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Exercise interventions for upper-limb dysfunction due to breast cancer treatment (Review)

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TABLE OF CONTENTS

[Intervention Review]

Exercise interventions for upper-limb dysfunction due to breast cancer treatment

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ABSTRACT

Background

Upper-limb dysfunction is a commonly reported side effect of treatment for breast cancer and may include decreased shoulder range of motion (the range through which a joint can be moved) (ROM) and strength, pain and lymphedema.

Objectives

To review randomized controlled trials (RCTs) evaluating the effectiveness of exercise interventions in preventing, minimi sing, or improving upper-limb dysfunction due to breast cancer treatment.

Search methods

We searched the Specialised Register of the Cochrane Breast Cancer Group, MEDLINE, EMBASE, CINAHL, and LILACS (to August 2008); contacted experts, handsearched reference lists, conference proceedings, clinical practice guidelines and other unpublished literature sources.

Selection criteria

RCTs evaluating the effectiveness and safety of exercise for upper-limb dysfunction.

Data collection and analysis

Two authors independently performed the data abstraction. Investigators were contacted for missing data.

Main results

We included 24 studies involving 2132 participants. Ten of the 24 were considered of adequate methodological quality.

Ten studies examined the effect of early versus delayed implementation of post-operative exercise. Implementing early exercise was more effective than delayed exercise in the short term recovery of shoulder flexion ROM (Weighted Mean Difference (WMD): 10.6 degrees; 95% Confidence Interval (CI): 4.51 to 16.6); however, early exercise also resulted in a statistically significant increase in wound drainage volume (Standardized Mean Difference (SMD) 0.31; 95% CI: 0.13 to 0.49) and duration (WMD: 1.15 days; 95% CI: 0.65 to 1.65).

Fourteen studies examined the effect of structured exercise compared to usual care/comparison. Of these, six were post-operative, three during adjuvant treatment and five following cancer treatment. Structured exercise programs in the post-operative period significantly improved shoulder flexion ROM in the short-term (WMD: 12.92 degrees; 95% CI: 0.69 to 25.16). Physical therapy treatment yielded additional benefit for shoulder function post-intervention (SMD: 0.77; 95% CI: 0.33 to 1.21) and at six-month follow-up (SMD: 0.75; 95% CI: 0.32 to 1.19). There was no evidence of increased risk of lymphedema from exercise at any time point.

Authors' conclusions

Exercise can result in a significant and clinically meaningful improvement in shoulder ROM in women with breast cancer. In the post-operative period, consideration should be given to early implementation of exercises, although this approach may need to be carefully weighed against the potential for increases in wound drainage volume and duration. High quality research studies that closely monitor exercise prescription factors (e.g. intensity), and address persistent upper-limb dysfunction are needed.

PLAIN LANGUAGE SUMMARY

Exercise interventions for upper-limb dysfunction due to breast cancer

This summary of a Cochrane review presents what we know about the effect of exercise on arm and shoulder movement problems due to breast cancer.

Upper-limb dysfunction following breast cancer surgery:

The use of upper-limb ROM, stretching and strengthening exercises after breast cancer surgery have been shown to improve recovery of shoulder movement. However, there are different views on what type of exercise is best and how soon exercises should be started following surgery. Moreover, it is not known if exercise is helpful in addressing upper-limb problems that persist following surgery and there is some concern that upper-limb exercise may increase the risk of developing lymphedema in the arm. In this review, a total of 24 studies examined the benefit of exercise on upper-limb dysfunction. Ten studies examined whether it was better to start exercise early after surgery or to delay exercise by about one week. Six studies examined structured exercise programs compared to usual care (exercise pamphlet or no exercise) following surgery. Three studies examined exercise interventions carried out during cancer treatment and five studies examined exercise interventions carried out following cancer treatment.

Best estimate of the effect of upper-limb exercise for women with breast cancer:

1) This review found that upper-limb exercise (e.g. shoulder ROM and stretching) is helpful in recovering upper-limb movement following surgery for breast cancer. Starting exercise early after surgery (day 1 to day 3) may result in better shoulder movement in the short term; however, it may also result in more wound drainage and require the drains to be in place longer than if exercise is delayed by about one week.

2) This review showed that more structured exercise programs, such as physical therapy, delivered in the early weeks following surgery are beneficial to regain movement in, and use of the shoulder and arm for daily activities such as reaching overhead.

3) This review did not find any evidence that upper-limb exercise, whether carried out following surgery, or during/ following other cancer treatments, resulted in more patients developing arm lymphedema.

BACKGROUND

Description of the condition

Upper-limb dysfunction is commonly reported as a side effect of breast cancer treatment and may include one or more of the following impairments: decreased shoulder range of motion (the range through which a joint can be moved) (ROM) and strength, pain and lymphedema (an accumulation of lymphatic fluid in the tissue of the hand, arm, breast and/or trunk) (Chen 1999; Gosselink 2003; Reitman 2003). A systematic review examining upper-limb symptoms following surgery and radiation therapy found a wide variation among studies in the reported prevalence of impaired shoulder ROM (< 1% to 67%), arm weakness (9% to 28%), shoulder/arm pain (9% to 68%), and lymphedema (0% to 34%) (Lee 2008). Despite the reported variability, it is clear from the literature that many breast cancer survivors present with upper-limb dysfunction that may persist for many years following treatment (Reitman 2003; Senkus-Konefka 2006). More recently, the presence of upper-limb dysfunction in breast cancer survivors has been found to have a negative impact on quality of life (Ahmed 2008).

Description of the intervention

Exercise interventions include a range of rehabilitative exercises aimed at preventing, minimizing or improving shoulder ROM, upper-limb strength and function, pain and lymphedema. An exercise program may include active, active-assisted, and/or passive ROM exercises, stretching or movement exercises, and upper-limb strengthening exercises. Exercises may also include manual stretching or ROM techniques, applied by a physical therapist or manual therapist, that are performed to restore muscular length and joint mobility. Exercise programs may be self-directed or supervised by a healthcare professional such as a physical or occupational therapist, or exercise specialist.

How the intervention might work

Exercise is prescribed to restore shoulder joint mobility, movement and strength in muscles of the upper-limb, and to reduce pain (Box 2002; Harris 2001). Thus, exercise helps optimize function of the upper-limb (the ability to perform a physical activity or task). Exercise is believed to be most beneficial when it is continued over an extended period of time following surgery (e.g. 6 to 12 months) as soft tissues heal and remodel (Box 1998).

Why it is important to do this review

At present, there are many gaps in our knowledge on the benefits of exercise at different time points over the course of breast cancer treatment and recovery. Some controversy remains over the optimal time to start upper-limb exercise following surgery, the appropriate type and intensity of post-operative exercise, and the relative benefit of exercise in addressing late onset or persistent upper-limb dysfunction in breast cancer survivors.

There is some concern that unskilled or early aggressive shoulder movement performed immediately post-operatively may interfere with the regeneration of lymphatic channels potentially damaged by the surgery, and increase the amount and duration of wound drainage (Box 2002). An increase in wound drainage may result in delayed wound healing, seroma formation, increase the risk of infection, and has been found to parallel the incidence of long-term lymphedema (Chen 1999; Schultz 1997; Tadych 1987). Previous systematic reviews examining early versus delayed post-operative exercises have favoured delayed exercises due to reported negative effects from early exercise on wound drainage and seroma formation and findings of only marginal benefit from early exercise for shoulder function (Karki 2001; Shamley 2005). Other authors, however, continue to recommend early exercise post-operatively and suggest that prescription factors such as the type, intensity and method of progression of exercise may be more important than when exercise is started following surgery (Bendz 2002; Box 2002; Harris 2001).

While considerable attention has been paid to issues surrounding the post-operative time period, questions also remain over whether exercise administered at any time in the recovery from breast cancer treatment is beneficial in addressing late onset or persistent upper-limb dysfunction.

OBJECTIVES

The purpose of this systematic review was to examine the evidence of effectiveness from randomized controlled trials (RCTs) involving exercise interventions for preventing, minimizing and/or improving upper-limb dysfunction due to breast cancer treatment.

METHODS

Criteria for considering studies for this review

Types of studies

We included studies if they were RCTs (abstract/title or methods included the term 'random', 'randomized' or 'random allocation'). We excluded exercise studies that included cancers other than breast cancer (e.g. melanoma) unless separate data were available for the breast cancer subgroup. We grouped studies by the type of comparison and timing of the exercise program relative to breast cancer treatment:

Comparison 1: Studies examining early upper-limb exercise intervention (commenced day 1 to day 3 following surgery) versus delayed upper-limb exercise intervention (day 4 or later following surgery) following surgery. (In these studies the upper-limb exercise intervention was the same in both groups with the timing of initiating the exercise intervention differing between the groups.)

Comparison 2: Studies examining upper-limb exercise interventions administered following surgery compared to usual care/comparison/control.

Comparison 3: Studies examining upper-limb exercise interventions that were carried out during adjuvant cancer treatment (i.e. during radiation therapy or chemotherapy).

Comparison 4: Studies examining upper-limb exercise interventions carried out following cancer treatment.

Types of participants

1) Confirmed breast cancer diagnosis;
2) Surgical removal of breast tumour (e.g. radical mastectomy, modified radical mastectomy, local wide excision and lumpectomy);
3) Axillary lymph node dissection (AND)/Sentinel node biopsy/dissection (SNB);
4) Adults: 17 years and older.

Types of interventions

The intervention included one or more of the following therapeutic exercise interventions for the upper-limb delivered through a physical or occupational therapy program (programs that focus on enhancing or restoring mobility in a joint or body region) or a supervised or self-directed exercise program:
1) Active or active-assisted ROM exercises;
2) Passive ROM/manual stretching exercises;
3) Stretching exercises (including formal exercise interventions such as yoga and Tai Chi Chuan);
4) Strengthening or resistance exercises.

Types of outcome measures

Primary outcomes

Upper-extremity ROM, muscular strength, lymphedema and pain

Secondary outcomes

Upper-extremity/shoulder function (e.g. reaching overhead, fastening a brassiere, doing a zipper up from behind) and quality of life. We sought information on early post-operative complications (adverse events) such as seroma formation, post-operative wound drainage, wound healing and effect modifiers such as adherence to exercise.

Search methods for identification of studies

1) Electronic databases, no language or publication restrictions.

a. Cochrane Breast Cancer Group Specialised Register
We searched The Specialised Register (March 2006). Details of the search strategy used by the Group for the identification of studies for the Register, and the procedure used to code references, are outlined in the Group's module (www.mrw.interscience.wiley.com/cochrane/clabout/articles/BREASTCA/frame.html). We extracted studies with the keywords 'exercise' for consideration.

b. MEDLINE (January 1, 1980 to August 1, 2008) (Appendix 1)

c. EMBASE (January 1, 1982 to August 1, 2008) (Appendix 2)

d. PEDro (January 1, 1980 to August 1, 2008) (Appendix 3)

e. LILACS (January 1, 1997 to August 1, 2008) (Appendix 4)

2) Grey Literature

We updated searches to August 2008 and, where possible, we examined literature as far back as 1966. We performed an expanded search to identify articles potentially missed through the database searches and in order to identify "grey literature". This included the following:

a. Handsearching of reference lists of all retrieved articles, texts and other reviews on the topic;
b. Handsearching the journals *Breast Cancer Research and Treatment*, *Physical Therapy*, *Journal of Surgical Oncology*;
c. Pub Med: related articles feature;
d. Web of Science: citation searching of key authors;
e. Search of SIGLE (System for Information on Grey Literature in Europe);
f. We contacted local and foreign experts for further information (Cochrane Breast Cancer review group, key authors of publications included in this review);

3) Websites
We also searched the following websites:
a. http://clinicaltrials.gov
b. http://www.controlled-trials.com
c. http://www.ctu.mrc.ac.uk/ukccr
d. http://cancernet.nci.nih.gov
e. http://www.cancer.gov/search/clinical_trials/

Where appropriate we used the following terms in the search:

Terms related to the condition: breast cancer (neoplasm/tumor/tumour), mastectomy, axillary dissection, sentinel node dissection, adhesive capsulitis, cording, axillary web syndrome.
Terms related to the intervention: physical therapy (physiotherapy), rehabilitation, exercise(s), stretching, mobilization (mobilization), physical activity (exertion).
Terms related to the outcome: ROM, strength, lymphedema, pain, and quality of life.

Data collection and analysis

One author (MMC) performed the initial pre-screen of all the databases to identify potential trials and screened the results to exclude articles that were clearly irrelevant. Two independent authors (MMC and KLC) screened the reduced search results. If either or both authors felt that the article potentially met the inclusion criteria, or if there was inadequate information to make a decision, we retrieved full text copies of the article (and translated them into English, if necessary). Using the defined eligibility criteria, the two authors independently decided on trial inclusion. A priori, authors made the decision to exclude any data that were available only in abstract form. Review authors were not blinded to study authors, journal or study results. Agreement was measured and assessed by using kappa (k) statistics. We compared results at each stage and resolved any disagreements by consensus. Where necessary, we referred any disagreements to a third reviewer (KCO).

Methodological quality assessment

KLC/MO and MMC independently assessed quality . We evaluated each study using a 6-point scale that included allocation concealment and a modified version of the validated Jadad 5-point scale (Jadad 1996). We scored each trial for allocation concealment as Yes: Adequate concealment, Unclear: Inadequate information, or No: Clearly inadequate concealment. We used the Jadad scale to assess randomization, double blinding, and withdrawals and dropouts. In these studies, however, double blinding is not possible (i.e. participants know if they are exercising or not). Therefore, we summarized quality using a modification of the Jadad scoring system as follows: 1) Was the study described as randomized (1 = yes; 0 = no)?; 2) Was the outcome assessment described as blinded (1 = yes; 0 = no)?; 3) Was there a description of withdrawals and dropouts (1 = yes; 0 = no)?; 4) Was the method of randomization well-described and appropriate (1 = yes; 0 = no)?; 5) Was the method of blinding of the assessment of outcomes well-described and appropriate (1 = yes; 0 = no)?; 6) Deduct 1 point if methods for randomization OR blinding were inappropriate.

Data extraction

MO/MMC and KLC extracted data independently using a standardized form. MMC and KLC attempted to contact authors (using e-mail, letter and/or fax) to search for additional papers and/or to obtain missing data.

1) Characteristics of the studies
a. The sponsors of the study and their contributions as well as authors' affiliations.
b. Methods: design, recruitment, method of randomization, sample size, trial inclusion and exclusion criteria, withdrawals.

2) Characteristics of the study population
a. Stage breast cancer/ tumour/lymph node status
b. Radiation/other therapies
c. Type of surgery
d. Time from surgery
e. Age
f. Weight/Body Mass Index (BMI)

3) Characteristics of the interventions
a. Type of exercise intervention: ROM, stretching, strength/ resistance exercise training
b. Description/details of exercise intervention: frequency, intensity, type and time
c. Description/details of usual care/comparison intervention
d. Adherence/contamination
e. Co-interventions (e.g. medication use)

4) Characteristics of the outcomes
a. Self-reported (e.g. pain, functional outcome, QOL)
b. Clinician performed (e.g. ROM, arm volume, muscular strength)

Data analysis

Where data were sufficient, we conducted a meta-analysis. We combined trials using Review Manager (RevMan, Version 5.0). Where continuous data resulted from the same method of measurement (e.g. ROM), we calculated the weighted mean difference (WMD). Where continuous data resulted from different scales (e.g. scales used to assess symptoms such as pain), we summarized these as the standardized mean difference (SMD). For dichotomous data, such as the presence or absence of a symptom, we expressed the impact of treatment as the odds ratio (OR) together with their 95% confidence intervals (CI). All point estimates were reported with their associated 95% confidence intervals. We pooled the results of comparable trials using random-effects estimates, 95% confidence intervals, the Chi^2test for heterogeneity and the I^2 statistic.

If data were statistically heterogeneous, we considered the following as possible explanations:

1) Exercise prescription factors: type of exercise/program, supervised versus self-directed exercise, variables of exercise (e.g. frequency, intensity and time)
2) Timing of intervention
3) Stage of breast cancer
4) Type of surgery

We planned subgroup analyses, where possible, for the following:
1) Type of exercise intervention
2) Type of surgery (e.g. mastectomy versus breast conserving surgery)
3) Type of axillary dissection (e.g. complete, level 1 and II, sentinel node)
4) Age: < 65 years versus 65 years and older
5) Time period of the study (prior to 1995 versus 1995 and later)

RESULTS

Description of studies

Please see Characteristics of included studies; Characteristics of excluded studies.

Results of the search

We identified 82 papers of which 50 were considered potentially relevant. Independent review of these 50 papers led to the inclusion of 24 studies involving 2132 participants. Kappa statistics were 0.94 for agreement on inclusion and 0.84 for quality score.

Included studies

Twenty-two studies were published in English. One study was published in Portuguese and another in French and both of these studies were translated. Most studies included participants who had undergone modified radical mastectomy (MRM) alone or participants who had undergone either MRM or breast conserving surgery (BCS). Where reported, the mean age of participants ranged from 46.3 to 62.1 years.

Post-operative: early versus delayed exercises

Ten studies (Abe 1998; Bendz 2002; Chen 1999; e Silva 2004; Flew 1979; Jansen 1990; Le Vu 1997; Petrek 1990; Schultz 1997; van der Horst 1985) including 1304 participants examined the benefit of early versus delayed exercises. Studies in this subgroup were conducted in the Netherlands (2), Sweden (2), United States (1), Brazil (1), France (1), Taiwan (1), Japan (1) and the United Kingdom (1).

Seven studies (Abe 1998; Bendz 2002; e Silva 2004; Jansen 1990; Le Vu 1997; Schultz 1997; van der Horst 1985) introduced exercise on day 1 following surgery, two studies (Flew 1979; Petrek 1990) on day 2 following surgery and one study (Chen 1999) on day 3 following surgery. Four studies (Chen 1999; Jansen 1990; Schultz 1997; van der Horst 1985) prescribed ROM exercises with the 'point of pain' limiting the extent of movement, two studies (e Silva 2004; Flew 1979) prescribed 'unrestricted' exercises, one (Petrek 1990) study prescribed graduated ROM, one study (Le Vu 1997) did not provide information beyond 'active movements', one study (Abe 1998) limited the ROM to 90 degrees for day 1 with the goal of attaining 180 degrees elevation on day 2, and one study (Bendz 2002) limited movement to 90 degrees elevation until day 14.

There was also considerable variation across studies in the delayed exercise intervention. In three studies participants in the delayed exercise group were required to wear a sling during the first five-to-seven days post-surgery (Flew 1979; Jansen 1990; Petrek 1990), in three other studies movement was allowed within a restricted ROM (Chen 1999; e Silva 2004; van der Horst 1985), in two studies delayed exercise participants were advised to limit movement to usual activities/ within comfort (Abe 1998; Bendz 2002) and in two studies no exercise was prescribed (Le Vu 1997; Schultz 1997).

Post-operative: exercise versus comparison

Six studies with 354 participants examined the effect of exercise versus usual care or comparison or control intervention following breast cancer surgery (Beurskens 2007; Box 2002; Cinar 2008; de Rezende 2006; Kilgour 2008; Wingate 1989). The included trials were all conducted in different countries and included Australia (1), Brazil (1), Canada (1), Netherlands (1), Turkey (1) and the United States (1).

The exercise group was provided with individual physical therapy treatments in three studies (Beurskens 2007; Cinar 2008; Wingate 1989), a progressive home based exercise program in one study (Box 2002), a directed group exercise program in one study (de Rezende 2006) and a home-based video lead exercise program in one study (Kilgour 2008).

In three studies the comparison group was provided with an exercise pamphlet as per usual care (Beurskens 2007; Box 2002; Kilgour 2008), in one study the comparison group was advised to perform general movements of the shoulder within comfort (de Rezende 2006), in another study the comparison group was prescribed a home exercise program after wound drains were removed (Cinar 2008) and in the final study the comparison group was not prescribed any exercise (Wingate 1989).

Exercise versus comparison during adjuvant cancer treatment

Three studies (Courneya 2007; Hwang 2008; Lee 2007) with 262 participants examined the effect of exercise versus usual care or comparison or control during adjuvant cancer treatment. One study (Courneya 2007) was carried out during adjuvant chemotherapy and two studies (Hwang 2008; Lee 2007) were carried out during adjuvant radiation therapy. The included trials were conducted in Australia (1), Canada (1) and Korea (1).

Courneya 2007 examined the effect of resistance exercise compared to usual care (normal activities). Hwang 2008 examined the effect of a mixed exercise program (including aerobic exercise, resistance exercise and specific shoulder stretches) compared to self-directed shoulder ROM exercises. Lee 2007 examined a pectoral muscle stretching program compared to usual care (self-directed shoulder ROM).

Exercise versus comparison following cancer treatment

Five studies (Ahmed 2006; Cho 2006; Lauridsen 2000; Mustian 2006; Sandel 2005) with 212 participants examined the effect of exercise versus usual care or comparison or control following cancer treatment.

Ahmed 2006 examined the effect of resistance exercise to a nonintervention control group. Cho 2006 examined the effect of a mixed aerobic and stretching program to a nonintervention (wait-list) control group. Lauridsen 2000 compared individual physical therapy sessions including specific stretching exercises to a group exercise program. Mustian 2006 compared the effect of Tai Chi Chuan to a comparison group participating in group psychosocial therapy. Sandel 2005 compared the effect of an upper-extremity movement and dance program to a nonintervention (wait-list) control group.

Risk of bias in included studies

All 24 studies were RCTs. Only one study (Lee 2007) met all quality criteria and this study was carried out during adjuvant cancer treatment.

Studies with a cut-off point of 3.0 out of 6.0 points were considered of adequate quality:

- 2 of 10 studies examining early versus delayed exercise were considered of adequate quality (Flew 1979; Jansen 1990);
- 3 of 6 studies examining post-operative exercise versus comparison were considered of adequate quality (Beurskens 2007; Cinar 2008; Kilgour 2008);
- 2 of 3 exercise studies carried out during adjuvant cancer treatment were considered of adequate quality (Courneya 2007; Lee 2007);
- 3 of 5 exercise studies carried out following cancer treatment were considered of adequate quality (Ahmed 2006; Mustian 2006; Sandel 2005).

