unclear	Low
Bok 2016	Unclear	Unclear	Low	N/A	Low	N/A	Low	Unclear	Low
Buchan 2016	Low	Low	Low	High	Low	High	Low	Unclear	Low
Buragadda 2015	Unclear	Unclear	Low	High	Low	High	Low	Unclear	Low
Chmielewska 2016	Unclear	Unclear	Low	High	Low	High	Low	Unclear	Low
Cormie 2013	Low	Low	Low	High	Low	High	Low	Low	Low
Dayes 2013	Low	Low	Low	High	Low	High	Low	Low	Low
Didem 2005	Unclear	Unclear	Low	High	Low	High	Low	Unclear	Low
Do 2015	Low	Low	Low	High	Low	High	Low	Unclear	Low
Do 2017	Unclear	Unclear	Low	High	Low	High	Low	Unclear	Low
Gradalski 2015	Low	Low	Low	High	Low	High	Low	Unclear	Low
Gurdal 2012	Low	Low	Low	High	Low	High	Unclear	Unclear	Low
Haghighat 2010	Low	Low	Low	High	Low	High	Low	Unclear	Low
Hayes 2009	Low	Low	Low	High	Low	High	Low	Unclear	Low
Jeffs 2013	Low	Low	Low	High	Low	High	Low	Unclear	Low
Johansson 1998	Unclear	Unclear	Low	High	Low	High	Low	Unclear	Low
Johansson 2013	Low	Low	Low	High	Low	High	Low	Unclear	Low
Letellier 2014	Low	Low	Low	High	Low	High	High	Unclear	Low
Ligabue 2019	Low	Low	Low	High	Low	High	High	Unclear	Low
Loudon 2014	Low	Low	Low	High	Low	High	High	Low	Low
Luz 2018	High	High	Low	High	Low	High	Unclear	High	Unclear
McClure 2010	Unclear	Unclear	Low	High	Low	High	High	Unclear	Low
McKenzie 2003	Unclear	Unclear	Low	High	Low	High	Unclear	Unclear	Low
McNeely 2004	Low	Low	Low	N/A	Low	N/A	Low	Unclear	Low
Park 2017	Unclear	Unclear	N/A	High	N/A	High	Low	Unclear	Low
Pasyar 2019	Unclear	Unclear	Low	High	Low	High	High	Low	Low
Schmitz 2009	Low	Low	Low	High	Low	High	Low	Low	Low
Schmitz 2019	Low	Low	Low	High	Low	High	Low	Low	Low
Sitzia 2002	Low	Low	Low	N/A	Low	N/A	Low	Unclear	Low
Sanal Toprak 2019	Unclear	Unclear	Low	High	Low	High	Low	Unclear	Low

Szolnoky 2009	Unclear	Unclear	Low	High	Low	High	Low	Unclear	Low
Szuba 2002	Unclear	Unclear	Low	High	Low	High	Low	Unclear	Low
Tambour 2018	Low	Unclear	Low	High	Low	High	Low	Low	Low
Uzkeser 2011	High	High	Low	High	Low	High	Low	Unclear	Low
Wigg 2009	Unclear	Unclear	Low	N/A	Low	N/A	High	Unclear	Low

N/A = Not applicable.

Objective outcomes = Lymphedema volume, Function measures. Subjective outcomes = Lymphedema swelling and symptoms, Return to work and usual activities of daily living & Decrease in physical activity, Fatigue, Quality of life, Pain. For risk of bias marked “N/A,” this is for studies where the objective/subjective outcome was not reported.

Appendix Table 8. Narrative summary included interventions on lymphedema volume.