Allocation

Only three of the 24 studies reported appropriate methods for allocation concealment (Courneya 2007; Lee 2007; Sandel 2005). Two of these studies were performed during adjuvant cancer treatment (Courneya 2007; Lee 2007) and one study was performed following cancer treatment (Sandel 2005).

Blinding

Nine of the 24 studies reported blinding of outcome assessors (Beurskens 2007; Cinar 2008; Kilgour 2008; Lauridsen 2000; Lee 2007; Mustian 2006; Sandel 2005; van der Horst 1985; Wingate 1989). Of these nine studies, one study was in the early versus delayed exercise comparison (van der Horst 1985), four studies (Beurskens 2007; Cinar 2008; Kilgour 2008; Wingate 1989) in the exercises versus comparison, one study (Lee 2007) was carried out during adjuvant cancer treatment, and three studies (Lauridsen 2000; Mustian 2006; Sandel 2005) were carried out following cancer treatment.

Of these nine studies, only three provided details on the method of blinding (Beurskens 2007; Cinar 2008; Lee 2007).

Incomplete outcome data

Lauridsen 2000: data were not presented by group for the late symptoms. Lee 2007: data on measures of variability were not provided for outcomes of upper-extremity strength and pain.

Other potential sources of bias

Our study has limitations at the review level. Despite our extensive literature search, we may have missed eligible studies.

Effects of interventions

The studies included in this review varied greatly in exercise design and timing, choice of comparison intervention, choice and timing of outcome measurements, and reporting methods (e.g. dichotomous versus continuous) that precluded pooling of overall data. In the next section we describe effects of the intervention by type of comparison and by specific outcome. When meta-analysis was not possible or appropriate, we discuss results from individual studies.

Comparison 1: Early versus delayed exercise

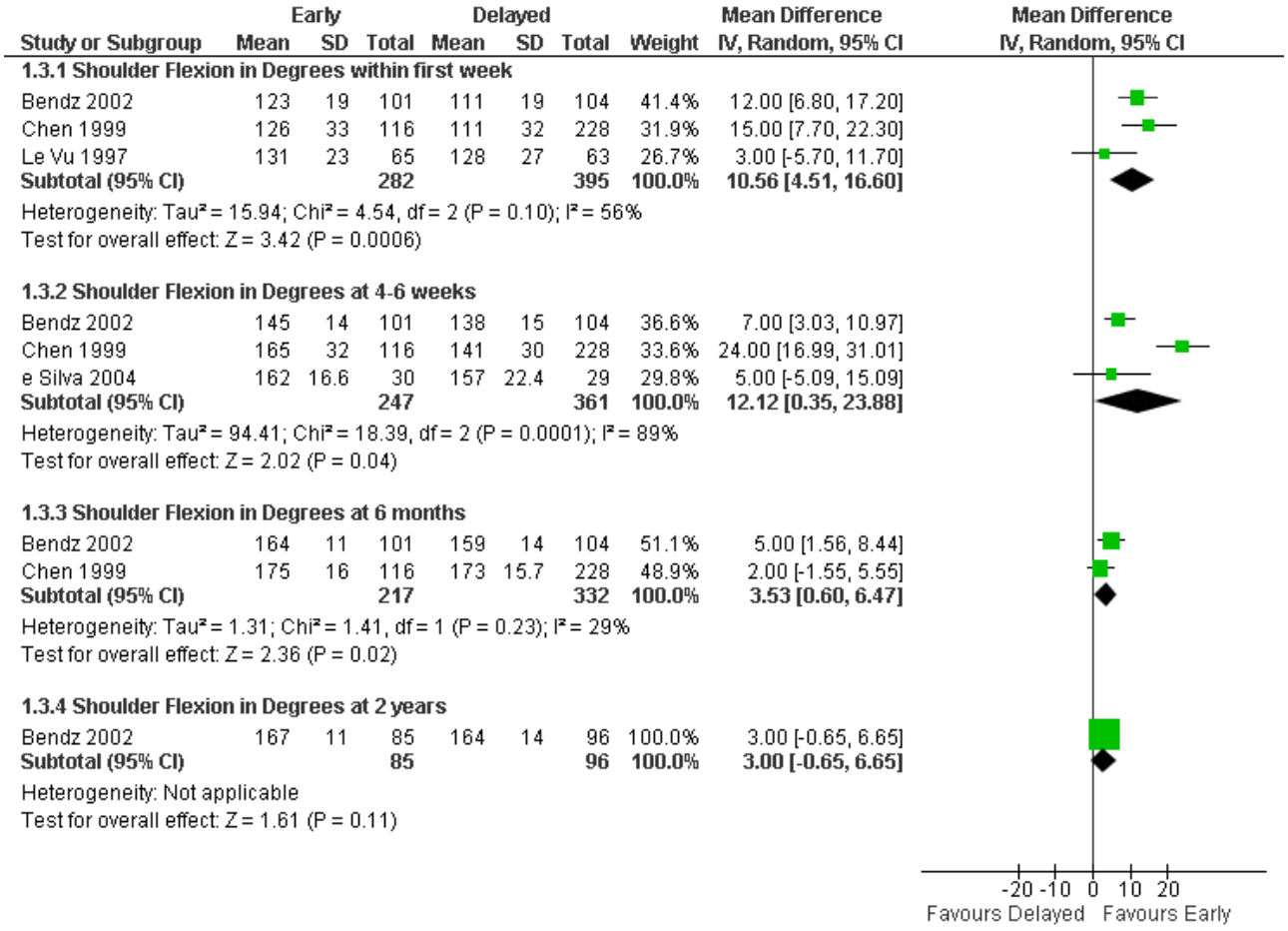
1.1-1.4 Shoulder flexion ROM

Post-Intervention: week 1

Nine studies reported the effect of early versus delayed exercises on shoulder flexion ROM one week following surgery (Abe 1998; Bendz 2002; Chen 1999; e Silva 2004; Flew 1979; Jansen 1990; Le Vu 1997; Schultz 1997; van der Horst 1985). Shoulder flexion ROM was reported in three ways: 1) the number of patients presenting with limitation (restriction) in ROM (Flew 1979; Jansen 1990; Schultz 1997; van der Horst 1985); 2) the degrees limitation in shoulder flexion ROM (Abe 1998; e Silva 2004); 3) extent of shoulder flexion ROM in degrees (Bendz 2002; Chen 1999; e Silva 2004; Le Vu 1997).

The pooled data from three studies (Bendz 2002; Chen 1999; Le Vu 1997) examining shoulder flexion ROM demonstrated a statistically significant benefit from early exercise at one week (WMD: 10.6 degrees; 95% CI: 4.51 to 16.6). (Figure 1)

Figure 1. Forest plot of comparison: 1 Post-operative: Early versus Delayed Exercise, outcome: 1.3 Shoulder Flexion ROM in degrees.



Individual studies had varying results in the short term. Abe 1998 reported statistically more limitation in shoulder flexion in the delayed exercise group when compared to the early exercise group (MD: -12.3 degrees; 95% CI: -7.02 to -17.58). Schultz 1997, however, found no significant difference in the number of patients presenting with shoulder ROM limitation (OR: 0.97; 95% CI: 0.56 to 1.67) at one week.

Follow-up assessment

Follow-up assessment of shoulder flexion ROM was reported in eight studies (Abe 1998; Bendz 2002; Chen 1999; e Silva 2004; Flew 1979; Jansen 1990; Schultz 1997; van der Horst 1985). Three studies (Bendz 2002; Chen 1999; e Silva 2004) examined shoulder flexion ROM at four-to-six weeks and found a significant benefit from early exercise for shoulder flexion ROM (MD: 12.12 degrees; 95% CI: 0.35 to 23.88); however, this analysis showed considerable statistical heterogeneity (I^2 = 89%). Two studies reported on the degrees limitation in shoulder flexion at one month (Abe 1998; e Silva 2004) and pooled data showed no significant difference between the groups (MD: 0.94 degrees; 95% CI: -2.62 to 4.49).

Follow-up data on the incidence of shoulder restriction at four-to-six month follow-up were reported in four studies (Flew 1979; Jansen 1990; Schultz 1997; van der Horst 1985). The pooled data showed no statistically significant difference between the groups in the incidence of shoulder restriction (OR: 0.97; 95% CI: 0.56 to 1.67).

One individual study (Bendz 2002) examined shoulder flexion in degrees at two-year follow-up and found no statistically significant

difference between early and delayed exercise groups (MD: 3.00 degrees; 95% CI: -0.65 to 6.65).

1.5 Shoulder abduction ROM

Five studies examined the effect of early versus delayed exercises on shoulder abduction ROM (Bendz 2002; Chen 1999; e Silva 2004; Flew 1979; Le Vu 1997).

Post-intervention: week 1

Three studies (Bendz 2002; Chen 1999; Le Vu 1997) examined the effect of early versus delayed exercises on shoulder abduction ROM one week following surgery. The pooled data showed a statistically significant benefit in favour of early exercise (MD: 11.65; 95% CI: 2.93 to 20.38). This analysis, however, showed considerable heterogeneity (I^2 = 85%).

Follow-up assessment

Three studies (Bendz 2002; Chen 1999; Le Vu 1997) performed follow-up assessment of shoulder abduction ROM at four-to-six weeks post-surgery. Although the pooled data showed no statistically significant difference between early and delayed exercise groups (MD: 14.47 degrees, 95% CI: -2.28 to 31.21); the analysis showed considerable heterogeneity I^2 = 93%. Two studies (Bendz 2002; Chen 1999) performed follow-up measures of shoulder abduction ROM at six-month follow-up. The pooled data showed a statistically significant benefit from early exercise (MD: 4.31 degrees; 95% CI: 1.38 to 7.25).

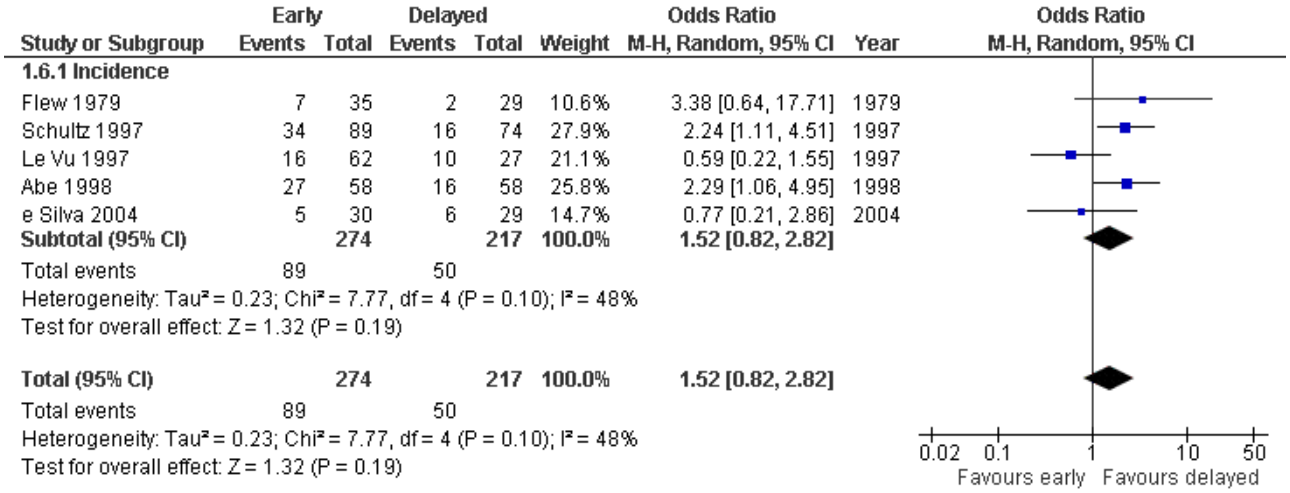
Two individual studies (e Silva 2004; Flew 1979) reported follow-up measures for the degrees limitation in shoulder abduction ROM. e Silva 2004 found no statistically significant difference between early and delayed exercise groups at six-week follow-up (MD: -5.00 degrees; 95% CI: -19.82 to 9.82) and Flew 1979 found no statistically significant difference between groups at four-month follow-up (MD: 1.40; 95% CI: -8.17 to 10.97).

Bendz 2002 reported follow-up measures of shoulder abduction ROM at two years post-surgery and found a statistically significant benefit in favour of early exercise (MD: 9.0 degrees; 95% CI: 1.13 to 16.87).

1.6 Incidence of seroma

Five studies examined the effect of early versus delayed exercises on the incidence of seroma formation (Abe 1998; e Silva 2004; Flew 1979; Le Vu 1997; Schultz 1997). Seroma occurred in 80 of 274 patients in the early exercise group and in 50 of 217 patients in the delayed group. The pooled odds ratio was not statistically significant (OR 1.52; 95% CI: 0.82 to 2.82) (Figure 2).

Figure 2. Forest plot of comparison: 1 Post-operative: Early versus Delayed Exercise, outcome: 1.6 Incidence of Seroma.



1.7-1.9 Wound drainage volume and duration

Seven studies provided data on wound drainage volume (Abe 1998; Chen 1999; Flew 1979; Jansen 1990; Le Vu 1997; Petrek 1990; van der Horst 1985). The pooled data showed a statistically significant increase in wound drainage volume from early exercise (favouring delayed exercise) (SMD 0.31; 95% CI: 0.13 to 0.49) (Figure 3). We performed a subgroup analysis by pooling the three studies published from 1995 or later. This analysis also showed a statistically significant increase in wound drainage volume from early exercise (favouring delayed exercise) (SMD 0.33; 95% CI: 0.02 to 0.64) (Figure 4).

Figure 3. Forest plot of comparison: 1 Post-operative: Early versus Delayed Exercise, outcome: 1.7 Wound Drainage Volume in ml.

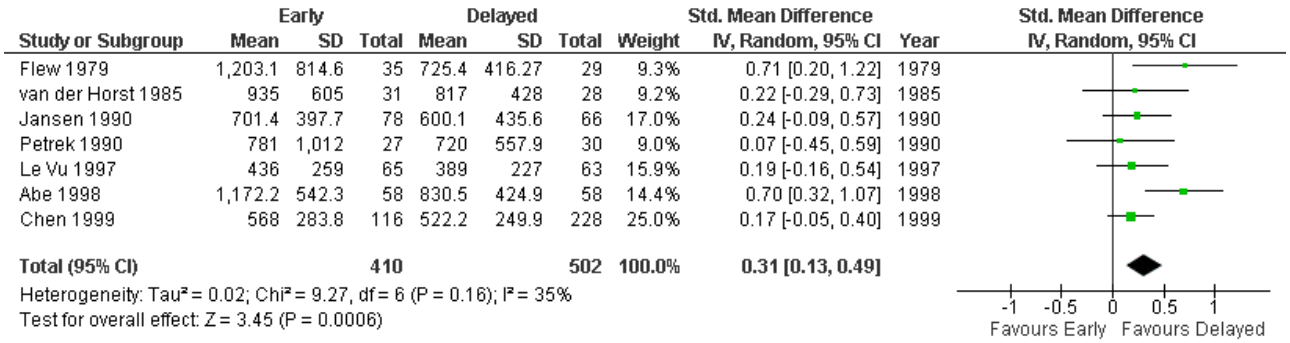
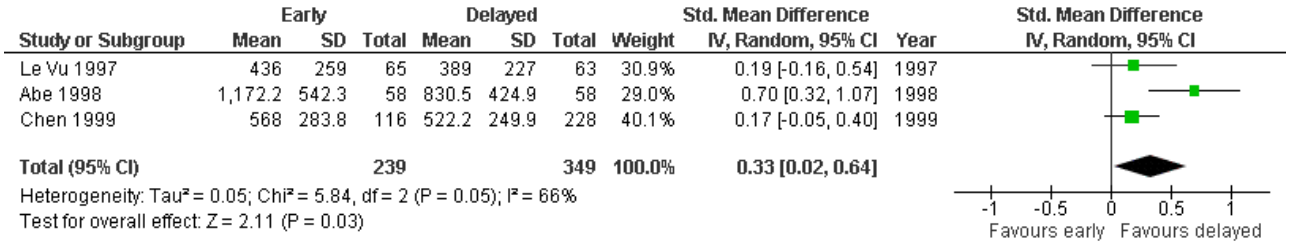
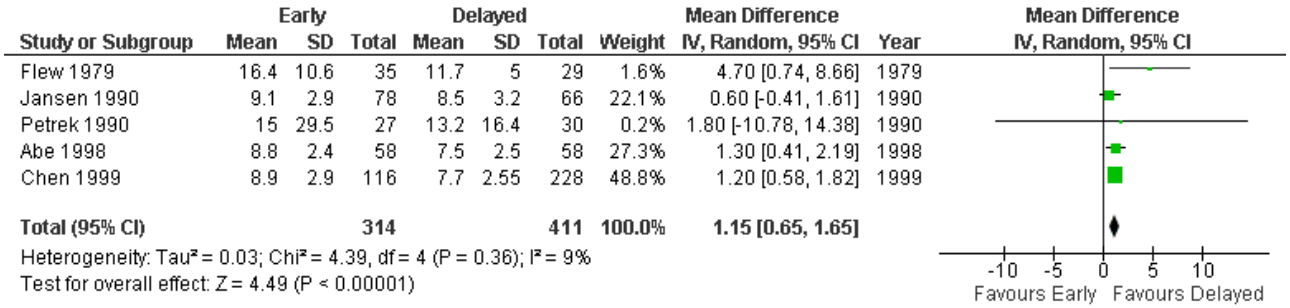


Figure 4. Forest plot of comparison: 1 Post-operative: Early versus Delayed Exercise, outcome: 1.8 Wound Drainage Volume in ml: Studies 1995 and later.



Five studies provided data on the total number days of wound drainage (Abe 1998; Chen 1999; Flew 1979; Jansen 1990; Petrek 1990). The pooled data showed a statistically significant increase in drainage duration of approximately one day from early exercise (favouring delayed exercise) (WMD: 1.15; 95% CI: 0.65 to 1.65) (Figure 5).

Figure 5. Forest plot of comparison: 1 Post-operative: Early versus Delayed Exercise, outcome: 1.9 Duration of Drainage in days.



1.10 Mean number of fluid aspirations

Three studies examined the mean number of fluid aspirations per patient following removal of wound drains (Chen 1999; Jansen 1990; Petrek 1990). The pooled data showed no statistically significant difference between early and delayed exercise in the mean number of fluid aspirations per patient (WMD: 0.11; 95% CI: -0.23 to 0.45).

1.11 Delayed wound healing

Four studies (Abe 1998; e Silva 2004; Flew 1979; Jansen 1990) examined the number of patients with delayed wound healing in the early post-operative period. The pooled data showed no statistically significant difference in wound healing between early and delayed exercise (OR: 1.39; 95% CI: 0.83 to 2.31).

1.12 Pain

The incidence of pain was reported in two studies (Bendz 2002; Le Vu 1997); however, as measurements were taken at different time points data were not pooled.

Bendz 2002 found no significant difference between rates of pain between the groups at two-week, one-month, six-month and two-year follow-up. Le Vu 1997 found no significant difference between groups in reported pain at three-month follow-up.

1.13 Lymphedema

The incidence of lymphedema was reported in four studies (Bendz 2002; Flew 1979; Jansen 1990; van der Horst 1985). Three studies (Bendz 2002; Jansen 1990; van der Horst 1985) reported lymphedema rates at six-to-eight month follow-up. Pooled data showed no statistically significant difference between groups in the incidence of lymphedema (OR: 1.24; 95% CI: 0.45 to 3.41).

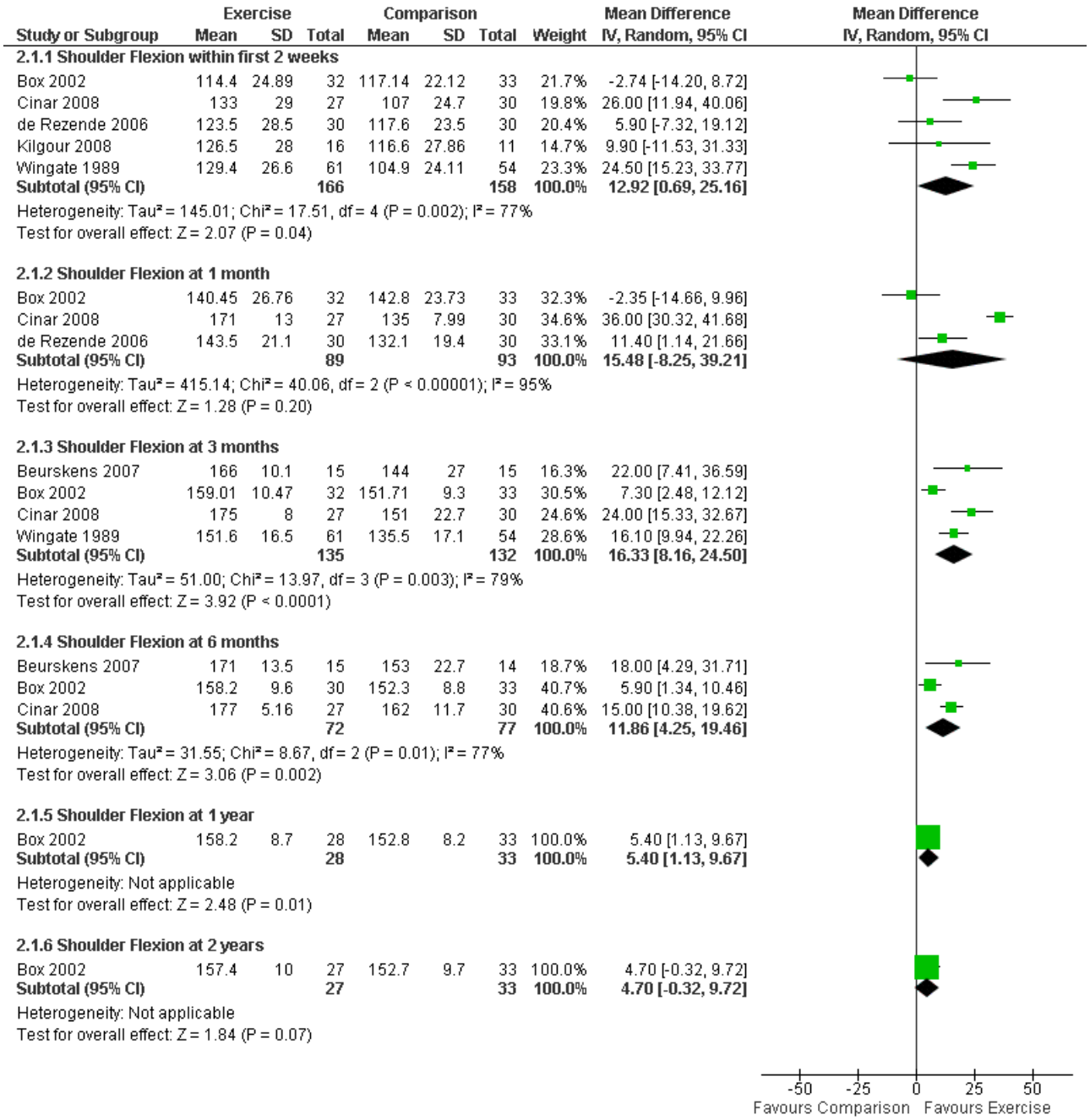
Two Individual studies reported lymphedema incidence rates at other follow-up time points. Bendz 2002 found no statistically significant difference between groups in lymphedema incidence at one-month (OR: 0.34; 95% CI: 0.03 to 3.29) or at two-year follow-up (OR: 1.15; 95% CI: 0.47 to 2.80). Flew 1979, however, reported a statistically significantly greater incidence of lymphedema in the delayed exercise group (favouring early exercise) at four-month follow-up (OR: 0.22; 0.08 to 0.64). In this latter study, participants in the delayed exercise group were immobilized in a sling for the first seven days following surgery.

Comparison 2: Exercise versus comparison

2.1-2.2 Shoulder flexion ROM

Five studies (Box 2002; Cinar 2008; de Rezende 2006; Kilgour 2008; Wingate 1989) examined the effect of a structured exercise program versus comparison on shoulder flexion ROM. All five studies reported shoulder flexion ROM in degrees. Pooled data from the five studies demonstrated benefit from exercise at one-to-two weeks post-operatively (MD: 12.92 degrees; 95% CI: 0.69 to 25.16); however, the analysis showed considerable heterogeneity (I^2 = 77%), as did the analyses at one-month (I^2 = 95%), three-month (I^2 = 79%) and six-month follow-up (I^2 = 77%) (Figure 6). This heterogeneity may be explained by differences in exercise prescription variables and exercise supervision among studies.

Figure 6. Forest plot of comparison: 2 Post-operative: Exercise versus Comparison/ control, outcome: 2.1 Shoulder Flexion.

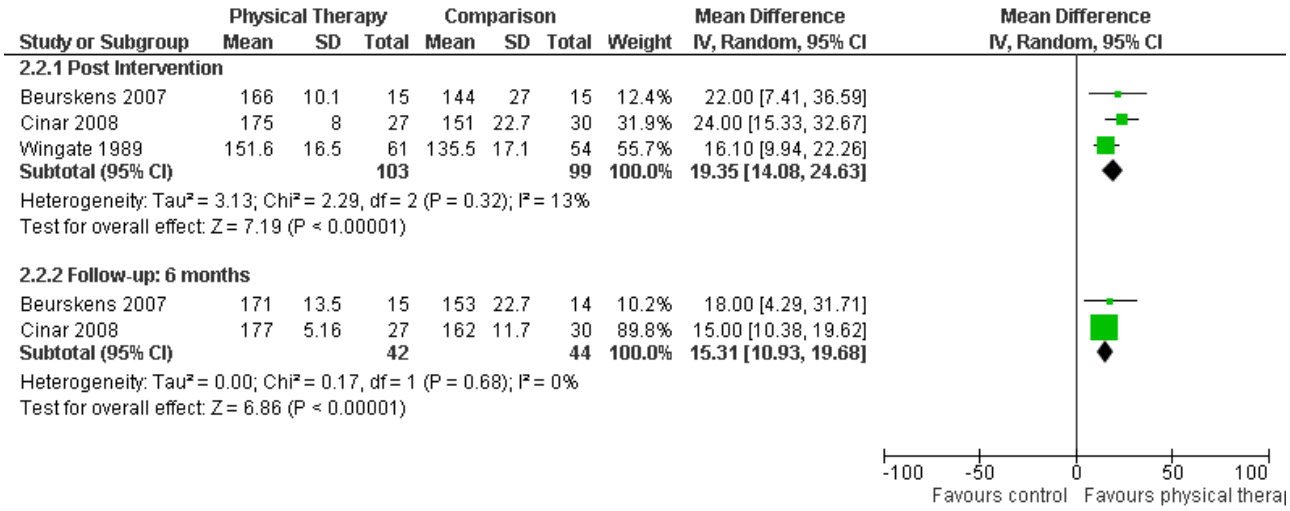


One individual study (Box 2002) reported a statistically significant benefit from exercise at one-year follow-up (MD: 5.40 degrees; 95% CI: 1.13 to 9.67) but no statistically significant difference at two-year follow-up (MD: 4.70 degrees; 95% CI: -0.32 to 9.72).

2.2 Physical therapy subgroup

Due to identified clinical and statistical heterogeneity among studies, subgroup analysis was performed on studies that were identified as providing physical therapy treatment. In these studies, patients received between nine and 15 supervised physical therapy treatments over a three-month period. Three studies (Beurskens 2007; Cinar 2008; Wingate 1989) reported measurements of shoulder flexion ROM in degrees and found a statistically significant benefit in favour of exercise at post-intervention (MD: 19.35 degrees; 95% CI: 14.08 to 24.63). Two studies (Beurskens 2007; Cinar 2008) reported follow-up measures and the pooled data showed a statistically significant benefit from exercise at six-month follow-up (MD: 15.31 degrees; 95% CI: 10.93 to 19.68) (Figure 7).

Figure 7. Forest plot of comparison: 2 Post-operative: Exercise versus Comparison/ control, outcome: 2.2 Shoulder Flexion: Physical Therapy subgroup.



2.3-2.4 Shoulder abduction ROM

Four studies examined the effect of exercise versus comparison on shoulder abduction ROM (Box 2002; de Rezende 2006; Kilgour 2008; Wingate 1989). All four studies measured abduction ROM in degrees. No statistically significant difference was found between exercise and comparison groups for measurements taken within the first two weeks (MD: 9.72 degrees; 95% CI: -8.62 to 28.06); however, this analysis showed significant statistical heterogeneity (I^2 = 89%). Pooled data from three studies (Box 2002; Cinar 2008; de Rezende 2006) found a statistically significant benefit from exercise at one month (MD: 22.05 degrees; 95% CI: 0.97 to 43.13); however this analysis also showed significant heterogeneity (I^2 = 89%) as did analyses for three-month (I^2 = 72%) and six-month follow-ups (I^2 = 80%).

In individual studies, Box 2002 demonstrated benefit from exercise at one-year follow-up (MD: 7.00 degrees; 95% CI: 1.30 to 12.70) but not at two-year follow-up (MD: 7.00 degrees; 95% CI: -0.82 to 14.82).

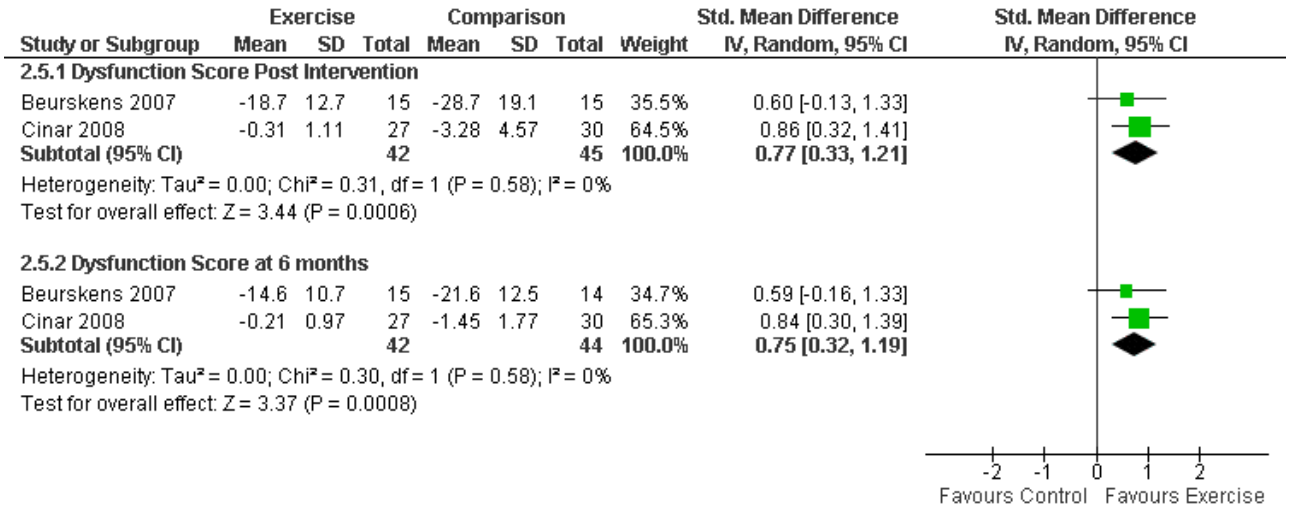
2.4 Physical therapy subgroup

We performed subgroup analyses for three studies (Beurskens 2007; Cinar 2008; Wingate 1989) in the physical therapy subgroup. The pooled data showed a statistically significant benefit in favour of physical therapy for shoulder abduction ROM at post-intervention (MD: 24.88 degrees; 95% CI: 14.46 to 35.30). The pooled results of two studies (Beurskens 2007; Cinar 2008) providing follow-up data demonstrated continued benefit at six-month follow-up (MD: 22.62 degrees; 95% CI: 15.05 to 30.19).

2.5 Shoulder function

Two studies (Beurskens 2007; Cinar 2008) examined the effect of exercise on shoulder dysfunction score. In both of these studies, participants received physical therapy intervention carried out over a three-month period. The pooled results showed a statistically significant difference in favour of exercise at post-intervention (SMD: 0.77; 95% CI: 0.33 to 1.21) and six-month follow-up (SMD: 0.75; 95% CI: 0.32 to 1.19) (Figure 8).

Figure 8. Forest plot of comparison: 2 Post-operative: Exercise versus Comparison/ control, outcome: 2.5 Shoulder Function.



2.6 Incidence of seroma

One study (Cinar 2008) reported the incidence of seroma formation. No significant difference was found in the incidence of seroma formation between exercise and comparison groups (OR: 1.18; 95% CI: 0.40 to 3.50).

2.7 Wound drainage volume

Two studies provided data on wound drainage volume (de Rezende 2006; Kilgour 2008). The pooled data showed no statistically significant difference between exercise and comparison on wound drainage volume (SMD -0.03; 95% CI: -0.45 to 0.40).

2.8 Pain

Only one study provided data on the incidence of pain (Beurskens 2007). No statistically significant differences were found in pain incidence between the exercise group and the usual care group post-intervention (OR: 1.65; 95% CI: 2.50 to 0.81) or at six-month follow-up (OR: 1.51; 95% CI: 2.35 to 0.67)

2.9 Lymphedema

Only one study provided follow-up data on the incidence of lymphedema (Box 2002). No statistically significant differences were found between exercise and comparison at one-month (OR: 1.03; 95% CI: 0.06 to 17.24), three-month (OR: 0.32, 95% CI: 0.08 to 1.35), six-month (OR: 0.18; 95% CI: 0.02 to 1.64), one year (OR: 0.48; 95% CI: 0.08 to 2.84) and two-year follow-up (OR: 0.28; 95% CI: 0.07 to 1.13).

2.10 Arm volume in mL

One study (Beurskens 2007) provided data on arm volume in mL. No statistically significant difference was found in arm volume measurements between exercise and comparison groups post-intervention (MD: -2.00 mL; 95% CI: -40.12 to 36.12).

Comparison 3: Studies examining exercise interventions for upper-limb dysfunction that were carried out during adjuvant cancer treatment (i.e., during radiation therapy or chemotherapy)

3.1 Shoulder flexion ROM

Two studies (Hwang 2008; Lee 2007) examined the effect of exercise on shoulder flexion ROM. The pooled results showed no statistically significant difference between exercise and comparison groups for shoulder flexion ROM post-intervention (MD: 7.25; 95% CI: -3.52 to 18.02).

3.2 Shoulder abduction ROM

One study (Hwang 2008) examined the effect of exercise on shoulder abduction ROM and demonstrated a significant benefit from exercise post-intervention (MD: 11 degrees; 95% CI: 2.38 to 19.62).

3.3 Upper extremity strength

One study (Courneya 2007) examined the effect of resistance exercise compared to usual care on upper-extremity strength. A statistically significant benefit in one-repetition maximum strength for the chest press (arm extension with shoulder protraction) was found in favour of resistance exercise (MD: 7.30 kg; 95% CI: 4.42 to 10.18).

3.4 Pain

One study (Hwang 2008) reported the effect of a supervised exercise program compared to usual care (self-directed shoulder exercises) on pain as measured on a visual analogue scale (VAS). No significant difference was found between the groups for post-intervention pain score (MD: -5.40 points; CI: -19.16 to 8.36).

3.5 Quality of life

Three studies (Courneya 2007; Hwang 2008; Lee 2007) examined the effect of exercise on quality of life. The pooled result showed no statistically significant difference between exercise and usual care groups for quality of life (SMD: 0.14; 95% CI: -0.10 to 0.38).

3.6 Lymphedema

Two studies (Courneya 2007; Lee 2007) reported on lymphedema incidence. One study (Courneya 2007) found no significant difference in incidence of lymphedema between the resistance exercise group and usual care group post-intervention (OR: 0.48; 95% CI: 0.12 to 1.99). One study (Lee 2007) found no significant difference in the incidence of lymphedema between stretching and usual care groups at 7-month follow-up (OR: 0.24; 95% CI: 0.02 to 2.31).

Comparison 4: Studies examining exercise interventions for upper-limb dysfunction carried out following cancer treatment

4.1 Shoulder movement restriction

One study (Lauridsen 2000) examined the effect of individual versus group exercise on the incidence of restriction in shoulder movement. No statistically significant difference was found between the groups (OR: 0.32; 95% CI: 0.03 to 3.29).

4.2 Shoulder ROM: sum of directions

One study (Sandel 2005) examined the effect of upper-extremity movement and dance compared to wait-list control on shoulder ROM. The authors reported the sum of shoulder ROM movements (shoulder flexion, abduction, internal and external rotation and extension) and found no statistically significant difference between the groups (MD: 1.00 degrees; 95% CI: -30.79 to 32.79).

4.3 Shoulder flexion ROM

Two studies (Cho 2006; Mustian 2006) reported the effect of exercise on shoulder flexion ROM post-intervention. The pooled data showed no statistically significant difference between groups (MD: 3.14 degrees; -5.27 to 11.55).

4.4. Shoulder abduction ROM

Two studies (Cho 2006; Mustian 2006) reported the effect of exercise on shoulder abduction ROM post-intervention. The pooled data showed no significant difference between groups (MD: 8.86 degrees; 95% CI: -1.86 to 19.59).

4.5 Upper extremity strength

Two studies (Ahmed 2006; Mustian 2006) examined the effect of exercise on upper-extremity strength. As there was significant statistical and clinical heterogeneity between these two studies, we did not pool the data.

Ahmed 2006 examined the effect of resistance exercise and demonstrated a significant effect on one-repetition maximum upper-extremity strength (SMD:1.49; 95% CI: 0.83 to 2.15). Mustian 2006 examined the effect of Tai Chi Chuan and found no significant effect on upper-limb muscle strength as measured by a biodex isokinetic dynamometer (SMD: -0.08, 95% CI: -0.93 to 0.78).

4.6 Upper extremity strength impairment

One study (Lauridsen 2000) reported the incidence of upper-extremity impairment and found no statistically significant difference between participants receiving individual exercise and participants taking part in a group exercise program.

4.7 Quality of life

Three studies (Cho 2006; Sandel 2005) examined the effect of exercise on quality of life. The pooled data demonstrated a statistically significant benefit from exercise on quality of life (SMD: 0.47; 95% CI: 0.16 to 0.77).

4.8 Incidence of lymphedema

One study (Ahmed 2006) examined the effect of resistance exercise compared to a nonintervention control on the incidence of lymphedema. No statistically significant difference was found between the groups in the incidence of lymphedema (OR: 0.32; 95% CI: 0.01 to 8.25).

4.9 Lymphedema: arm circumference

One study (Sandel 2005) examined the effect of an upper-extremity movement and dance program compared to wait-list control on arm circumference (sum of the points). No statistically significant difference was found between the exercise and wait-list control groups (MD: -0.08 cm; 95% CI: -0.73 to 0.56).

DISCUSSION

The ability to perform meta-analyses in this review was limited due to the variability in the timing, type and intensity of exercise, the rate of progression of exercise, and the lack of data on compliance/adherence to prescribed regimens. Differences in the chosen outcome measures, measurement methods and in the timing of the measurements precluded pooling of data. Taking into account these limitations, the following is a summary of the main findings of the review:

Summary of main results

Early versus delayed exercise

Findings of the meta-analyses support the implementation of early exercise to restore shoulder flexion and abduction ROM in early weeks post-operatively; however, there is inconclusive evidence of benefit from early exercise beyond this time point.

A small-to-moderate negative effect of increased wound drainage volume and an increase in wound duration of approximately 1 day were found from early exercise. The clinical significance of these negative effects on wound drainage is unclear and may be offset by the need to attain adequate shoulder ROM in preparation for adjuvant radiation therapy. No statistically significant difference was found between early and delayed exercise in the incidence of seroma formation, delayed wound healing, wound aspirations, pain or lymphedema. These findings, however, should be interpreted with caution as few studies examining early versus delayed exercises were considered of adequate quality. Moreover, many of the included studies were conducted more than ten years ago. Thus, results may not be generalizable to patients undergoing more recent, potentially less invasive, surgical procedures.

Exercise versus comparison

Findings of the meta-analyses suggest benefit from more structured post-operative exercise programs compared to usual care (exercise pamphlet or no exercise instruction) for shoulder flexion ROM in both the short and long-term and shoulder abduction ROM in the long-term.

There is no evidence of a negative effect from exercise on post-operative wound drainage volume, or in the reported incidence of seroma formation, pain or lymphedema. The findings in this comparison group, however, are limited by the small number of studies and the statistical and clinical heterogeneity among the included studies. More research is needed to confirm these findings.

Physical therapy versus comparison subgroup

Findings of the meta-analyses provide evidence of benefit from physical therapy intervention on shoulder flexion ROM, shoulder abduction ROM and shoulder function. The findings suggest a statistically and clinically significant benefit from exercise post-intervention and at six-month follow-up. Positive effects were the result of three studies that introduced physical therapy treatment within the early weeks following surgery.

Exercise versus comparison during adjuvant cancer treatment

There is some evidence of benefit from exercise programs carried out during adjuvant cancer treatment for shoulder abduction ROM and upper-extremity strength; however, these findings are from single studies. There is no evidence of benefit from exercise for shoulder flexion ROM, pain or quality of life. There is no evidence of increased lymphedema risk from exercise programs carried out during adjuvant cancer treatment.

Exercise versus comparison following cancer treatment

Three studies provide evidence of benefit from exercise programs carried out following cancer treatment for quality of life. The significance of this finding is unclear as all studies examined general exercise programs compared to wait-list control. Thus the findings may be due to other exercise benefits or factors such as attention and social interaction. There is evidence of benefit from resistance exercise for upper-extremity strength; however, this finding was from a single study. There is no evidence of a beneficial effect from exercise for shoulder ROM or upper-extremity strength impairment, or from Tai Chi Chuan for upper-extremity strength. Most studies included in this category were exercise-based rather than physiotherapeutic-type interventions and were not addressing upper-limb dysfunction as their primary outcome. Research is needed that specifically addresses persistent or late onset upper-limb dysfunction.

Quality of the evidence

The 24 studies included in this review were of variable quality and only 10 were considered of adequate methodological quality. In particular, inadequate randomization and allocation concealment, and lack of blinding of outcome measurements may have led to bias in the study findings. Further progress must be made to improve research quality.

Potential biases in the review process

The ability to perform meta-analyses in this review was limited by the variability in the timing, type and intensity of exercise, and the rate of progression of exercise. Moreover, differences in the chosen outcome measures, measurement methods and in the timing of the measurements precluded pooling of data. Despite inter-study heterogeneity, we proceeded with the meta-analyses for many outcomes as the intervention effects were largely consistent among studies, although to varying degrees.

Heterogeneity among studies also precluded subgroup analysis to determine the appropriate type of exercise. Furthermore, we were not able to evaluate the influence of participant demographic and treatment factors such as age or type of surgery/node dissection as data were not available. Similarly, the limited number of total studies in each category precluded evaluation of the influence of the time period of the study (1995 or later) for outcomes other than wound drainage.

Agreements and disagreements with other studies or reviews

Karki 2001 examined the effect of physical therapy methods and exercise after breast cancer surgery. The meta-analysis included five prospective clinical trials with 597 participants that examined the effect of early versus delayed shoulder exercise on wound drainage volume. The authors concluded that there was evidence of a negative effect from early exercise (favouring delayed exercise) for wound drainage volume. The results of the present review including seven RCTs with 912 participants also suggest a negative effect on wound drainage from early exercise. However, our estimated negative effect (SMD: 0.31; 95% CI: 0.13 to 0.49) was smaller than that of Karki 2001 (SMD: 0.46; 95% CI: 0.42 to 0.50).

Shamley 2005 performed a systematic review and meta-analysis also examining early versus delayed exercises. The meta-analysis included six RCTs with 540 participants. The authors did not find a statistically significant difference between early and delayed exercise for wound drainage volume. The authors did find a statistically significant increase in seroma incidence from early exercise (OR: 0.41; 95% CI: 0.27 to 0.61), whereas the present review did not. Differences in our findings compared to the two previous reviews may reflect the addition of newer studies and our more stringent study eligibility criteria.