Studies, Design (patients)	Treatment arm	Effect
CDT vs Standard care		
Chmielewska 2016 (21)	N/A	There are statistically significant differences in hand and upper limb circumference after treatment as compared to its values before treatment (Wilcoxon test) both in [the CDT group] and [the standard care group]. Comparison of average percentage changes of circumference after treatment did not confirm the advantage of treatment with pneumatic compression and physical exercises in reducing upper limb edema and improving hand function.
Didem 2005 (53)	N/A	The mean percentage reduction in edema was 55.7% in CDP group and 36% in [standard care] group. All patients demonstrated sustained improvement in both groups. But the reduction in edema was found to be better in the CDP group than [standard care] group ($p < 0.05$).
CDT vs CDT		
Buragadda 2016 (60)	CDT group 1	Lymphedema volume before treatment = mean 1,974 (SD 171.3), lymphedema volume after treatment = mean 1,599.7 (SD 191.4)
	CDT group 2	Lymphedema volume before treatment = mean 1,996.4 (SD 279.3), lymphedema volume after treatment = mean 1,412.5 (SD 219.2)
Ligabue 2019 (34)	CDT group 1	Lymphedema volume before treatment = mean 2,727 (SD 636), lymphedema volume after treatment = mean 2,495 (SD 734)
	CDT group 2	Lymphedema volume before treatment = mean 2,624 (SD 902), lymphedema volume after treatment = mean 2,665 (SD 977)
Sitzia 2002 (28)	CDT group 1	Mean reduction = 33.8% (SD = 21.2)
	CDT group 2	Mean reduction = 22.0% (SD = 17.3)
CDT vs CDT + Resistance exercise		
Bok 2016 (32)	N/A	Upper limb circumference in the [CDT + resistance exercise] group did not significantly change after 4 weeks of exercises; however, both distal and proximal circumferences showed a significant reduction after 8 weeks. These parameters did not significantly change in the [CDT] group.
Aerobic exercise vs Resistance exercise		
Buchan 2016 (41)	Aerobic exercise	Mean interlimb difference (%) = 6.5 (95% CI 3.8, 9.2)

Resistance
exercise

Mean interlimb difference (%) = 5.1 (95% CI 2.1, 8.1)

CDT vs Compression pumpsSanal Toprak 2019
(46)

N/A

There were no significant differences between the groups with both treatment modalities resulting in significant decreases from baseline ($p < 0.05$) in the five measurement levels of the arm circumference at the fifth week and the third month. In both groups, differences in the five measurement levels of the 2-arm circumference were higher in the third month than in the fifth week. However, this difference was statistically significant only in [the CDT] group at the level of medial epicondyle and 15 cm proximally from the medial epicondyle.

CDT = Complete Decongestive Therapy. N/A = Not applicable. SD = Standard deviation.

Appendix Table 9. Network meta-analysis of lymphedema volume league table.

Standard care									
-0.33 (-1.07,0.41)	MLD								
-0.29 (-0.77,0.19)	0.04 (-0.84,0.92)	Water-based/yoga exercise							
0.01 (-0.48,0.50)	0.34 (-0.55,1.23)	0.30 (-0.39,0.98)	Resistance exercise						
0.19 (-0.34,0.72)	0.52 (-0.40,1.43)	0.48 (-0.24,1.19)	0.18 (-0.54,0.90)	Aerobic and resistance exercise					
-0.08 (-0.82,0.66)	0.25 (-0.55,1.05)	0.21 (-0.67,1.09)	-0.09 (-0.98,0.80)	-0.27 (-1.18,0.64)	Compression pumps				
-0.26 (-0.99,0.47)	0.07 (-0.93,1.07)	0.03 (-0.84,0.90)	-0.27 (-1.15,0.61)	-0.45 (-1.35,0.45)	-0.18 (-1.12,0.76)	CDT + Resistance exercise			
-0.13 (-1.21,0.96)	0.20 (-1.07,1.48)	0.16 (-1.02,1.35)	-0.13 (-1.32,1.05)	-0.31 (-1.52,0.90)	-0.05 (-1.28,1.19)	0.13 (-1.07,1.34)	CDT + Compression pumps + Aerobic and resistance exercise		
-0.24 (-0.84,0.36)	0.09 (-0.82,1.00)	0.05 (-0.71,0.82)	-0.25 (-1.02,0.53)	-0.43 (-1.23,0.38)	-0.16 (-1.00,0.68)	0.02 (-0.77,0.82)	-0.11 (-1.01,0.79)	CDT + Compression pumps	
0.07 (-0.29,0.43)	0.40 (-0.38,1.17)	0.36 (-0.24,0.96)	0.06 (-0.55,0.67)	-0.12 (-0.76,0.52)	0.15 (-0.54,0.84)	0.33 (-0.30,0.96)	0.19 (-0.83,1.22)	0.31 (-0.18,0.79)	CDT

CDT = Complete decongestive therapy. MLD = Manual lymphatic drainage.

Cells highlighted in red denote very low-certainty evidence, cells highlighted in orange denote low-certainty evidence.

Appendix Table 10. Inconsistency test between direct and indirect treatment comparisons.