AUTHORS' CONCLUSIONS

Implications for practice

Patients and clinicians with a preference for improved shoulder ROM in the short term and limited aversion to increased wound drainage volume and duration may opt for early implementation of post-operative exercise, while those with an aversion to increased wound drainage volume and duration, may prefer to delay implementation of post-operative exercises by approximately one week. There is evidence that patients benefit from exercise interventions that include more structured instruction and/or supervision when compared to exercise instruction via a pamphlet or no exercise instruction. Of note, larger benefits were found for shoulder ROM and shoulder function outcomes from physical therapy treatment that was introduced in the early weeks following surgery. There was no evidence of a negative effect from upper-extremity exercise on the incidence of upper-limb lymphedema at any time point following surgery.

Implications for research

Methodologically rigorous studies are needed to further explore the required degree of supervision and intensity of post-operative upper-extremity exercise regimens. Studies carried out following surgery should provide detailed information on the exercise prescription and include measurement of shoulder movement (ROM) and function. As well, future studies should monitor adherence to exercise and adverse effects such as seroma

formation, wound drainage, lymphedema, and pain. Where appropriate, outcomes should be assessed in both the short and long-term.

There is a clear need for research studies that consider the benefit of exercise relative to patient demographic and treatment variables. In particular, studies are needed that examine the benefit of exercise in older individuals. Further research is also needed that examines the benefit of exercise for late onset and persistent upper-limb dysfunction and for outcomes such as pain and upper-extremity strength.

ACKNOWLEDGEMENTS

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abe 1998

Methods	RCT Japan
Participants	116 women MRM and BCS with AND Mean age: 52.8 years
Interventions	Post-operative: Early versus delayed exercises Early (Day 1): 90° flexion on Day 1; 180° flexion on Day 2. Details on exercise intervention not provided. Delayed (Day 7): usual activities for first week.
Outcomes	Total drainage, Drainage Time, Incidence of seroma, Number of aspirations, Total volume aspirated, Delayed wound healing Wound infection, Hemorrhage days to resolution Shoulder Flexion (two weeks and one month)
Notes	Quality score: 1
Risk of bias	

Abe 1998 *(Continued)*

Bias	Authors' judgement	Support for judgement
Blinding of Outcome Assessment	High risk	
Randomisation	Low risk	
Withdrawals and drop-outs	High risk	

Ahmed 2006

Methods	RCT United States
Participants	46 women undergoing MRM/BCS with AND Mean age: 52 years
Interventions	Post-treatment study: Exercise versus comparison Exercise: six-month upper-extremity resistance training program; timing: 4-36 months post-treatment Comparison: nonintervention control
Outcomes	Upper-body 1-Repetition Maximum strength Lymphedema: measurement, symptoms
Notes	Quality score: 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Block randomization
Randomisation	Low risk	
Withdrawals and drop-outs	Low risk	

Bendz 2002

Methods	RCT Sweden
Participants	205 women RM/ BCS with AND Mean age: 58 years
Interventions	Post-operative: Early versus delayed exercises

Bendz 2002 *(Continued)*

	Early exercise (day 1): day 1-2: intermittent hand contractions with ball, elbow flexion and extension, forearm pronation and supination; day 3-7: limit of 90° for elevation and abduction with elbow bent; day 8-13: 90° elevation and abduction with elbow straight. Full range exercises starting day 14. Delayed (day 14): use within comfort, avoid heavy lifting and forced movements day 1-13. Full range exercises starting day 14.
Outcomes	Shoulder ROM, grip strength, lymphedema, pain, heaviness and tension
Notes	Quality score: 1 No data on adverse events of wound drainage, seroma formation

Risk of bias

Bias	Authors' judgement	Support for judgement
Randomisation	Low risk	

Beurskens 2007

Methods	RCT Netherlands
Participants	30 women MRM/ BCS with AND Mean age: 54.5 years
Interventions	Post-operative: Exercise versus comparison Intervention: 9 physical therapy sessions over 3 month period starting 2 weeks post surgery: exercises for arm/shoulder, posture correction, coordination and strengthening exercises, exercises to prevent lymphedema. Frequency of treatments: 1-2x/ week for first 3 weeks, then 1x/ 2-week period thereafter. Comparison: Leaflet with advice and exercises for arm and shoulder
Outcomes	Shoulder ROM, pain, arm volume via water displacement, grip strength, function (Disabilities of the Arm, Shoulder and Hand scale), quality of life (Sickness Impact Profile- short version)
Notes	Quality score: 5 Leaflet group: no contact with physical therapists

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	
Blinding of Outcome Assessment	Low risk	
Randomisation	Low risk	

Beurskens 2007 *(Continued)*

Withdrawals and drop-outs	Low risk
Blinding method	Low risk

Box 2002

Methods	RCT Australia
Participants	65 women MRM/BCS with AND Mean age: 56 years
Interventions	Post-operative: Exercise versus comparison Exercise: home exercise program starting day 2 post-surgery: exercises restricted first 2 days ≤ 100°, gradual increase in ROM with 3/10 limit for rating of discomfort. Patients received preoperative instruction, daily inpatient review and progression. Home exercise program: sustained movements and stretches incorporated after 14-21 days. Progressive exercises and stretches introduced at 1 month. Outpatient follow-up with medical appointments. versus Usual care: exercise booklet
Outcomes	Shoulder ROM Function Lymphedema
Notes	Quality score: 1 Data on ROM measurements provided by author.

Risk of bias

Bias	Authors' judgement	Support for judgement
Blinding of Outcome Assessment	Unclear risk	Outcomes were not consistently measured by blinded assessor
Randomisation	Low risk	

Chen 1999

Methods	RCT Taiwan
Participants	344 women MRM with AND Mean age: 49 years

Chen 1999 *(Continued)*

Interventions	Post-operative: Early versus delayed exercises; three groups Exercise (day 3): pulleys, wall climbing and pendular exercises to point of painful shoulder Late (day 6)/delayed (drains removed): hand squeezing exercise and forearm elevation to 40°
Outcomes	Shoulder ROM, Drainage volume and number of days, # aspirations
Notes	Quality score: 1

Risk of bias

Bias	Authors' judgement	Support for judgement
Randomisation	Low risk	

Cho 2006

Methods	RCT Korea
Participants	55 women Cancer stage: I and II MRM Mean age: 49 years
Interventions	Post-treatment: Exercise versus comparison Exercise: 90 minutes of aerobic exercise at 40%-60% maximum heart rate 2x per week and home-based stretching program 2x per week; Timing: post-treatment, mean of 14 months after diagnosis Comparison: wait-list control
Outcomes	Shoulder ROM, psychosocial adjustment, quality of life
Notes	Quality score:1

Risk of bias

Bias	Authors' judgement	Support for judgement
Blinding of Outcome Assessment	High risk	
Randomisation	Low risk	
Blinding method	High risk	

Cinar 2008

Methods	RCT Turkey

Cinar 2008 *(Continued)*

Participants	57 women MRM with AND Mean age: 52.6 years
Interventions	Post-operative: Exercise versus comparison Exercise: Supervised exercise (day 1), followed by 15 physiotherapy sessions (after drains removed), followed by 8 weeks of home exercises Comparison: no exercise (day 1 until drains removed) followed by home exercise (after drains removed)
Outcomes	Shoulder ROM, drainage, seroma, lymphedema, function
Notes	Quality score: 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Blinding of Outcome Assessment	Low risk	
Randomisation	Low risk	
Blinding method	Low risk	

Courneya 2007

Methods	RCT: multi-centre Canada 3 groups: Aerobic exercise, resistance exercise and usual care groups
Participants	164 women MRM/BCS with AND Mean age: 49.2 years
Interventions	Resistance exercise program during adjuvant treatment Timing: 1-2 weeks after start of adjuvant chemotherapy, ending 3 weeks after chemotherapy completion Exercise: upper and lower body resistance exercise; 2 sets of 8-12 repetitions of 9 exercises at 60%-70% of estimated 1 repetition maximum strength; 3 days/week Comparison: usual care
Outcomes	Upper-body strength Quality of Life
Notes	Quality score: 4 Data were provided by author. Data included only resistance exercise and usual care arms of the study. Data on participants in the aerobic exercise group were not included.

Courneya 2007 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	
Allocation concealment?	Low risk	
Blinding of Outcome Assessment	High risk	
Randomisation	Low risk	
Withdrawals and dropouts	Low risk	
Blinding method	High risk	

de Rezende 2006

Methods	RCT Brazil
Participants	60 women RM/MRM or Quadrantectomy with AND Mean age: 54.7 years
Interventions	Post-operative: Exercise versus comparison Timing: both groups starting day 3 Exercise: directed exercise program including 19 exercises performed 10x each Comparison: free exercises; general movements of the shoulder, no specified sequence or number of repetitions. Both groups supervised in group setting
Outcomes	Shoulder ROM, wound drainage, post surgical infection, arm circumference
Notes	Quality score: 1

Risk of bias

Bias	Authors' judgement	Support for judgement
Randomisation	Low risk	

e Silva 2004

Methods	RCT

e Silva 2004 *(Continued)*

	Brazil
Participants	59 women MRM/BCS with complete AND Mean age: not stated
Interventions	Post-operative: Early versus delayed exercises Early (day 1): 40 minute session consisting of 19 exercises; 10 repetitions each, 3 sessions/week for 6 weeks. No restrictions in ROM. Delayed (day 16): restricted exercises for first 15 days (shoulder ROM limited to 90°)
Outcomes	Shoulder ROM, Seroma, dehiscence
Notes	Quality score: 2

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	
Randomisation	Low risk	

Flew 1979

Methods	RCT United Kingdom
Participants	64 women early stage breast cancer MRM and complete AND Mean age: 52.5 years
Interventions	Post-operative: Early versus delayed exercises Exercise (day 2): unrestricted arm movement, supervised by physiotherapist: undefined protocol Delayed (day 8): immobilization with sling x 7 days
Outcomes	Drainage, aspirations, hospital stay, shoulder abduction, lymphedema, complications
Notes	Quality score: 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	
Randomisation	Low risk	

Flew 1979 *(Continued)*

Withdrawals and drop-outs	Low risk

Hwang 2008

Methods	RCT Korea
Participants	37 women MRM/ BCS with AND, or BCS with SNB Mean age: 46.3 years
Interventions	During Adjuvant Radiation Therapy: Exercise versus self-shoulder stretches Exercise: supervised program 3x/week; 50 minute program including aerobic exercise (e.g. walking), resistance exercise and stretching exercise for shoulders; monitored heart rate Comparison: self-directed shoulder ROM exercises and encouraged to continue with usual activities
Outcomes	Shoulder ROM, pain, quality of life
Notes	Data were provided by author. Quality score: 2

Risk of bias

Bias	Authors' judgement	Support for judgement
Randomisation	Low risk	
Withdrawals and drop-outs	Low risk	

Jansen 1990

Methods	RCT multi-centre Netherlands
Participants	144 women MRM/BCS with AND Mean age: 59.2 years
Interventions	Post-operative: Early versus delayed exercise Early (day 1): movements of shoulder were performed once/day under the supervision of a physiotherapist: flexion, abduction, horizontal abduction, external rotation; ROM performed until pain barrier reached Delayed (day 7): immobilization with sling x 7 days

Jansen 1990 *(Continued)*

Outcomes	Drainage, aspirations, wound complications, shoulder restriction, lymphedema, # physical therapy visits required
Notes	Quality score: 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	
Randomisation	Low risk	
Withdrawals and dropouts	Low risk	

Kilgour 2008

Methods	Pilot RCT Canada
Participants	27 women MRM with AND Mean age: 50 years
Interventions	Post-operative: Exercise versus comparison Exercise (Day 3): Home-based video: 11 day program: thirteen exercises with emphasis on proper technique, speed of movement, frequency and progression of exercise. Day 3 to 9: 3 sets/day of ROM and flexibility exercises; 5-7 minutes per set. Day 10-14: same exercises; 2 sets/day; 10-15 minutes per set. Usual care (Day 3): booklet including thirteen exercises consisting of stretching and ROM exercises of the shoulder. Exercises are performed 2x/day within pain-free range of motion.
Outcomes	Shoulder ROM, strength, pain, wound drainage volume
Notes	Quality score: 4 Data on ROM, strength measurements were provided by author.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	
Blinding of Outcome Assessment	Low risk	
Randomisation	Low risk	

Kilgour 2008 *(Continued)*

Withdrawals and drop-outs	Low risk

Lauridsen 2000

Methods	RCT Denmark
Participants	55 women MRM/ BCS with Level I/II AND Mean age: 54.6 years
Interventions	Post-treatment: Exercise versus comparison Timing: post operatively 1-4 years Exercise: physical Therapy 1x/ week for 10 weeks with addition of stretching of axillary tissue, skin and underlying pectoral muscles Comparison: group exercise in pool and out-of-water, 1x/ week for 10 weeks
Outcomes	Strength, shoulder movement, late symptoms (muscle tone, winging of scapula)
Notes	Quality score: 2 Data not presented by group for the late symptoms

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Blinding of Outcome Assessment	Low risk	
Randomisation	Low risk	

Le Vu 1997

Methods	RCT: 4 groups France
Participants	95 women MRM, BCS and AND Mean age: 56.4 years
Interventions	Post-operative: Early versus delayed exercises Early (day 1): active shoulder movements: abduction, flexion and rotation performed slowly, without resistance; 5 sessions/ 7 days

Le Vu 1997 *(Continued)*

	Delayed (day 7): no exercise; then provided with physical therapy and exercise until end of hospitalization
Outcomes	Drainage, shoulder movement, pain, fibrous cords, complications
Notes	Quality score: 1 Data from exercise group (n = 63) versus no exercise group (n = 63). Data from groups receiving massage were not included.

Risk of bias

Bias	Authors' judgement	Support for judgement
Randomisation	Low risk	

Lee 2007

Methods	RCT Australia
Participants	61 women MRM/BCS with AND/SNB Mean age: 54 years
Interventions	During adjuvant radiation therapy: Exercise versus comparison Exercise: Stretching exercise focusing on pectoral muscles stretching, 2x/ day for 6 weeks Comparison: usual care - self-directed shoulder ROM exercises for 6 weeks
Outcomes	Shoulder ROM, strength, pain, lymphedema and quality of life
Notes	Quality score: 6 Data for quality of life provided by author

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	
Allocation concealment?	Low risk	
Blinding of Outcome Assessment	Low risk	
Randomisation	Low risk	
Withdrawals and dropouts	Low risk	

Lee 2007 *(Continued)*

Blinding method	Low risk

Mustian 2006

Methods	RCT United States
Participants	21 women with Stage 0-III breast cancer MRM/BCS with AND Mean age: 52 years
Interventions	Post-treatment: Exercise versus comparison Timing: participants were < 36 months from diagnosis Exercise: Tai Chi Chuan 60 minutes/ session, 3 days/week for 12 weeks. Comparison: Psychological support group: 60 minutes/session, 3 days/week for 12 weeks; participants advised not to change current physical activity during study period
Outcomes	Shoulder ROM, strength (biodex isokinetic dynamometer)
Notes	Quality Score: 3

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	High risk	
Blinding of Outcome Assessment	Low risk	
Randomisation	Low risk	
Withdrawals and dropouts	Low risk	

Petrek 1990

Methods	RCT United States
Participants	57 women MRM, BCS and AND Mean age: 53.7 years
Interventions	Post-operative: Early versus delayed exercises

Petrek 1990 *(Continued)*

	Early (day 2): pendular exercises, pulleys, wall climbing; graduated ROM: 3x/day until complete range of motion Delayed (day 6): immobilization with sling by 5 days
Outcomes	Wound drainage, aspirations, days in hospital
Notes	Quality score: 1

Risk of bias

Bias	Authors' judgement	Support for judgement
Randomisation	Low risk	

Sandel 2005

Methods	RCT United States
Participants	35 women MRM/ BCS and AND Mean age: 59.6 years
Interventions	Post-treatment: Exercise versus comparison Timing: 12-week program during adjuvant chemotherapy/post-treatment (30 participants were post-treatment) Exercise: upper-extremity movement and dance: 60 minutes/session; 2x/week for 6 weeks and 1x/week for next 6 weeks Comparison: wait-list control group
Outcomes	Quality of life, shoulder ROM, lymphedema
Notes	Quality Score: 5

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	
Allocation concealment?	Low risk	
Blinding of Outcome Assessment	Low risk	
Randomisation	Low risk	
Withdrawals and drop-outs	Low risk	

Schultz 1997

Methods	RCT Sweden
Participants	163 women MRM and AND Age range: 35 to 84 years
Interventions	Post-operative: Early versus delayed exercises Early (day 1): Active flexion, abduction and rotations to full ROM, pain limiting factor for extent of motion Delayed (day 7): no exercise day 1 to day 6
Outcomes	Seroma, shoulder ROM, complications
Notes	Quality score: 0

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	High risk	day of birth
Allocation concealment?	High risk	
Randomisation	Low risk	deduct 1 point for inappropriate randomization

van der Horst 1985

Methods	RCT Netherlands
Participants	57 women RM/MRM/ BCS with AND Mean age: 62.1 years
Interventions	Post-operative: Early versus delayed exercises Early (day 1): daily exercises x 14 days: flexion, abduction and rotations until point of pain versus Delayed (day 7): exercise with restricted ROM (day1-6)
Outcomes	Shoulder movement, drainage volume and duration
Notes	Quality score: 2 Drainage volume and duration: measures of variability not provided

van der Horst 1985 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Blinding of Outcome Assessment	Low risk	
Randomisation	Low risk	

Wingate 1989

Methods	RCT United States
Participants	115 women MRM with AND Mean age: 57.2 years
Interventions	Post-operative: Exercise versus comparison Exercise (day 1): physical therapy twice daily for 30 minutes while hospitalized followed by 8-week home-based progressive program Comparison: nonintervention control
Outcomes	Shoulder ROM, function, lymphedema, post-operative complications
Notes	Quality Score: 2 Note: the sample included participants from a pilot study Follow-up measurements were taken between 1 and 3 months post-operatively

Risk of bias

Bias	Authors' judgement	Support for judgement
Blinding of Outcome Assessment	Low risk	
Randomisation	Low risk	

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aitken 1989	Not an exercise intervention
Andersen 2000	Same exercise intervention in both groups
Box 2002b	Duplicate publication: lymphedema results

Study	Reason for exclusion
Browse 1996	Mixed cancer group (included melanoma). Results not reported for breast cancer subgroup.
Cave 2006	Review of Lauridsen (2006) study
Cheema 2002	Not a randomized controlled trial
Dawson 1989	Details on exercise intervention not provided
Forchuk 2004	Not an exercise intervention
Gutman 1990	Not a randomized controlled trial
Hase 2006	Pharmacological intervention
Hladiuk 1992	Not a randomized controlled trial
Johansson 2005	Not a randomized controlled trial
Knight 1995	Did not meet inclusion criteria: undefined exercise
Kolden 2002	Not a randomized controlled trial
Kramer 1996	Not a randomized controlled trial
Lane 2005	Not a randomized controlled trial
Lotze 1981	Did not meet inclusion criteria: included patients with melanoma. Data not reported for breast cancer subgroup.
McKenzie 2003	Inadequate information on study participants for surgery and axillary dissection/sentinel node biopsy
Mutrie 2006	Did not meet inclusion criteria: inadequate information on axillary dissection/sentinel node biopsy
Na 1999	Not stated as random allocation
Petruseviciene 2002	Not an exercise intervention
Reitman 2003	Not an intervention study
Rodier 1987	Did not report upper-limb outcomes
Sprod 2005	Did not meet inclusion criterion of axillary node/ sentinel node biopsy for participants
Sugden 1998	Not a randomized controlled trial
Tadych 1987	Not an intervention study

Characteristics of studies awaiting assessment *[ordered by study ID]*

Chae 2001

Methods	Prospective Trial

Chae 2001 *(Continued)*

Participants	Breast Cancer Patients undergoing Radiation Therapy
Interventions	Exercise
Outcomes	Shoulder joint function Cardiopulmonary fitness
Notes	Published in Korean

Lauridsen 2005

Methods	Randomized Controlled Trial: cross-over
Participants	139 Breast Cancer Patients
Interventions	Team physical therapy commenced between weeks six-to-eight post-operatively Comparison: wait-list control (cross-over at week 26)
Outcomes	Shoulder function: Constant's shoulder scale
Notes	Awaiting further clarification on eligibility and data from author

Todd 2008

Methods	Randomized Controlled Trial
Participants	116 Breast Cancer Patients
Interventions	Early mobilization (within 48 hours) versus delayed (restricted ROM to 90 degrees for first seven days)
Outcomes	Lymphedema, wound drainage, shoulder ROM, grip strength, shoulder disability, quality of life
Notes	Awaiting further clarification on eligibility and data from author

Characteristics of ongoing studies *[ordered by study ID]*

Kilbreath 2006

Trial name or title	Progressive resistance exercise training and stretching following surgery for breast cancer: study protocol for a randomized controlled trial
Methods	Randomized, single blind
Participants	Women with early stage breast cancer
Interventions	Exercise group: daily exercises, 1x per week supervised Usual care: visit by physical or occupational therapist while inpatient and exercise pamphlet

Kilbreath 2006 *(Continued)*

Outcomes	Breast cancer specific questionnaire Range of motion, strength, swelling, pain and quality of life
Starting date	2006
Contact information	Sharon Kilbreath s.kilbreath@fhs.usyd.edu.au
Notes	

Mayo 2004

Trial name or title	Reducing Arm Morbidity through Physical Therapy Provided Pre and Post Breast Cancer Surgery
Methods	Randomized, single blind
Participants	Women with diagnosed breast cancer
Interventions	Prehabilitation versus exercise booklet
Outcomes	Arm morbidity Quality of Life
Starting date	August 2004
Contact information	Nancy Mayo, PhD 514-934-1934 ext 36906 McGill University, Montreal, Quebec
Notes	Anticipated end date: July 2009

Paskett 2006

Trial name or title	Education With or Without Exercise and Counseling in Preventing Lymphedema in Women With Stage I, Stage II, or Stage III Breast Cancer Who Are Undergoing Axillary Lymph Node Dissection
Methods	Randomized Study
Participants	Women with Stage I, II, III breast cancer undergoing axillary node dissection
Interventions	Education with or without exercise and counselling
Outcomes	Lymphedema Quality of Life
Starting date	June 2006
Contact information	Clinical Trials Office - OSU Comprehensive Cancer Center 614-293-4976

Paskett 2006 *(Continued)*

Notes	Anticipated end date: December 2012

Schmitz 2005

Trial name or title	Strength Training Intervention for Breast Cancer Survivors and the Effects on Lymphedema Status
Methods	Randomized
Participants	Women with breast cancer with or without lymphedema
Interventions	13 weeks of supervised strength training (twice weekly for 90 minutes per session), 39 weeks of unsupervised strength training (twice weekly for 90 minutes per session) versus no exercise control group
Outcomes	Upper-extremity range of motion and function, strength, lymphedema, quality of life
Starting date	October 2005
Contact information	Kathryn Schmitz, PhD, MPH University of Pennsylvania
Notes	Study closed to recruitment: June 2008

DATA AND ANALYSES

Comparison 1. Post-operative: Early versus Delayed Exercise

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Impaired Shoulder Mobility	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Shoulder limitation in first week	1	163	Odds Ratio (M-H, Random, 95% CI)	0.26 [0.13, 0.52]
1.2 Shoulder Limitation 4-6 months	4	423	Odds Ratio (M-H, Random, 95% CI)	0.97 [0.56, 1.67]
2 Degrees Limitation in Shoulder Flexion ROM	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Degrees Limitation in Shoulder Flexion first week	1	116	Mean Difference (IV, Random, 95% CI)	-12.30 [-17.58, -7.02]
2.2 Degrees Limitation in Shoulder Flexion at 4 weeks	2	175	Mean Difference (IV, Random, 95% CI)	0.94 [-2.62, 4.49]
3 Shoulder Flexion ROM in degrees	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 Shoulder Flexion in Degrees within first week	3	677	Mean Difference (IV, Random, 95% CI)	10.56 [4.51, 16.60]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2 Shoulder Flexion in Degrees at 4-6 weeks	3	608	Mean Difference (IV, Random, 95% CI)	12.12 [0.35, 23.88]
3.3 Shoulder Flexion in Degrees at 6 months	2	549	Mean Difference (IV, Random, 95% CI)	3.53 [0.60, 6.47]
3.4 Shoulder Flexion in Degrees at 2 years	1	181	Mean Difference (IV, Random, 95% CI)	3.0 [-0.65, 6.65]
4 Degrees Limitation in Shoulder Abduction ROM	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 Degrees Limitation in Shoulder Abduction at 4-6 weeks	1	59	Mean Difference (IV, Random, 95% CI)	-5.0 [-19.82, 9.82]
4.2 Degrees Limitation in Shoulder Abduction at 4-6 months	1	64	Mean Difference (IV, Random, 95% CI)	1.40 [-8.17, 10.97]
5 Shoulder Abduction ROM in degrees	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 Shoulder Abduction in Degrees First Week	3	677	Mean Difference (IV, Random, 95% CI)	11.65 [2.93, 20.38]
5.2 Shoulder Abduction in Degrees at 4-6 weeks	3	608	Mean Difference (IV, Random, 95% CI)	14.47 [-2.28, 31.21]
5.3 Shoulder Abduction in Degrees at 6 months	2	549	Mean Difference (IV, Random, 95% CI)	4.31 [1.38, 7.25]
5.4 Shoulder Abduction in Degrees at 2 years	1	181	Mean Difference (IV, Random, 95% CI)	9.0 [1.13, 16.87]
6 Incidence of Seroma	5	491	Odds Ratio (M-H, Random, 95% CI)	1.52 [0.82, 2.82]
6.1 Incidence	5	491	Odds Ratio (M-H, Random, 95% CI)	1.52 [0.82, 2.82]
7 Wound Drainage Volume	7	912	Std. Mean Difference (IV, Random, 95% CI)	0.31 [0.13, 0.49]
8 Wound Drainage Volume: Studies 1995 and later	3	588	Std. Mean Difference (IV, Random, 95% CI)	0.33 [0.02, 0.64]
9 Duration of Drainage in days	5	725	Mean Difference (IV, Random, 95% CI)	1.15 [0.65, 1.65]
10 Mean number of Aspirations	3	545	Mean Difference (IV, Random, 95% CI)	0.11 [-0.23, 0.45]
11 Delayed Wound Healing	4	383	Odds Ratio (M-H, Random, 95% CI)	1.39 [0.83, 2.31]
12 Pain	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
12.1 2 week follow-up	1	205	Odds Ratio (M-H, Random, 95% CI)	1.04 [0.54, 2.00]
12.2 1 month follow-up	1	205	Odds Ratio (M-H, Random, 95% CI)	1.34 [0.59, 3.02]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
12.3 3 month follow-up	1	118	Odds Ratio (M-H, Random, 95% CI)	0.88 [0.39, 1.99]
12.4 6 -8 month follow-up	1	205	Odds Ratio (M-H, Random, 95% CI)	1.87 [0.70, 4.96]
12.5 2 year follow-up	1	181	Odds Ratio (M-H, Random, 95% CI)	1.15 [0.49, 2.72]
13 Incidence of Lymphedema	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
13.1 1 month follow-up	1	205	Odds Ratio (M-H, Random, 95% CI)	0.34 [0.03, 3.29]
13.2 4 month follow-up	1	63	Odds Ratio (M-H, Random, 95% CI)	0.22 [0.08, 0.64]
13.3 6-8 month follow-up	3	408	Odds Ratio (M-H, Random, 95% CI)	1.24 [0.45, 3.41]
13.4 2 year follow-up	1	181	Odds Ratio (M-H, Random, 95% CI)	1.15 [0.47, 2.80]

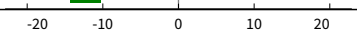
Analysis 1.1. Comparison 1 Post-operative: Early versus Delayed Exercise, Outcome 1 Impaired Shoulder Mobility.

Study or subgroup	Early n/N	Delayed n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
1.1.1 Shoulder limitation in first week					
Schultz 1997	16/89	34/74		100%	0.26[0.13,0.52]
Subtotal (95% CI)	**89**	**74**		**100%**	**0.26[0.13,0.52]**
Total events: 16 (Early), 34 (Delayed)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.75(P=0)					
1.1.2 Shoulder Limitation 4-6 months					
Flew 1979	13/35	8/29		26.39%	1.55[0.53,4.5]
Jansen 1990	14/78	14/66		43.8%	0.81[0.36,1.86]
Schultz 1997	3/89	3/67		11.22%	0.74[0.15,3.81]
van der Horst 1985	6/31	6/28		18.59%	0.88[0.25,3.13]
Subtotal (95% CI)	**233**	**190**		**100%**	**0.97[0.56,1.67]**
Total events: 36 (Early), 31 (Delayed)					
Heterogeneity: Tau²=0; Chi²=1.05, df=3(P=0.79); I²=0%					
Test for overall effect: Z=0.11(P=0.91)					

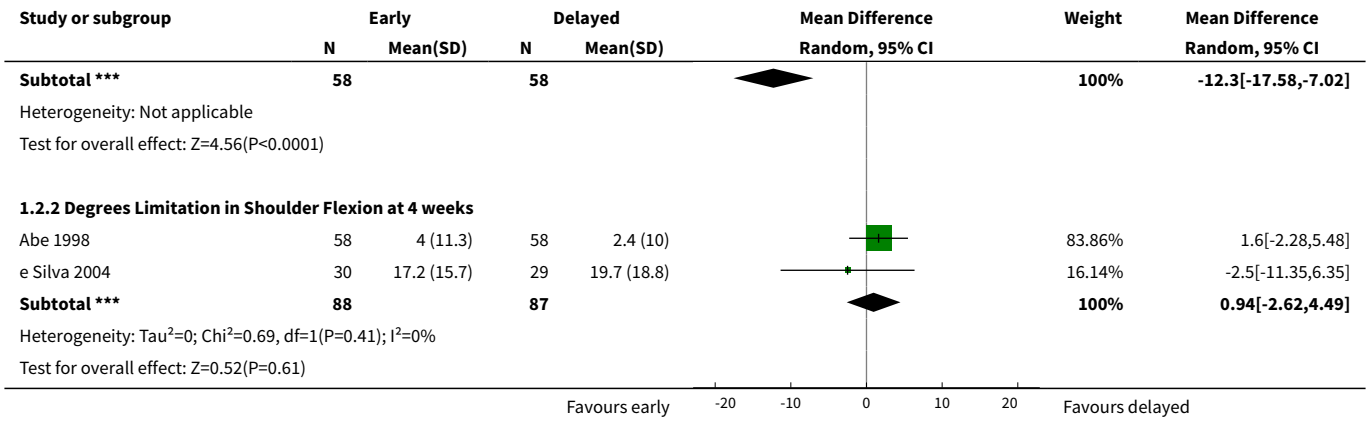
Favours early exercise — Favours delayed exercise

Analysis 1.2. Comparison 1 Post-operative: Early versus Delayed Exercise, Outcome 2 Degrees Limitation in Shoulder Flexion ROM.

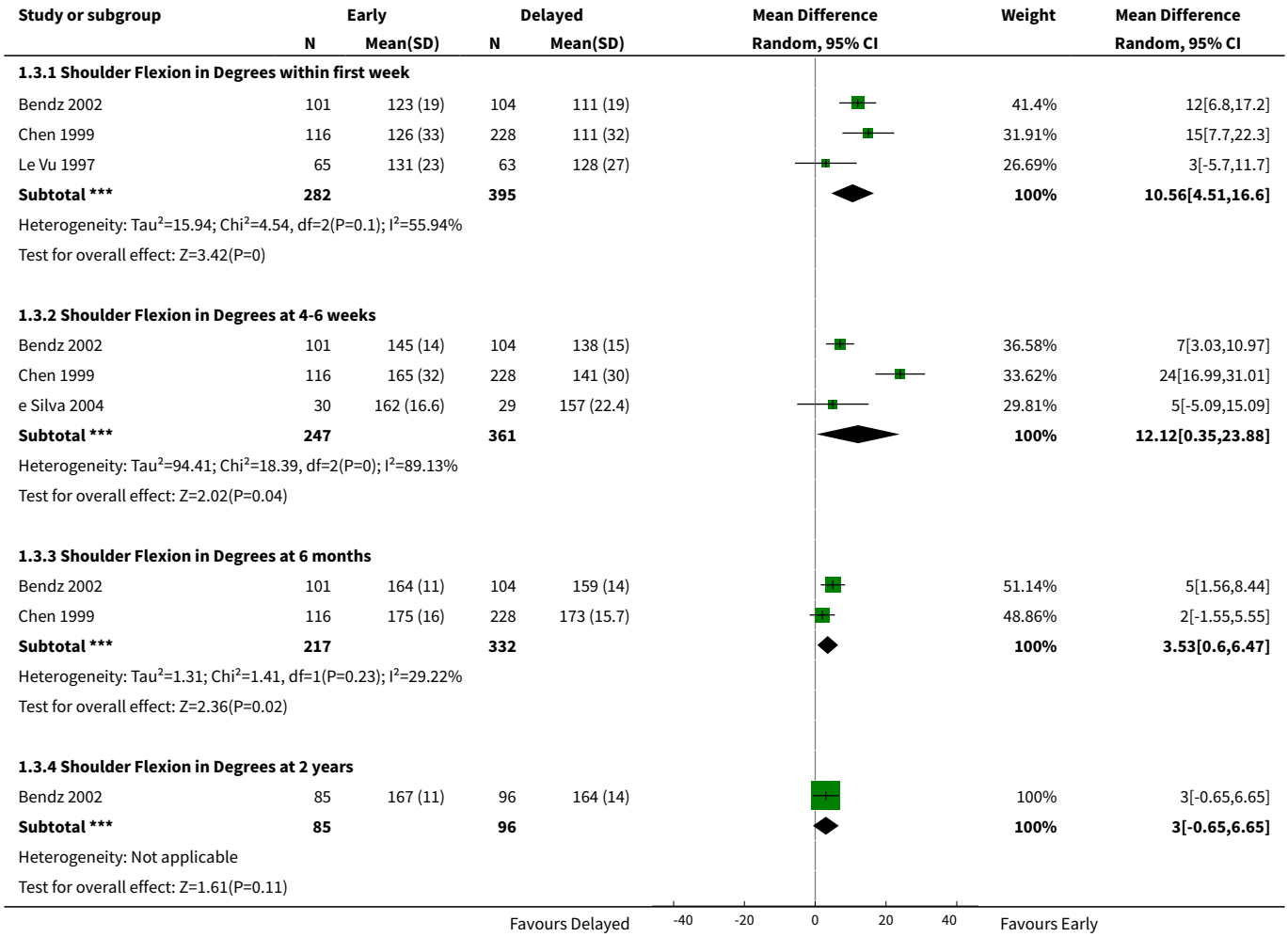
Study or subgroup	Early N	Early Mean(SD)	Delayed N	Delayed Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.2.1 Degrees Limitation in Shoulder Flexion first week							
Abe 1998	58	1.9 (5.4)	58	14.2 (19.8)		100%	-12.3[-17.58,-7.02]



Favours early — Favours delayed

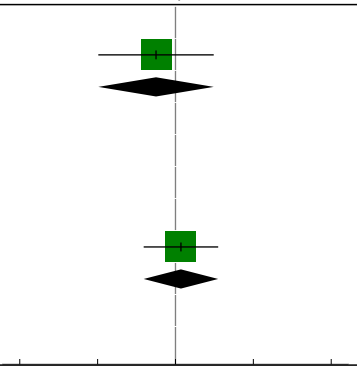


Analysis 1.3. Comparison 1 Post-operative: Early versus Delayed Exercise, Outcome 3 Shoulder Flexion ROM in degrees.



Analysis 1.4. Comparison 1 Post-operative: Early versus Delayed Exercise, Outcome 4 Degrees Limitation in Shoulder Abduction ROM.

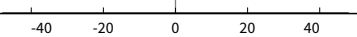
Study or subgroup	Early N	Early Mean(SD)	Delayed N	Delayed Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.4.1 Degrees Limitation in Shoulder Abduction at 4-6 weeks							
e Silva 2004	30	21.6 (26)	29	26.6 (31.7)		100%	-5[-19.82,9.82]
Subtotal ***	**30**		**29**			**100%**	**-5[-19.82,9.82]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.66(P=0.51)							
1.4.2 Degrees Limitation in Shoulder Abduction at 4-6 months							
Flew 1979	35	21.2 (21.3)	29	19.8 (17.8)		100%	1.4[-8.17,10.97]
Subtotal ***	**35**		**29**			**100%**	**1.4[-8.17,10.97]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.29(P=0.77)							



Favours early — Favours delayed

Analysis 1.5. Comparison 1 Post-operative: Early versus Delayed Exercise, Outcome 5 Shoulder Abduction ROM in degrees.

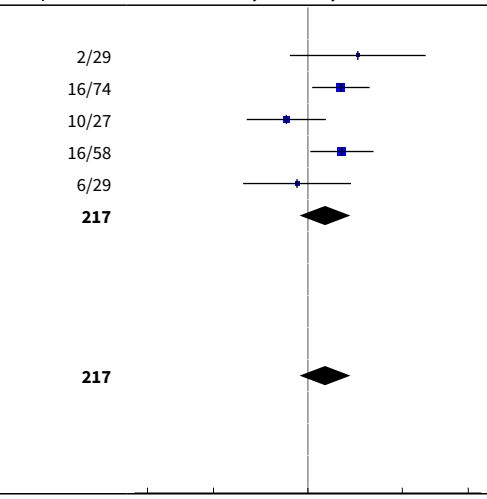
Study or subgroup	Early N	Early Mean(SD)	Delayed N	Delayed Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.5.1 Shoulder Abduction in Degrees First Week							
Bendz 2002	101	89 (21)	104	79 (19)		35.42%	10[4.51,15.49]
Chen 1999	116	126 (13)	228	107 (20.2)		38.59%	19[15.47,22.53]
Le Vu 1997	65	129 (31)	63	126 (29)		25.99%	3[-7.4,13.4]
Subtotal ***	**282**		**395**			**100%**	**11.65[2.93,20.38]**
Heterogeneity: Tau^2=48.06; Chi^2=13.18, df=2(P=0); I^2=84.82%							
Test for overall effect: Z=2.62(P=0.01)							
1.5.2 Shoulder Abduction in Degrees at 4-6 weeks							
Bendz 2002	101	115 (22)	104	109 (25)		35.47%	6[-0.44,12.44]
Chen 1999	116	163 (24)	228	135 (28.1)		35.88%	28[22.31,33.69]
e Silva 2004	30	157 (26.1)	29	149 (32.8)		28.65%	8[-7.16,23.16]
Subtotal ***	**247**		**361**			**100%**	**14.47[-2.28,31.21]**
Heterogeneity: Tau^2=194.96; Chi^2=26.83, df=2(P<0.0001); I^2=92.55%							
Test for overall effect: Z=1.69(P=0.09)							
1.5.3 Shoulder Abduction in Degrees at 6 months							
Bendz 2002	101	147 (25)	104	141 (29)		15.73%	6[-1.41,13.41]
Chen 1999	116	176 (13)	228	172 (16.6)		84.27%	4[0.8,7.2]
Subtotal ***	**217**		**332**			**100%**	**4.31[1.38,7.25]**
Heterogeneity: Tau^2=0; Chi^2=0.24, df=1(P=0.63); I^2=0%							
Test for overall effect: Z=2.88(P=0)							
1.5.4 Shoulder Abduction in Degrees at 2 years							
Bendz 2002	85	154 (25)	96	145 (29)		100%	9[1.13,16.87]
Subtotal ***	**85**		**96**			**100%**	**9[1.13,16.87]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.24(P=0.02)							



Favours Delayed — Favours Early

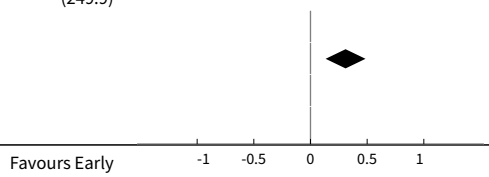
Analysis 1.6. Comparison 1 Post-operative: Early versus Delayed Exercise, Outcome 6 Incidence of Seroma.

Study or subgroup	Early n/N	Delayed n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
1.6.1 Incidence					
Flew 1979	7/35	2/29		10.56%	3.38[0.64,17.71]
Schultz 1997	34/89	16/74		27.86%	2.24[1.11,4.51]
Le Vu 1997	16/62	10/27		21.07%	0.59[0.22,1.55]
Abe 1998	27/58	16/58		25.83%	2.29[1.06,4.95]
e Silva 2004	5/30	6/29		14.67%	0.77[0.21,2.86]
Subtotal (95% CI)	**274**	**217**		**100%**	**1.52[0.82,2.82]**
Total events: 89 (Early), 50 (Delayed)					
Heterogeneity: Tau^2=0.23; Chi^2=7.77, df=4(P=0.1); I^2=48.5%					
Test for overall effect: Z=1.32(P=0.19)					
Total (95% CI)	**274**	**217**		**100%**	**1.52[0.82,2.82]**
Total events: 89 (Early), 50 (Delayed)					
Heterogeneity: Tau^2=0.23; Chi^2=7.77, df=4(P=0.1); I^2=48.5%					
Test for overall effect: Z=1.32(P=0.19)					



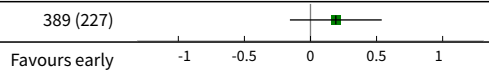
Analysis 1.7. Comparison 1 Post-operative: Early versus Delayed Exercise, Outcome 7 Wound Drainage Volume.

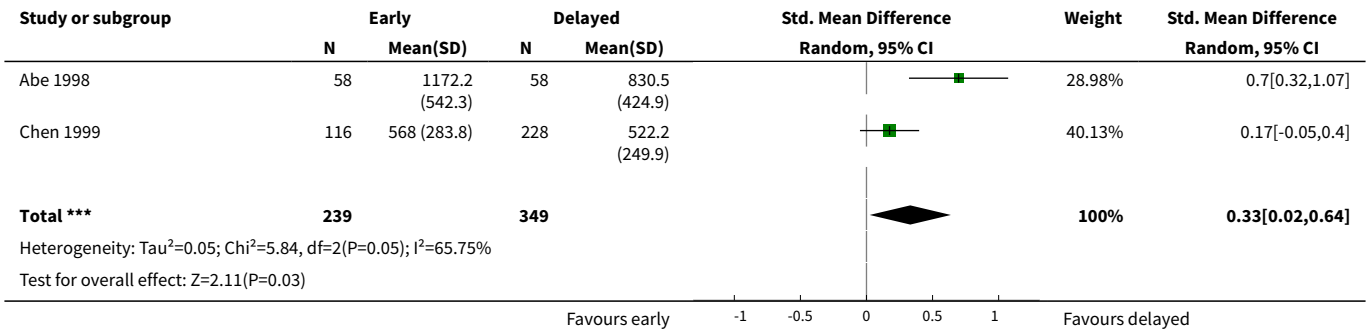
Study or subgroup	Early N	Early Mean(SD)	Delayed N	Delayed Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Flew 1979	35	1203.1 (814.6)	29	725.4 (416.3)		9.33%	0.71[0.2,1.22]
van der Horst 1985	31	935 (605)	28	817 (428)		9.21%	0.22[-0.29,0.73]
Jansen 1990	78	701.4 (397.7)	66	600.1 (435.6)		17.03%	0.24[-0.09,0.57]
Petrek 1990	27	781 (1012)	30	720 (557.9)		9%	0.07[-0.45,0.59]
Le Vu 1997	65	436 (259)	63	389 (227)		15.95%	0.19[-0.16,0.54]
Abe 1998	58	1172.2 (542.3)	58	830.5 (424.9)		14.45%	0.7[0.32,1.07]
Chen 1999	116	568 (283.8)	228	522.2 (249.9)		25.03%	0.17[-0.05,0.4]
Total ***	**410**		**502**			**100%**	**0.31[0.13,0.49]**
Heterogeneity: Tau^2=0.02; Chi^2=9.27, df=6(P=0.16); I^2=35.29%							
Test for overall effect: Z=3.45(P=0)							



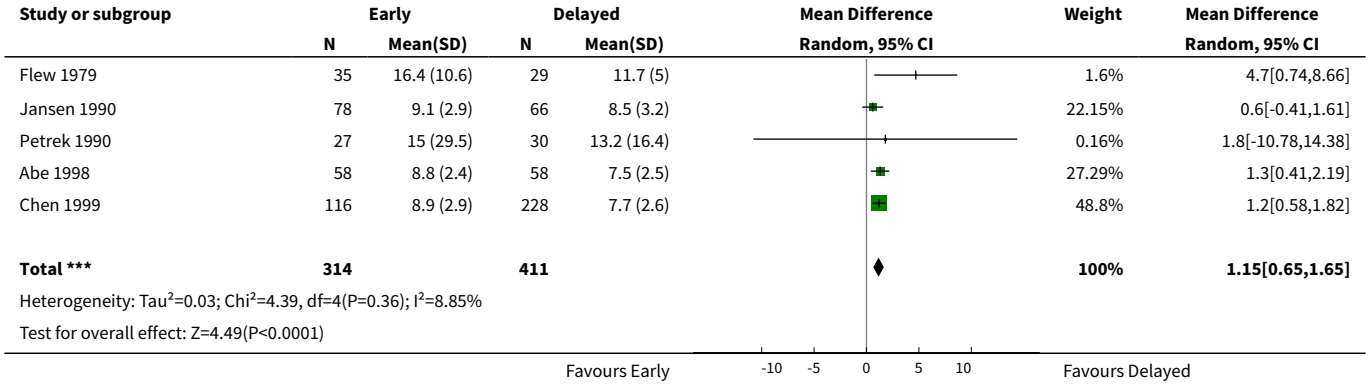
Analysis 1.8. Comparison 1 Post-operative: Early versus Delayed Exercise, Outcome 8 Wound Drainage Volume: Studies 1995 and later.