Comparison	Direct	Standard error	Indirect	Standard error	Difference	Standard error	Local test for incoherence P>z
CDT vs standard care	0.0276171	0.1872753	0.9004496	0.8065541	-0.8728326	0.8280364	0.292
CDT vs CDT + compression pumps	0.3070568	0.2465836	0.1321897	225.0125	0.1748671	225.0126	0.999
CDT vs CDT + resistance exercise	0.3286468	0.3226356	0.1977187	444.4788	0.130928	444.4789	1
CDT vs compression pumps	0.3575439	0.4039566	-0.515328	0.7228131	0.8728719	0.8280594	0.292
CDT + compression pumps vs CDT + compression pumps + aerobic and resistance exercise	-0.1121501	0.460676	-0.4706463	633.253	0.3584962	633.2532	1
Compression pumps vs MLD	0.614709	0.5351186	-0.2581647	0.6319275	0.8728737	0.8280606	0.292
MLD vs standard care	-0.0717611	0.4483715	-0.9446326	0.6961656	0.8728714	0.8280601	0.292

CDT = Complete decongestion therapy. MLD = Manual lymphatic drainage.

Appendix Table 11. Narrative summary of included interventions on pairwise comparisons.

Outcome	Comparisons	Studies, Design (patients)	Outcome measure instrument	Effect
Quality of life	Aerobic exercise vs Resistance exercise	Buchan 2016 (40)	FACT-B+4	At 24 weeks, the mean QoL was 111.8 (95% CI 102.6, 121.1) in the resistance exercise group and 118.4 (95% CI 108.4, 128.3) in the aerobic exercise group.
	Aerobic and resistance exercise vs Standard care	Hayes 2009 (31)	N/A	Themes, non-comparative: pervasive impact of lymphedema; grief, loss, and uncertainty; isolation/social impact; evolving feelings regarding exercise, including their sense of greater well-being; importance of the program being “supervised”.
	Resistance exercise vs Standard care	Jeffs 2013 (23)	LYMQOL	There was no improvement noted in quality of life.
	Aerobic and resistance exercise vs Standard care	McKenzie 2003 (14)	SF-36	P values ≤ 0.5 were found for four of the SF-36 domains. Physical functioning (P = 0.050), general health (P = 0.048), and vitality (P = 0.023) increased in the exercise group and decreased in the control group, although the changes were not significantly different between groups across time. Mental health increased over time in all subjects (P = 0.019), although, again, this was not statistically significant. There was a trend indicating that as percentage difference of calculated volume decreased, the general health domain increased (P = 0.052). There was a decrease, although it was not statistically apparent, in the bodily pain scores of both groups. The changes over time of the other three domains (role physical, social functioning, and role emotional) were not statistically significant.
Function measures	CDT vs Standard care	Bergmann 2014 (57)	NR	CDT: Normal before and after treatment=38.6%; Range improved after treatment=10.5%; Range remained incomplete=0 Standard care: Normal before and after treatment=45.6%; Range improved after treatment=3.5%; Range remained incomplete=1.8%

	Aerobic exercise vs Resistance exercise	Buchan 2016 (40)	DASH	At 24 weeks, the mean upper body function was 15.2 (95% CI 8.9, 21.5) in the resistance exercise group and 14.8 (95% CI 8.1, 21.6) in the aerobic exercise group.
	CDT vs CDT	Buragadda 2015 (60)	DASH	CDT group 1: function before treatment = mean 32.6 (SD 1.1), pain after treatment = mean 2.9 (SD 0.6) CDT group 2: pain before treatment = mean 6. (SD 0.9) pain after treatment = mean 1.4 (SD 0.2)
	Resistance exercise vs Standard care	Jeffs 2013 (23)	Shoulder abduction and extension	There was no improvement noted in range of motion. A non-significant improvement in the [resistance exercise's group] perceived function at week 12 was not sustained at week 26. Many of the [resistance exercise group] spontaneously reported that the deep ache/heaviness they experienced in the forearm was less intense during the exercise programme, although the overall frequency of the symptom was not reduced.
	Compression pumps vs MLD	Johansson 1998 (24)	Flexion of the elbow and flexion, abduction and rotation of the shoulder	Treatment with MLD or [compression pumps] did not change arm mobility [before and after the intervention].
	CDT vs CDT	Szuba 2002 (23)	Joint function*	After patients received therapy for initial volume reduction, joint mobility improved uniformly (P = 0.011; baseline compared with posttreatment), without regard to treatment group. There were no significant differences among the changes observed at the conclusion of treatment (Day 10) and at Day 40.
Lymphedema swelling and symptoms	CDT vs Standard care	Bergmann 2014 (57)	Swelling reduction	CDT group: poor or moderate = 13.3%, very much = 33.3% Standard care group: poor or moderate = 6.7%, very much = 46.7%
	Aerobic exercise vs Resistance exercise	Buchan 2016 (40)	Norman lymphedema survey	At 24 weeks, the mean upper body function was 0.5 (95% CI 0.3, 0.7) in the resistance exercise group and 0.7 (95% CI 0.4, 1) in the aerobic exercise group.