Study or subgroup	Early N	Early Mean(SD)	Delayed N	Delayed Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Le Vu 1997	65	436 (259)	63	389 (227)		30.89%	0.19[-0.16,0.54]

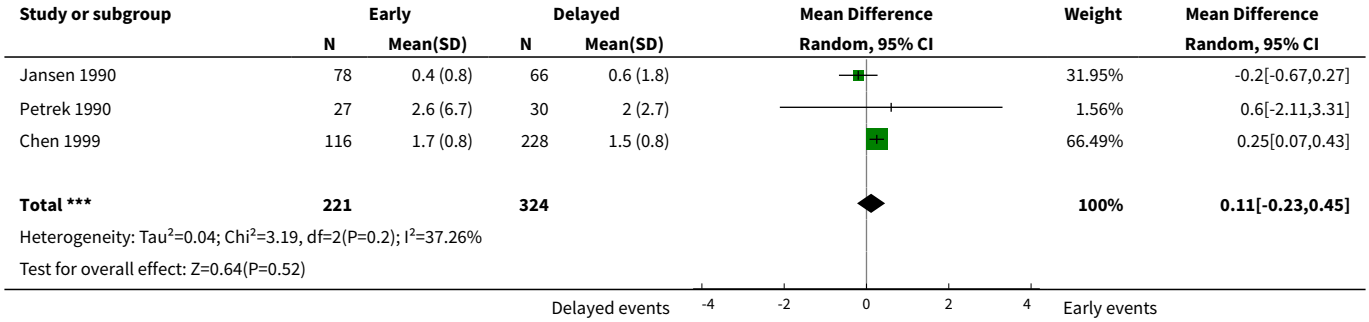




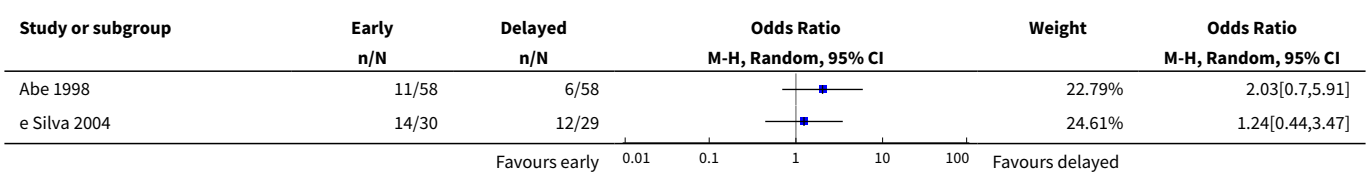
Analysis 1.9. Comparison 1 Post-operative: Early versus Delayed Exercise, Outcome 9 Duration of Drainage in days.

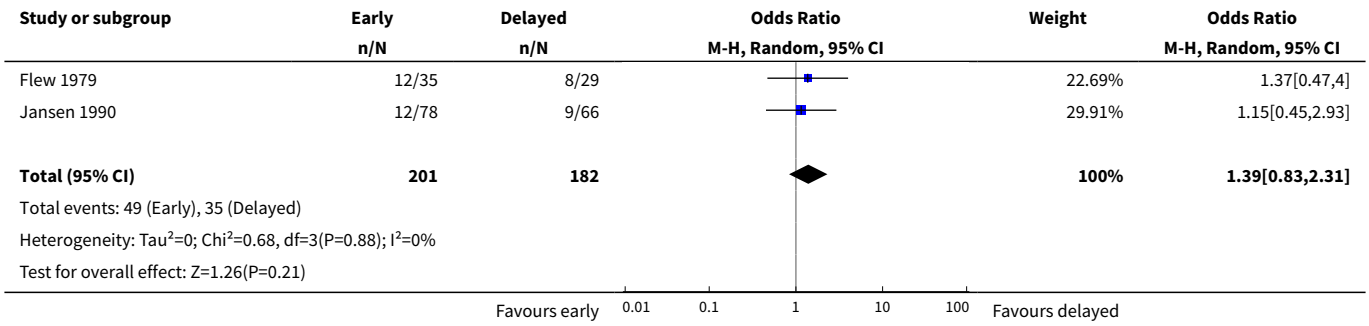


Analysis 1.10. Comparison 1 Post-operative: Early versus Delayed Exercise, Outcome 10 Mean number of Aspirations.

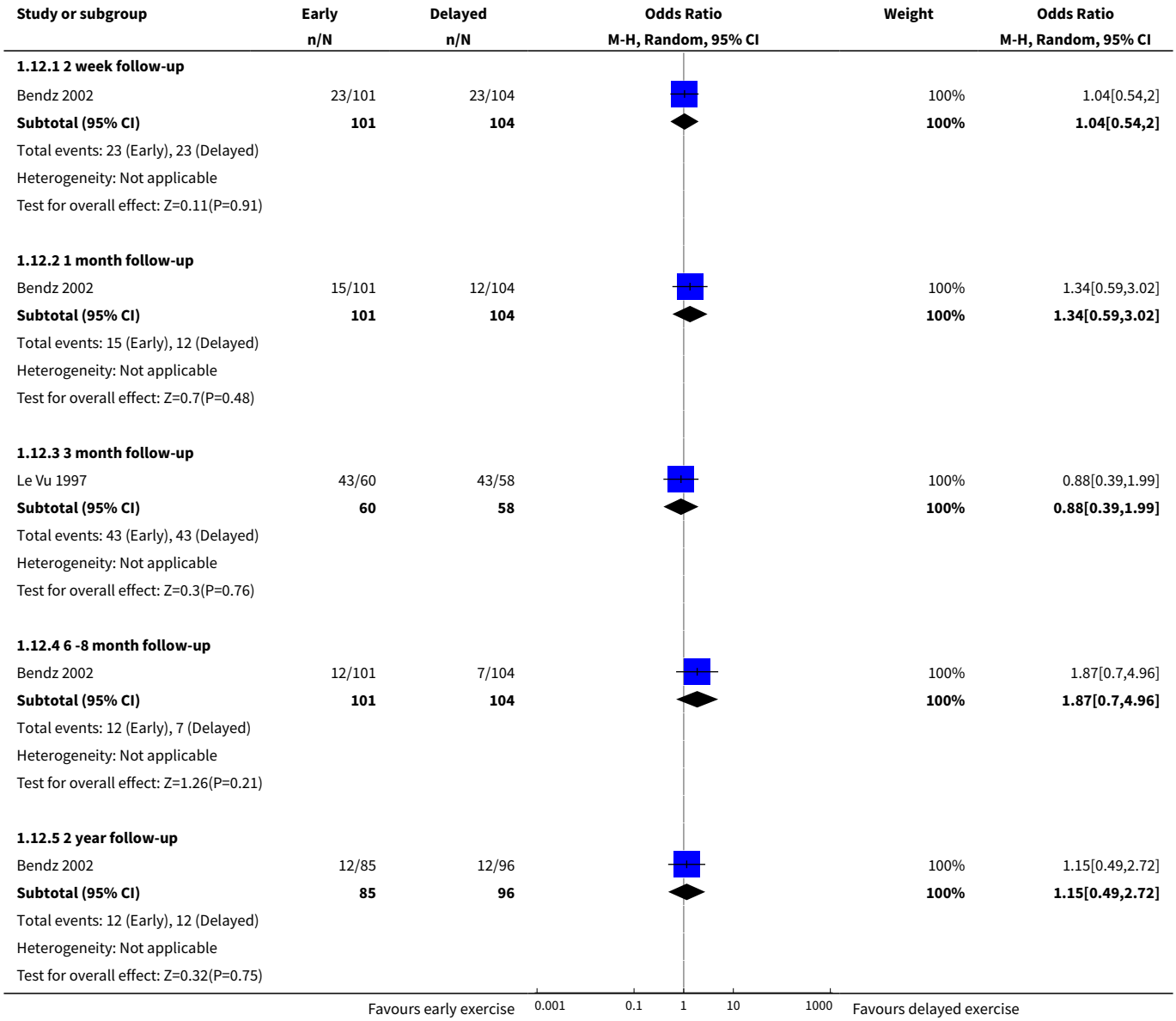


Analysis 1.11. Comparison 1 Post-operative: Early versus Delayed Exercise, Outcome 11 Delayed Wound Healing.

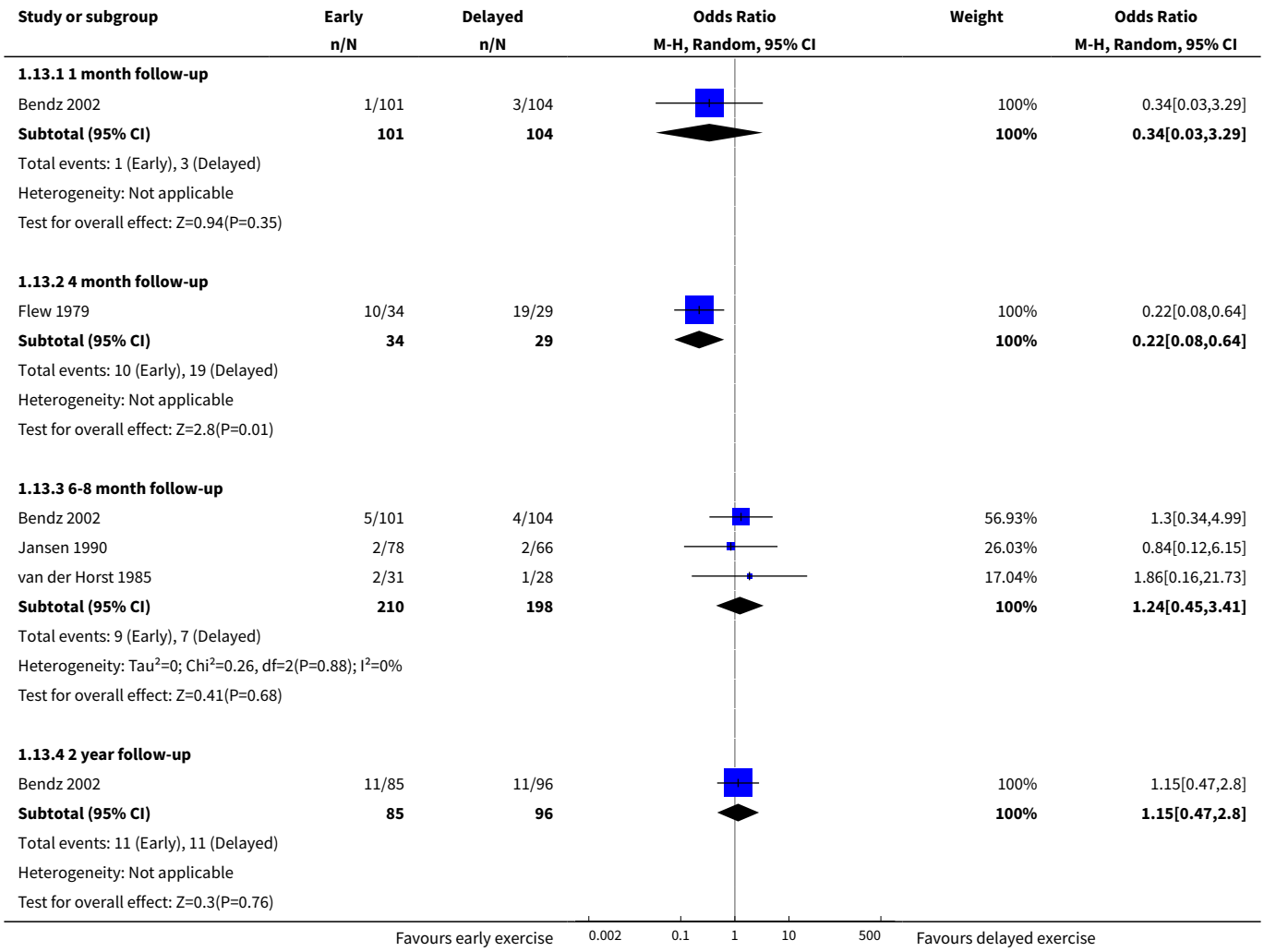




Analysis 1.12. Comparison 1 Post-operative: Early versus Delayed Exercise, Outcome 12 Pain.



Analysis 1.13. Comparison 1 Post-operative: Early versus Delayed Exercise, Outcome 13 Incidence of Lymphedema.



Comparison 2. Post-operative: Exercise versus Comparison/ control

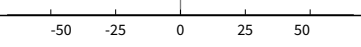
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Shoulder Flexion ROM in degrees	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Shoulder Flexion within first 2 weeks	5	324	Mean Difference (IV, Random, 95% CI)	12.92 [0.69, 25.16]
1.2 Shoulder Flexion at 1 month	3	182	Mean Difference (IV, Random, 95% CI)	15.48 [-8.25, 39.21]
1.3 Shoulder Flexion at 3 months	4	267	Mean Difference (IV, Random, 95% CI)	16.33 [8.16, 24.50]
1.4 Shoulder Flexion at 6 months	3	149	Mean Difference (IV, Random, 95% CI)	11.86 [4.25, 19.46]

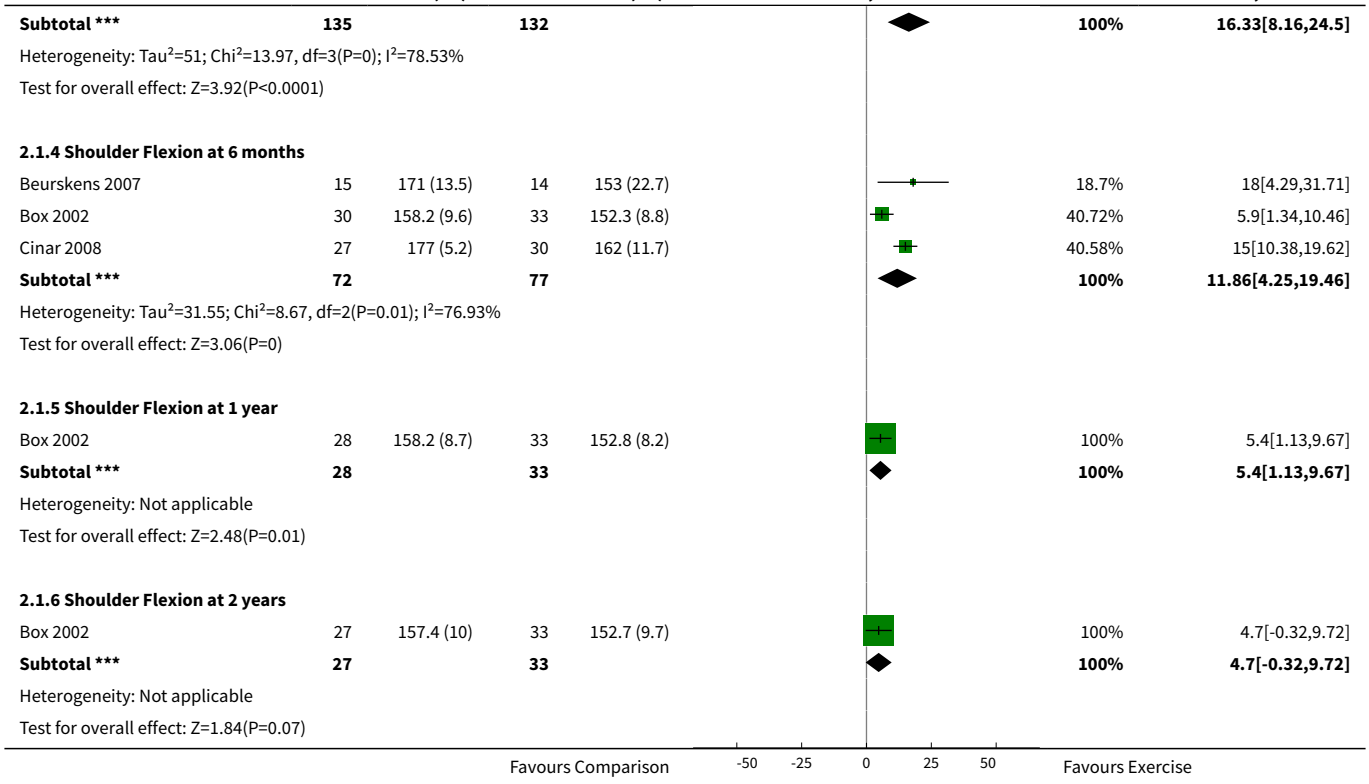
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.5 Shoulder Flexion at 1 year	1	61	Mean Difference (IV, Random, 95% CI)	5.40 [1.13, 9.67]
1.6 Shoulder Flexion at 2 years	1	60	Mean Difference (IV, Random, 95% CI)	4.70 [-0.32, 9.72]
2 Shoulder Flexion: Physical Therapy subgroup	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Post Intervention	3	202	Mean Difference (IV, Random, 95% CI)	19.35 [14.08, 24.63]
2.2 Follow-up: 6 months	2	86	Mean Difference (IV, Random, 95% CI)	15.31 [10.93, 19.68]
3 Shoulder Abduction ROM in degrees	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 Shoulder Abduction within first 2 weeks	4	267	Mean Difference (IV, Random, 95% CI)	9.72 [-8.62, 28.06]
3.2 Shoulder Abduction at 1 Month	3	182	Mean Difference (IV, Random, 95% CI)	22.05 [0.97, 43.13]
3.3 Shoulder Abduction at 3 months	4	267	Mean Difference (IV, Random, 95% CI)	21.42 [12.33, 30.52]
3.4 Shoulder Abduction at 6 Months	3	151	Mean Difference (IV, Random, 95% CI)	16.80 [4.27, 29.33]
3.5 Shoulder Abduction at 1 Year	1	61	Mean Difference (IV, Random, 95% CI)	7.0 [1.30, 12.70]
3.6 Shoulder Abduction at 2 Years	1	60	Mean Difference (IV, Random, 95% CI)	7.0 [-0.82, 14.82]
4 Incidence of Seroma	1	57	Odds Ratio (M-H, Random, 95% CI)	1.18 [0.40, 3.50]
5 Shoulder Function	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 Dysfunction Score Post Intervention	2	87	Std. Mean Difference (IV, Random, 95% CI)	0.77 [0.33, 1.21]
5.2 Dysfunction Score at 6 months	2	86	Std. Mean Difference (IV, Random, 95% CI)	0.75 [0.32, 1.19]
6 Shoulder Abduction: Physical Therapy subgroup	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 Post Intervention	3	202	Mean Difference (IV, Random, 95% CI)	24.88 [14.46, 35.30]
6.2 Follow up: 6 months	2	86	Mean Difference (IV, Random, 95% CI)	22.62 [15.05, 30.19]
7 Wound Drainage Volume	2	87	Std. Mean Difference (IV, Random, 95% CI)	-0.03 [-0.45, 0.40]
8 Pain	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
8.1 VAS post intervention	1	30	Std. Mean Difference (IV, Random, 95% CI)	-1.65 [-2.50, -0.81]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
8.2 VAS at 6 months	1	29	Std. Mean Difference (IV, Random, 95% CI)	-1.51 [-2.35, -0.67]
9 Incidence of Lymphedema	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 1 Month	1	65	Odds Ratio (M-H, Random, 95% CI)	1.03 [0.06, 17.24]
9.2 3 Months	1	65	Odds Ratio (M-H, Random, 95% CI)	0.32 [0.08, 1.35]
9.3 6 Months	1	65	Odds Ratio (M-H, Random, 95% CI)	0.18 [0.02, 1.64]
9.4 1 Year	1	65	Odds Ratio (M-H, Random, 95% CI)	0.48 [0.08, 2.84]
9.5 2 Years	1	65	Odds Ratio (M-H, Random, 95% CI)	0.28 [0.07, 1.13]
10 Arm Volume in mL	1	30	Mean Difference (IV, Random, 95% CI)	-2.0 [-40.12, 36.12]
10.1 Arm volume post-intervention (3 months)	1	30	Mean Difference (IV, Random, 95% CI)	-2.0 [-40.12, 36.12]

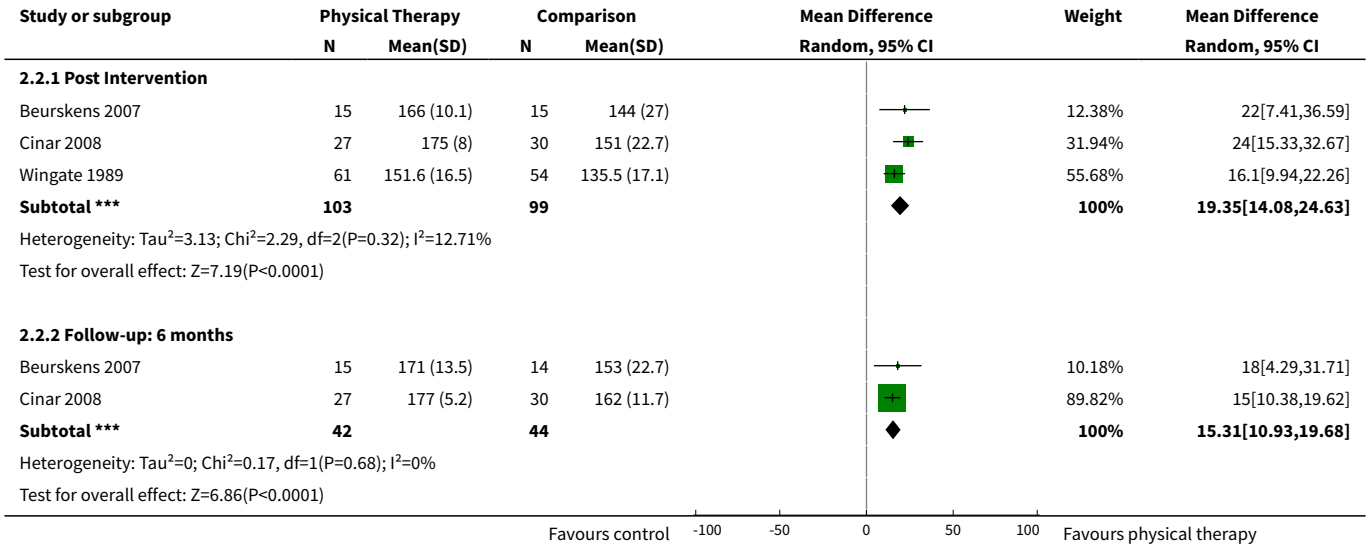
Analysis 2.1. Comparison 2 Post-operative: Exercise versus Comparison/ control, Outcome 1 Shoulder Flexion ROM in degrees.