	Resistance exercise vs Standard care	Jeffs 2013 (23)	Subjective comments	The [resistance exercise group] ... spontaneously reported benefits they had noticed in their arm, using words such as “lighter”, “softer”, “smoother in shape”, “looks normal” and “no longer looks like a manikin’s arm”.
	Compression pumps vs CDT	Sanal Toprak 2019 (46)	Heaviness - VAS	Compression pumps: score before treatment = 4.77, score after treatment = 2.27 CDT: score before treatment = 4.96, score after treatment = 2.29
Pain	CDT vs Standard care	Bergmann 2014 (57)	NR	CDT group: no pain = 26.3%, pain reduction = 19.3%, pain worsening = 3.5% Standard care group: no pain = 29.8%, pain reduction = 15.8%, pain worsening = 5.3%
	CDT vs CDT	Buragadda 2016 (60)	VAS	CDT group 1: pain before treatment = mean 6.9 (SD 1.1), pain after treatment = mean 2.9 (SD 0.6) CDT group 2: pain before treatment = mean 6. (SD 0.9) pain after treatment = mean 1.4 (SD 0.2)
	CDT vs CDT	Ligabue 2019 (34)	Numerical pain rating scale	CDT group 1: pain before treatment = mean 4.3 (SD 2.6), pain after treatment = mean 2.1 (SD 2.5) CDT group 2: pain before treatment = mean 3.8 (SD 2.8) pain after treatment = mean 3.8 (SD 3.3)
	Compression pumps vs CDT	Sanal Toprak 2019 (46)	VAS	Compression pumps: score before treatment = 4.36, score after treatment = 2.14 CDT: score before treatment = 4.69, score after treatment = 2.29
	CDT vs CDT + Compression pumps	Uzkeser 2015 (30)	VAS	CDT: before treatment = median 4 (range 0-7), after treatment = 1 (range 0-5) CDT + Compression pumps: before treatment = median 4 (range 0-10), after treatment = median 1 (range 0-8)

*Joint flexion included shoulder flexion, abduction, internal and external rotation; elbow flexion; forearm supination; and wrist flexion and extension.

CDT = Complete Decongestive Therapy; CI = Confidence Interval; DASH = Disabilities of the Arm, Shoulder, and Hand questionnaire; FACT-B+4 = Functional Assessment of Cancer Therapy Questionnaire for Breast Cancer - for patients with lymphedema; LYMQOL = Lymphoedema Quality of Life Questionnaire; MLD = Manual Lymphatic Drainage; NR = Not reported; QoL = Quality of Life; SD = Standard Deviation; SF-36 = Short-Form 36 Questionnaire; VAS = Visual Analog Scale.

Appendix Table 12. Narrative summary of adverse events of included interventions.