Study or subgroup	Exercise N	Exercise Mean(SD)	Comparison N	Comparison Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.1.1 Shoulder Flexion within first 2 weeks							
Box 2002	32	114.4 (24.9)	33	117.1 (22.1)		21.74%	-2.74[-14.2,8.72]
Cinar 2008	27	133 (29)	30	107 (24.7)		19.82%	26[11.94,40.06]
de Rezende 2006	30	123.5 (28.5)	30	117.6 (23.5)		20.45%	5.9[-7.32,19.12]
Kilgour 2008	16	126.5 (28)	11	116.6 (27.9)		14.72%	9.9[-11.53,31.33]
Wingate 1989	61	129.4 (26.6)	54	104.9 (24.1)		23.27%	24.5[15.23,33.77]
Subtotal * **	**166**		**158**			**100%**	**12.92[0.69,25.16]**
Heterogeneity: Tau^2=145.01; Chi^2=17.51, df=4(P=0); I^2=77.15%							
Test for overall effect: Z=2.07(P=0.04)							
2.1.2 Shoulder Flexion at 1 month							
Box 2002	32	140.5 (26.8)	33	142.8 (23.7)		32.25%	-2.35[-14.66,9.96]
Cinar 2008	27	171 (13)	30	135 (8)		34.62%	36[30.32,41.68]
de Rezende 2006	30	143.5 (21.1)	30	132.1 (19.4)		33.13%	11.4[1.14,21.66]
Subtotal * **	**89**		**93**			**100%**	**15.48[-8.25,39.21]**
Heterogeneity: Tau^2=415.14; Chi^2=40.06, df=2(P<0.0001); I^2=95.01%							
Test for overall effect: Z=1.28(P=0.2)							
2.1.3 Shoulder Flexion at 3 months							
Beurskens 2007	15	166 (10.1)	15	144 (27)		16.34%	22[7.41,36.59]
Box 2002	32	159 (10.5)	33	151.7 (9.3)		30.47%	7.3[2.48,12.12]
Cinar 2008	27	175 (8)	30	151 (22.7)		24.64%	24[15.33,32.67]
Wingate 1989	61	151.6 (16.5)	54	135.5 (17.1)		28.55%	16.1[9.94,22.26]



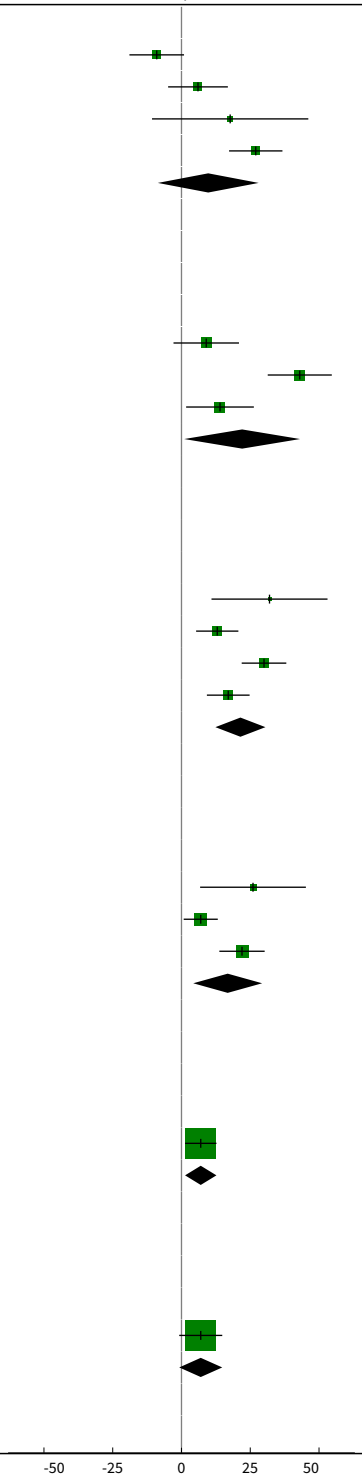


Analysis 2.2. Comparison 2 Post-operative: Exercise versus Comparison/ control, Outcome 2 Shoulder Flexion: Physical Therapy subgroup.

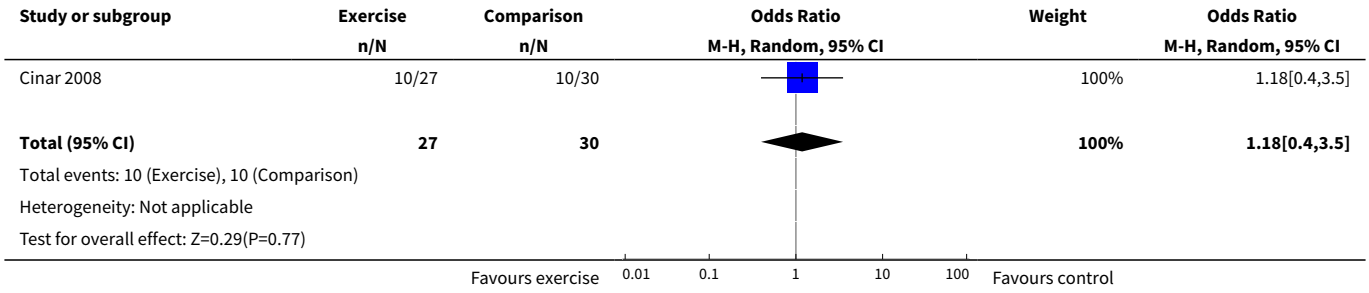


Analysis 2.3. Comparison 2 Post-operative: Exercise versus Comparison/ control, Outcome 3 Shoulder Abduction ROM in degrees.

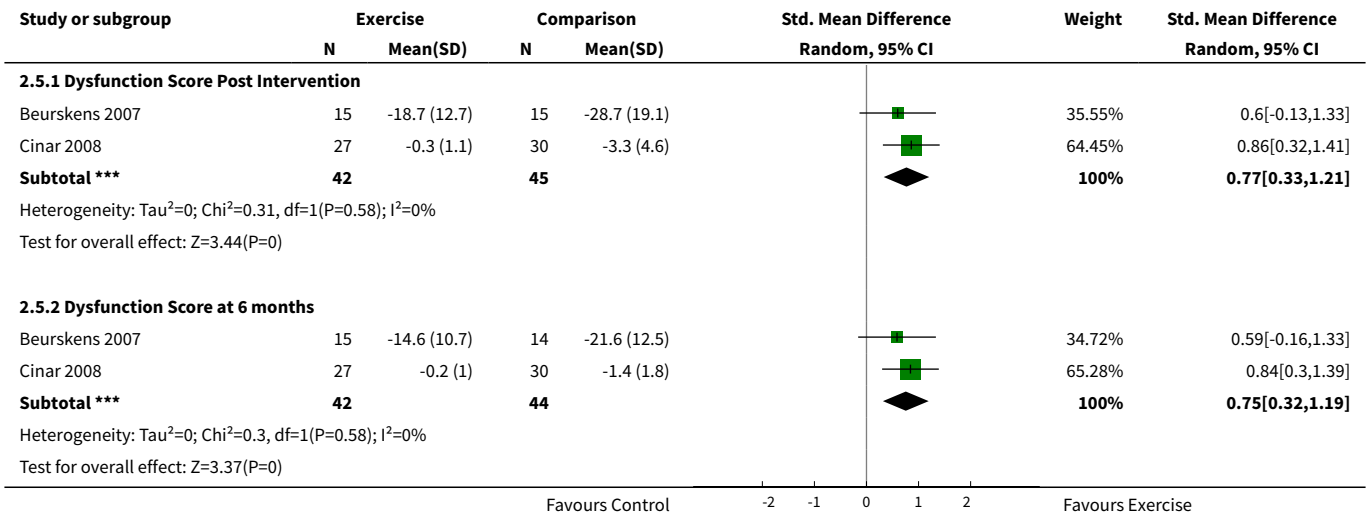
Study or subgroup	Exercise N	Exercise Mean(SD)	Comparison N	Comparison Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.3.1 Shoulder Abduction within first 2 weeks							
Box 2002	32	80 (21.6)	33	89 (19.1)		27.62%	-9[-18.92,0.92]
de Rezende 2006	30	101 (21)	30	95 (21.9)		27.19%	6[-4.86,16.86]
Kilgour 2008	16	134.5 (36.8)	11	116.8 (37.2)		17.46%	17.7[-10.71,46.11]
Wingate 1989	61	129 (29.5)	54	102 (23.5)		27.72%	27[17.3,36.7]
Subtotal ***	**139**		**128**			**100%**	**9.72[-8.62,28.06]**
Heterogeneity: Tau^2=291.34; Chi^2=26.52, df=3(P<0.0001); I^2=88.69%							
Test for overall effect: Z=1.04(P=0.3)							
2.3.2 Shoulder Abduction at 1 Month							
Box 2002	32	129 (25.9)	33	120 (22.9)		33.37%	9[-2.9,20.9]
Cinar 2008	27	166 (18.7)	30	123 (25.9)		33.51%	43[31.35,54.65]
de Rezende 2006	30	122 (25.3)	30	108 (23.3)		33.12%	14[1.69,26.31]
Subtotal ***	**89**		**93**			**100%**	**22.05[0.97,43.13]**
Heterogeneity: Tau^2=309.89; Chi^2=18.68, df=2(P<0.0001); I^2=89.29%							
Test for overall effect: Z=2.05(P=0.04)							
2.3.3 Shoulder Abduction at 3 months							
Beurskens 2007	15	167 (15.2)	15	135 (38.8)		12.42%	32[10.91,53.09]
Box 2002	32	157 (16.7)	33	144 (14.8)		29.47%	13[5.32,20.68]
Cinar 2008	27	174 (9.8)	30	144 (20.2)		28.78%	30[21.89,38.11]
Wingate 1989	61	155 (19.1)	54	138 (22.9)		29.34%	17[9.24,24.76]
Subtotal ***	**135**		**132**			**100%**	**21.42[12.33,30.52]**
Heterogeneity: Tau^2=57.77; Chi^2=10.84, df=3(P=0.01); I^2=72.33%							
Test for overall effect: Z=4.62(P<0.0001)							
2.3.4 Shoulder Abduction at 6 Months							
Beurskens 2007	15	170 (13.5)	14	144 (34.3)		21.84%	26[6.78,45.22]
Box 2002	32	155 (13.5)	33	148 (11.9)		40.51%	7[0.81,13.19]
Cinar 2008	27	176 (11.3)	30	154 (19.7)		37.65%	22[13.76,30.24]
Subtotal ***	**74**		**77**			**100%**	**16.8[4.27,29.33]**
Heterogeneity: Tau^2=90.87; Chi^2=9.94, df=2(P=0.01); I^2=79.87%							
Test for overall effect: Z=2.63(P=0.01)							
2.3.5 Shoulder Abduction at 1 Year							
Box 2002	28	155 (11.6)	33	148 (11)		100%	7[1.3,12.7]
Subtotal ***	**28**		**33**			**100%**	**7[1.3,12.7]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.4(P=0.02)							
2.3.6 Shoulder Abduction at 2 Years							
Box 2002	27	154 (15.6)	33	147 (15.1)		100%	7[-0.82,14.82]
Subtotal ***	**27**		**33**			**100%**	**7[-0.82,14.82]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.75(P=0.08)							



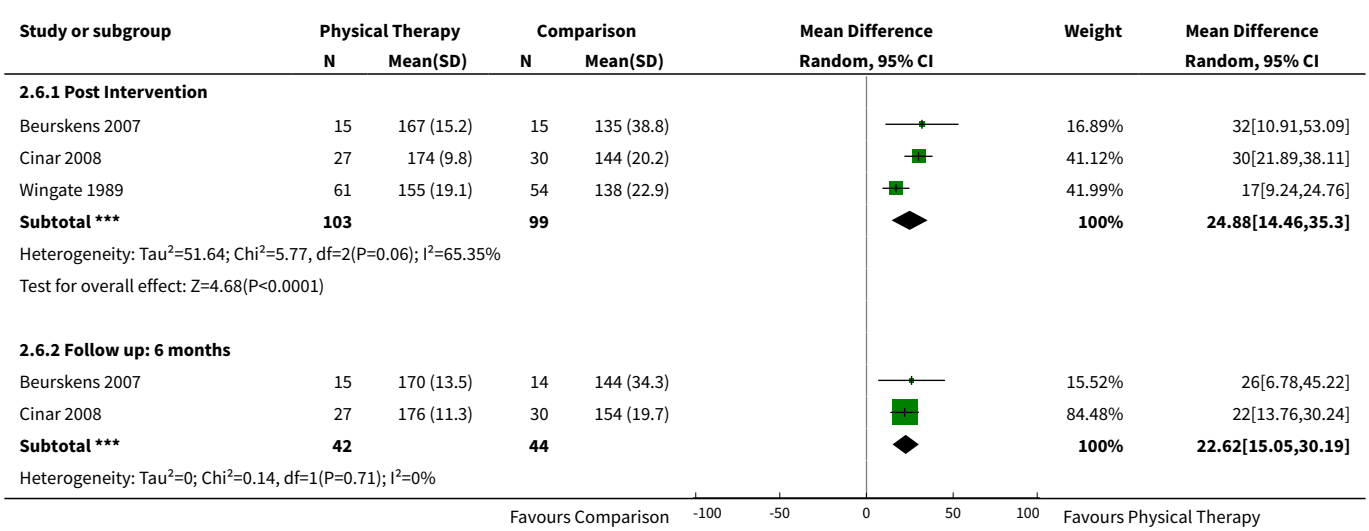
Analysis 2.4. Comparison 2 Post-operative: Exercise versus Comparison/ control, Outcome 4 Incidence of Seroma.

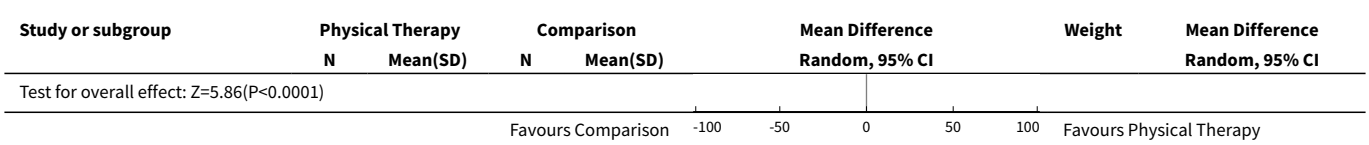


Analysis 2.5. Comparison 2 Post-operative: Exercise versus Comparison/ control, Outcome 5 Shoulder Function.

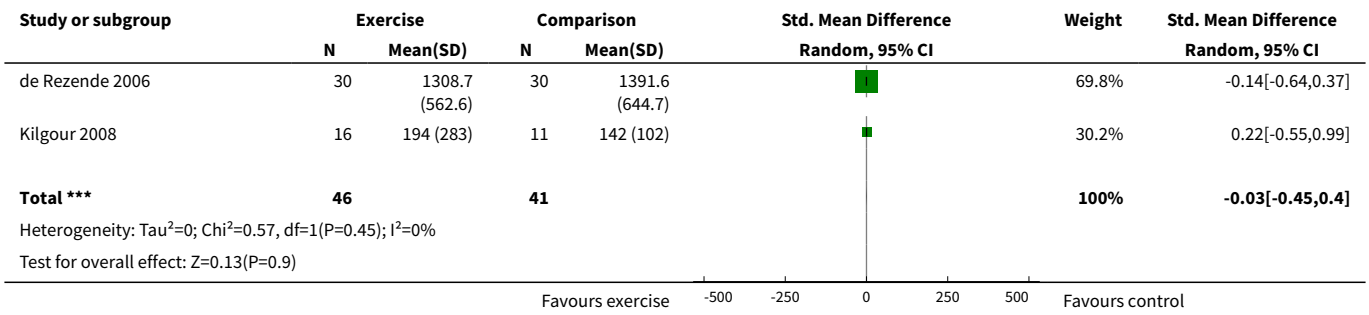


Analysis 2.6. Comparison 2 Post-operative: Exercise versus Comparison/ control, Outcome 6 Shoulder Abduction: Physical Therapy subgroup.

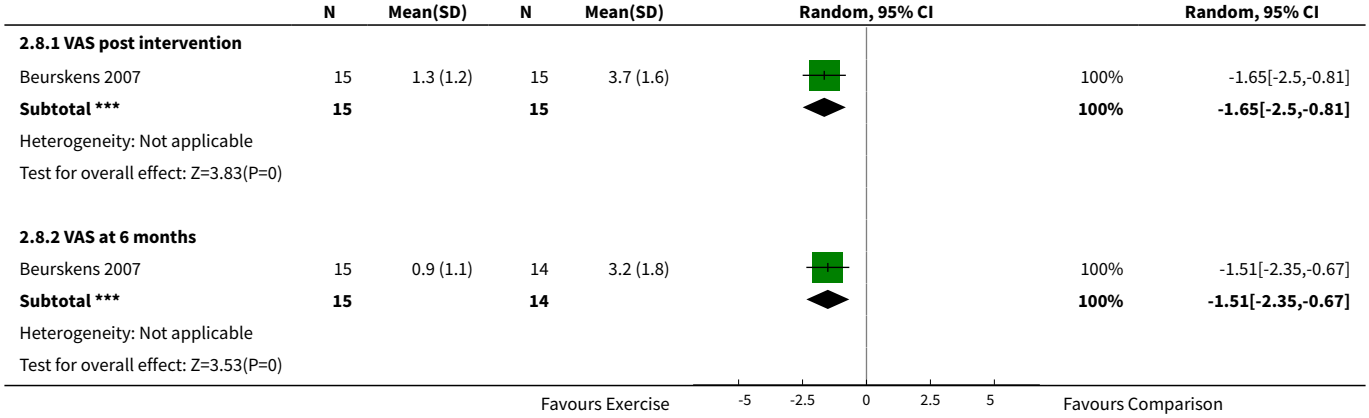




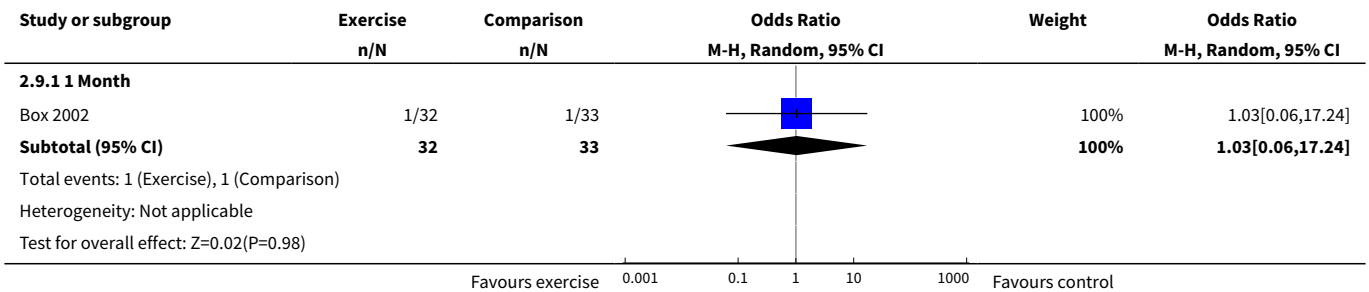
Analysis 2.7. Comparison 2 Post-operative: Exercise versus Comparison/ control, Outcome 7 Wound Drainage Volume.