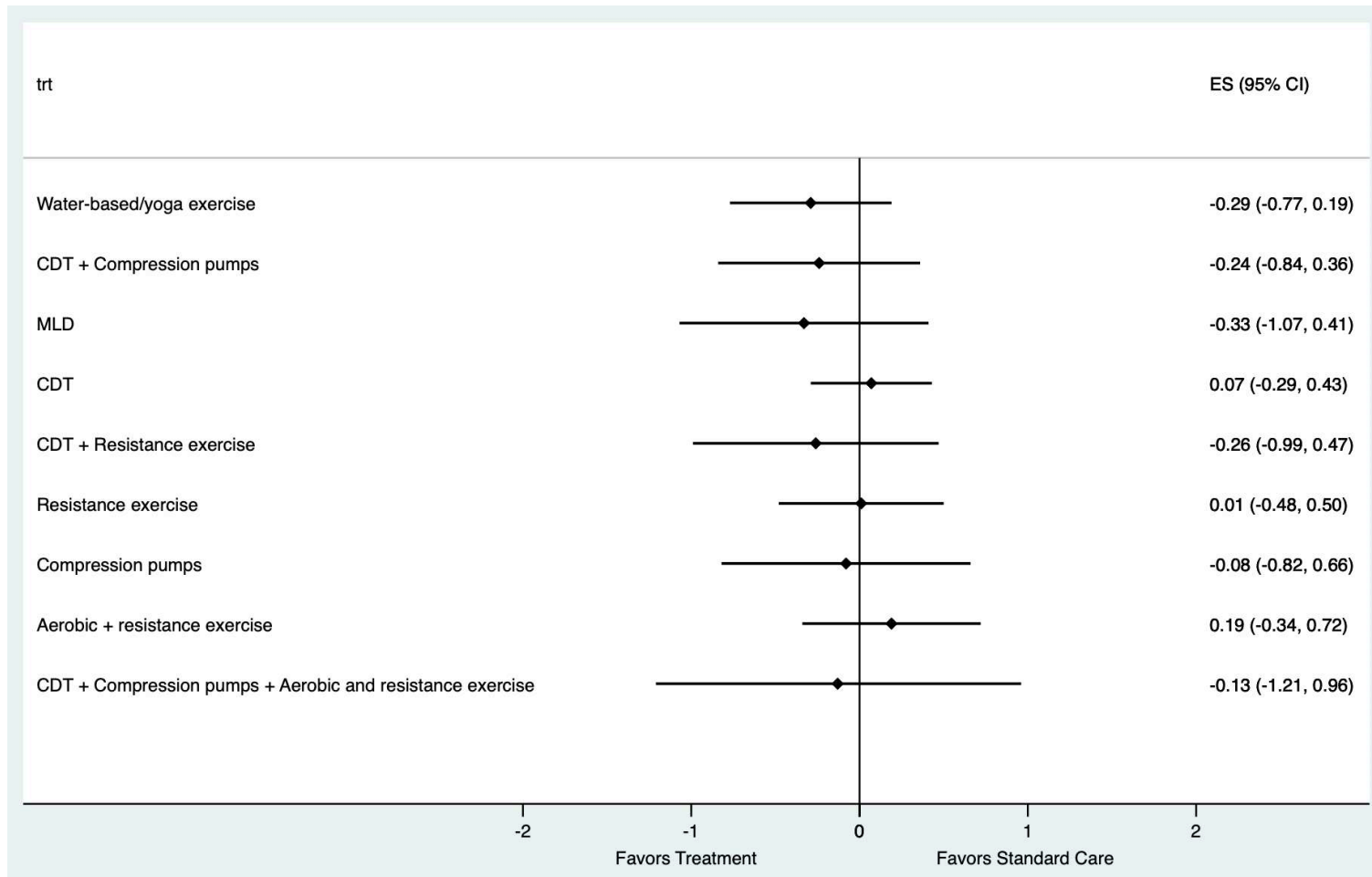
Study	Follow up duration (weeks)	Arm	Patients (n)	Adverse events	Notes
Resistance exercise vs Standard care					
Cormie 2013(57)	12	Resistance exercise	43	No lymphedema exacerbations or other adverse events occurred during this trial.	None.
		Standard care	19		
Jeffs 2013(65)	26	Resistance exercise	11	There were no reported adverse reactions to the intervention.	None.
		Standard care	11	N/A	
CDT vs Standard care					
Chmielewska 2016 (21)	4	CDT	11	No negative effects of physical exercises in women with upper limb lymphedema were observed.	None.
		Standard care	10		
Dayes 2013(58)	6	CDT	56	19 events in 17 patients; A single episode each of cellulitis and severe pain occurred in the CDT group.	Most events consisted of temporary rash or mild to moderate pain in the affected arm.
		Standard care	39	9 events in 7 patients	
Didem 2005(59)	NR	Control	28	2/28 patients withdrew due to infection in their arms	Authors do not classify this as an AE, report it as a reason for withdrawal.
McNeely 2004(39)	4	CDT	25	Withdrew due to skin reaction to bandaging (n =1)	Authors do not classify this as an AE, report it as a reason for withdrawal.
		Standard care	25	Dissatisfaction with treatment response (n = 2); discomfort from compression bandage (n = 1)	
Tambour 2019(82)	28	CDT	39	Allergic reaction to the bandage (n=2), Erysipelas (n=1)	Authors do not classify this as an AE, report it as a reason for withdrawal.
		Standard care	38	Allergic reaction to the bandage (n=5)	
Resistance exercise vs Aerobic exercise					

Buchan 2016(54)	24	Both groups	40	No exercise-related adverse events or lymphedema exacerbations were reported during the trial or follow-up.	None.
--------------------	----	-------------	----	---	-------

Aerobic and resistance exercise vs Standard care					
Schmitz 2019(78)	52	Control	90	Lymphedema exacerbations or cellulitis n=28 (31.1%)	None.
		Aerobic and resistance exercise	87	Lymphedema exacerbations or cellulitis n=28 (32.2%)	None.
		Both groups	177	No significant adverse events were noted.	None.

AE = Adverse event. CDT = Complex Decongestive Therapy. N/A = Not applicable.

Appendix Figure 1. Network meta-analysis of conservative interventions compared to standard care on lymphedema volume change.



CDT = Complete decongestion therapy. CI = Confidence interval. ES = Effect size. MLD = Manual lymphatic drainage. TRT = Treatment.