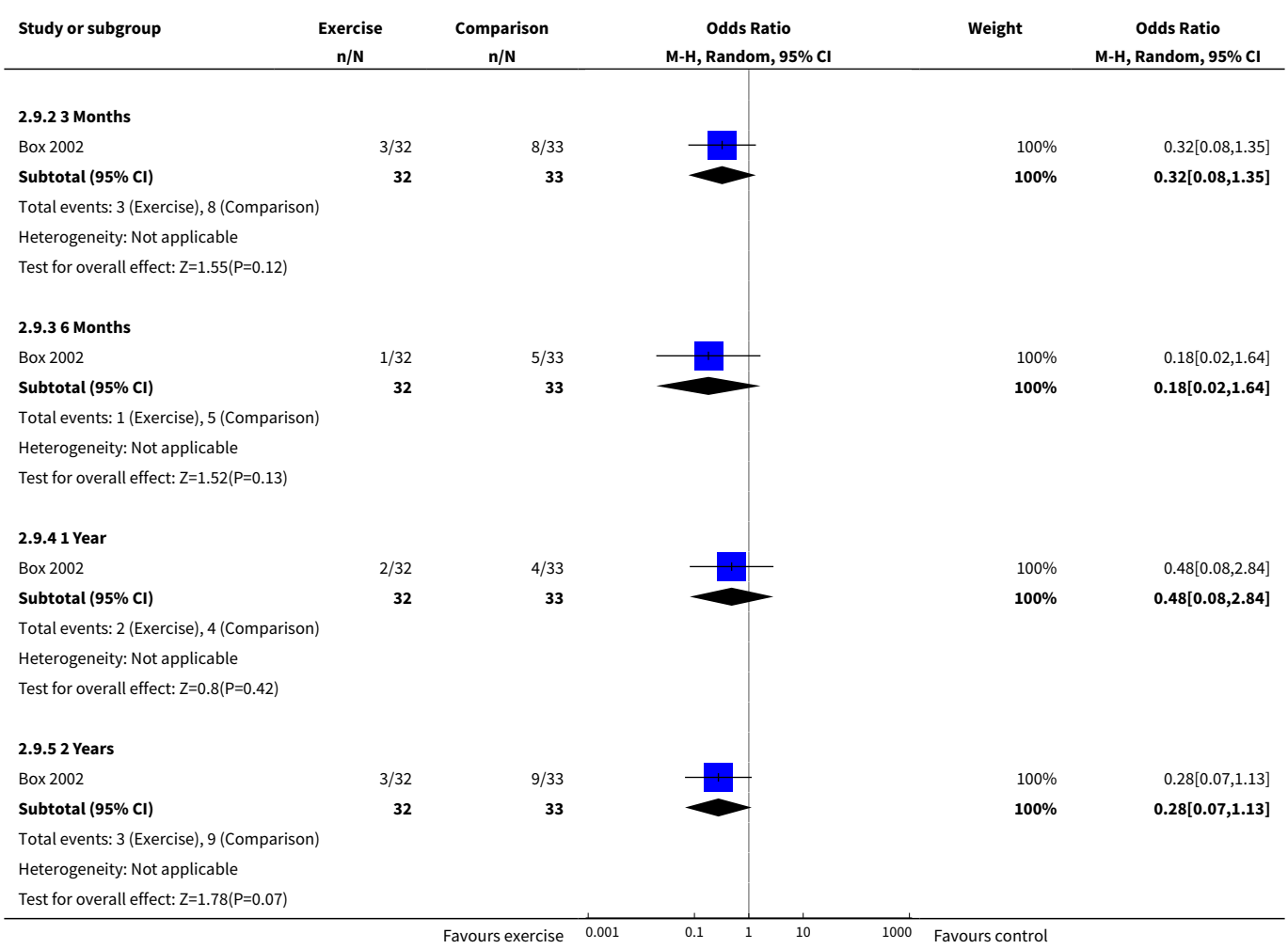


Analysis 2.8. Comparison 2 Post-operative: Exercise versus Comparison/ control, Outcome 8 Pain.

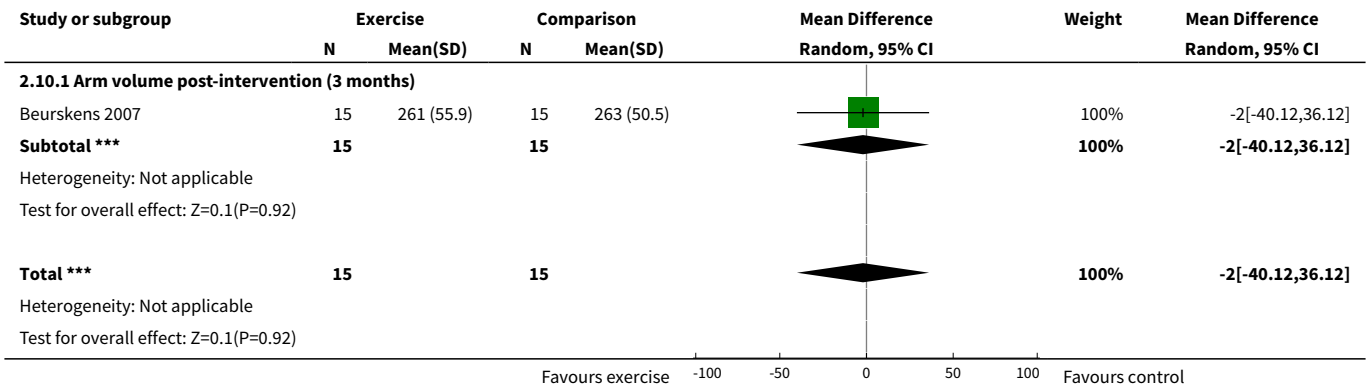


Analysis 2.9. Comparison 2 Post-operative: Exercise versus Comparison/ control, Outcome 9 Incidence of Lymphedema.





Analysis 2.10. Comparison 2 Post-operative: Exercise versus Comparison/ control, Outcome 10 Arm Volume in mL.

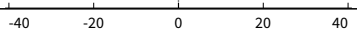


Comparison 3. During Adjuvant Treatment: Exercise versus Comparison/ control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Shoulder Flexion ROM Post Intervention	2	98	Mean Difference (IV, Random, 95% CI)	7.25 [-3.52, 18.02]
2 Shoulder Abduction ROM Post Intervention	1	37	Mean Difference (IV, Random, 95% CI)	11.0 [2.38, 19.62]
3 Upper-Extremity Strength Post Intervention	1	164	Mean Difference (IV, Random, 95% CI)	7.30 [4.42, 10.18]
3.1 One Repetition Maximum Testing	1	164	Mean Difference (IV, Random, 95% CI)	7.30 [4.42, 10.18]
4 Pain VAS	1	37	Mean Difference (IV, Random, 95% CI)	-5.40 [-19.16, 8.36]
5 Quality of Life Post Intervention	3	262	Std. Mean Difference (IV, Random, 95% CI)	0.14 [-0.10, 0.38]
6 Incidence of Lymphedema	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Incidence Post Intervention	1	164	Odds Ratio (M-H, Random, 95% CI)	0.48 [0.12, 1.99]
6.2 Lymphedema Incidence at 7-month follow-up	1	50	Odds Ratio (M-H, Random, 95% CI)	0.24 [0.02, 2.31]

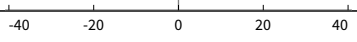
Analysis 3.1. Comparison 3 During Adjuvant Treatment: Exercise versus Comparison/ control, Outcome 1 Shoulder Flexion ROM Post Intervention.

Study or subgroup	Exercise N	Exercise Mean(SD)	Comparison N	Comparison Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Hwang 2008	17	174 (7.6)	20	161 (12.8)		47.7%	13[6.33,19.67]
Lee 2007	31	165 (8.8)	30	163 (10.3)		52.3%	2[-2.81,6.81]
Total ***	**48**		**50**			**100%**	**7.25[-3.52,18.02]**
Heterogeneity: Tau²=51.69; Chi²=6.87, df=1(P=0.01); I²=85.43%							
Test for overall effect: Z=1.32(P=0.19)							

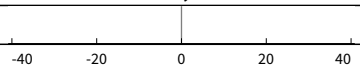


Analysis 3.2. Comparison 3 During Adjuvant Treatment: Exercise versus Comparison/ control, Outcome 2 Shoulder Abduction ROM Post Intervention.

Study or subgroup	Exercise N	Exercise Mean(SD)	Comparison N	Comparison Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Hwang 2008	17	169 (7.9)	20	158 (17.7)		100%	11[2.38,19.62]
Total ***	**17**		**20**			**100%**	**11[2.38,19.62]**
Heterogeneity: Not applicable							



Study or subgroup	Exercise N	Exercise Mean(SD)	Comparison N	Comparison Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Test for overall effect: Z=2.5(P=0.01)							

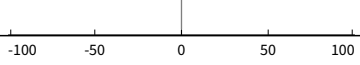


Analysis 3.3. Comparison 3 During Adjuvant Treatment: Exercise versus Comparison/ control, Outocme 3 Upper-Extremity Strength Post Intervention.

Study or subgroup	Exercise N	Exercise Mean(SD)	Comparison N	Comparison Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
3.3.1 One Repetition Maximum Testing							
Courneya 2007	82	31.9 (10.8)	82	24.6 (7.8)		100%	7.3[4.42,10.18]
Subtotal ***	**82**		**82**			**100%**	**7.3[4.42,10.18]**
Heterogeneity: Not applicable							
Test for overall effect: Z=4.96(P<0.0001)							
Total ***	**82**		**82**			**100%**	**7.3[4.42,10.18]**
Heterogeneity: Not applicable							
Test for overall effect: Z=4.96(P<0.0001)							

Analysis 3.4. Comparison 3 During Adjuvant Treatment: Exercise versus Comparison/ control, Outocme 4 Pain VAS.

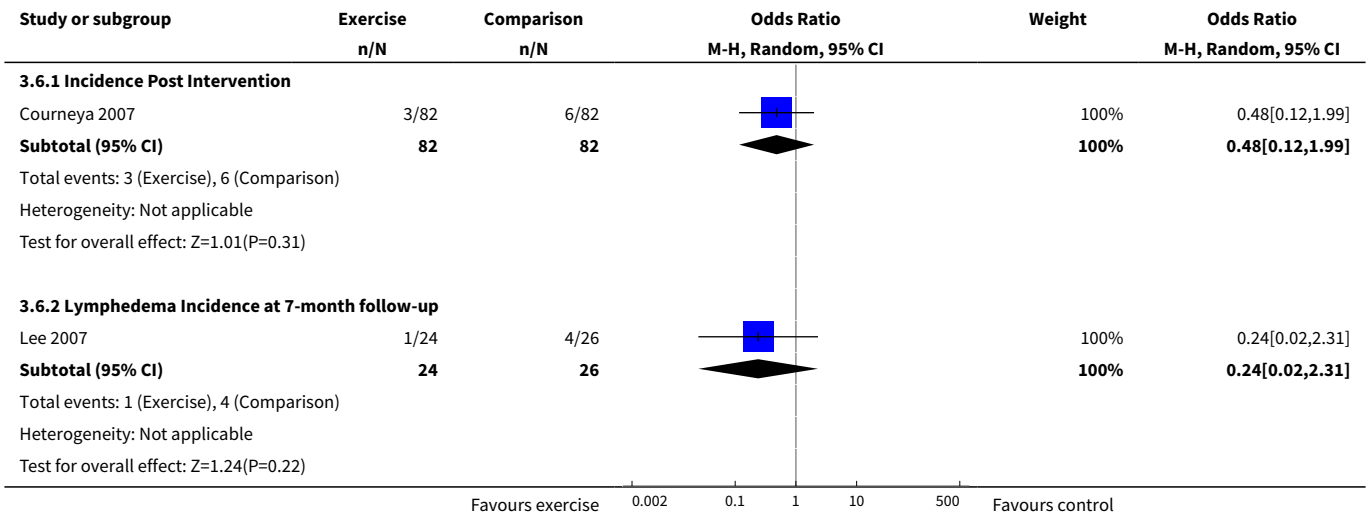
Study or subgroup	Exercise N	Exercise Mean(SD)	Comparison N	Comparison Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Hwang 2008	17	24.4 (21.6)	20	29.8 (20.9)		100%	-5.4[-19.16,8.36]
Total ***	**17**		**20**			**100%**	**-5.4[-19.16,8.36]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.77(P=0.44)							



Analysis 3.5. Comparison 3 During Adjuvant Treatment: Exercise versus Comparison/ control, Outocme 5 Quality of Life Post Intervention.

Study or subgroup	Exercise N	Exercise Mean(SD)	Comparison N	Comparison Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Courneya 2007	82	140.9 (24.8)	82	139.9 (28.2)		62.97%	0.04[-0.27,0.34]
Hwang 2008	17	3.2 (0.4)	20	3 (0.5)		13.83%	0.38[-0.27,1.04]
Lee 2007	31	73.9 (17.7)	30	68.6 (21.4)		23.2%	0.27[-0.24,0.77]
Total ***	**130**		**132**			**100%**	**0.14[-0.1,0.38]**
Heterogeneity: Tau^2=0; Chi^2=1.2, df=2(P=0.55); I^2=0%							
Test for overall effect: Z=1.11(P=0.27)							

Analysis 3.6. Comparison 3 During Adjuvant Treatment: Exercise versus Comparison/ control, Outcome 6 Incidence of Lymphedema.

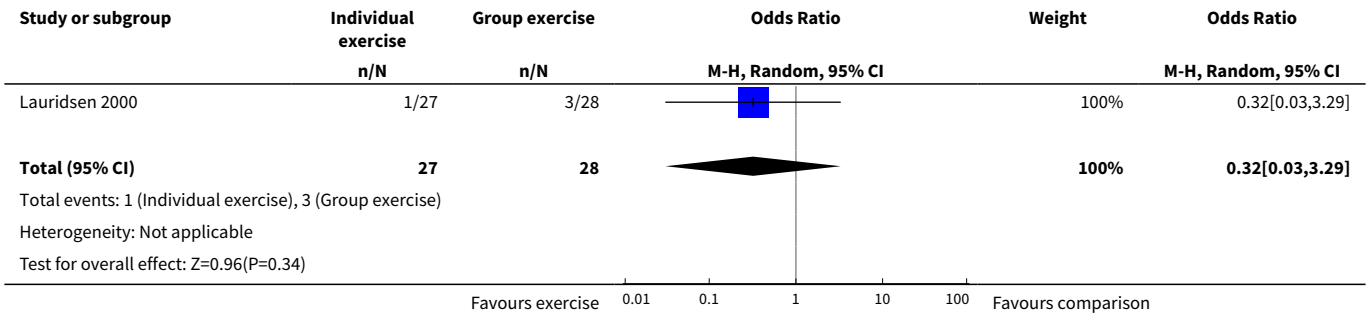


Comparison 4. Post Cancer Treatment: Exercise versus Comparison/ control

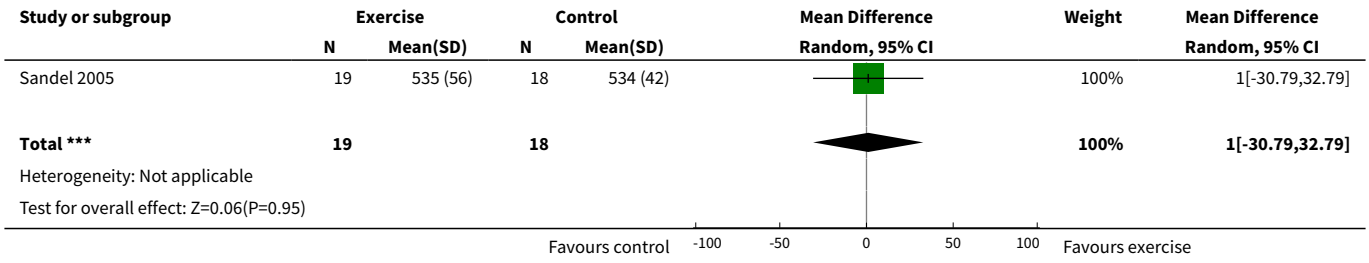
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of Shoulder Movement Restriction	1	55	Odds Ratio (M-H, Random, 95% CI)	0.32 [0.03, 3.29]
2 Shoulder ROM: Sum of Directions Post Intervention	1	37	Mean Difference (IV, Random, 95% CI)	1.0 [-30.79, 32.79]
3 Shoulder Flexion ROM Post Intervention	2	76	Mean Difference (IV, Random, 95% CI)	3.14 [-5.27, 11.55]
4 Shoulder Abduction ROM Post Intervention	2	76	Mean Difference (IV, Random, 95% CI)	8.86 [-1.86, 19.59]
5 Upper-Extremity Strength	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 Resistance Exercise Program	1	46	Std. Mean Difference (IV, Random, 95% CI)	1.49 [0.83, 2.15]
5.2 Tai Chi Chuan	1	21	Std. Mean Difference (IV, Random, 95% CI)	-0.08 [-0.93, 0.78]
6 Incidence of Upper-Extremity Strength Impairment	1	55	Odds Ratio (M-H, Random, 95% CI)	1.04 [0.06, 17.49]
7 Quality of Life Post Intervention	3	173	Std. Mean Difference (IV, Random, 95% CI)	0.47 [0.16, 0.77]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
8 Incidence of Lymphedema	1	46	Odds Ratio (M-H, Random, 95% CI)	0.32 [0.01, 8.25]
9 Arm Circumference	1	37	Std. Mean Difference (IV, Random, 95% CI)	-0.08 [-0.73, 0.56]

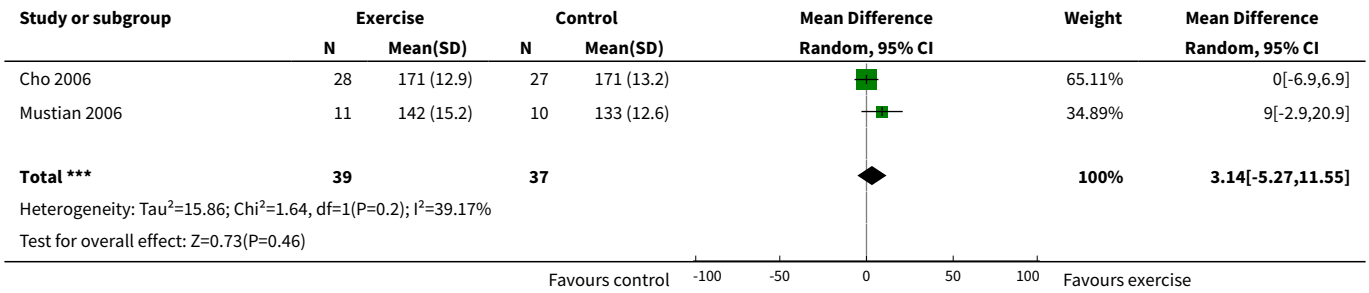
Analysis 4.1. Comparison 4 Post Cancer Treatment: Exercise versus Comparison/ control, Outcome 1 Incidence of Shoulder Movement Restriction.



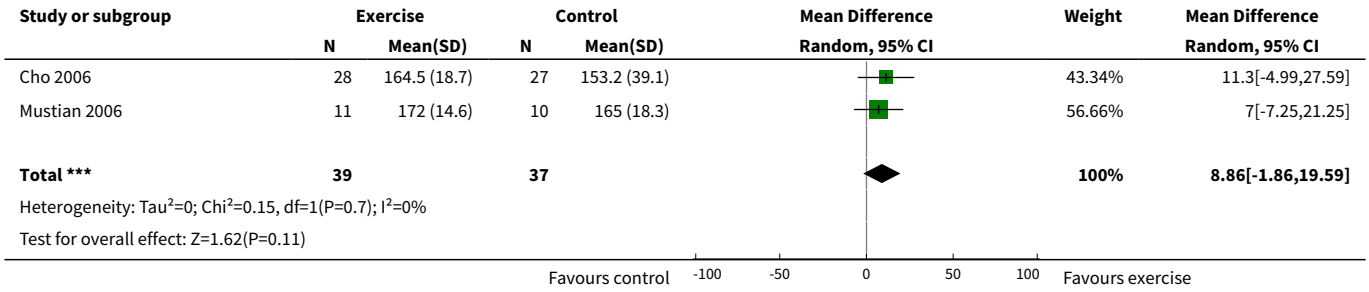
Analysis 4.2. Comparison 4 Post Cancer Treatment: Exercise versus Comparison/ control, Outcome 2 Shoulder ROM: Sum of Directions Post Intervention.



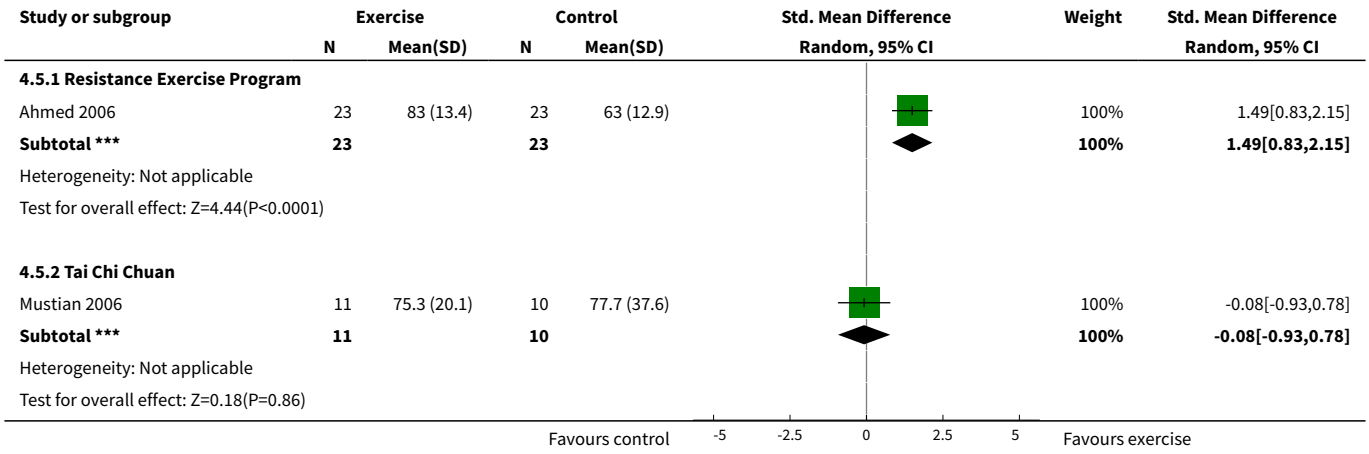
Analysis 4.3. Comparison 4 Post Cancer Treatment: Exercise versus Comparison/ control, Outcome 3 Shoulder Flexion ROM Post Intervention.



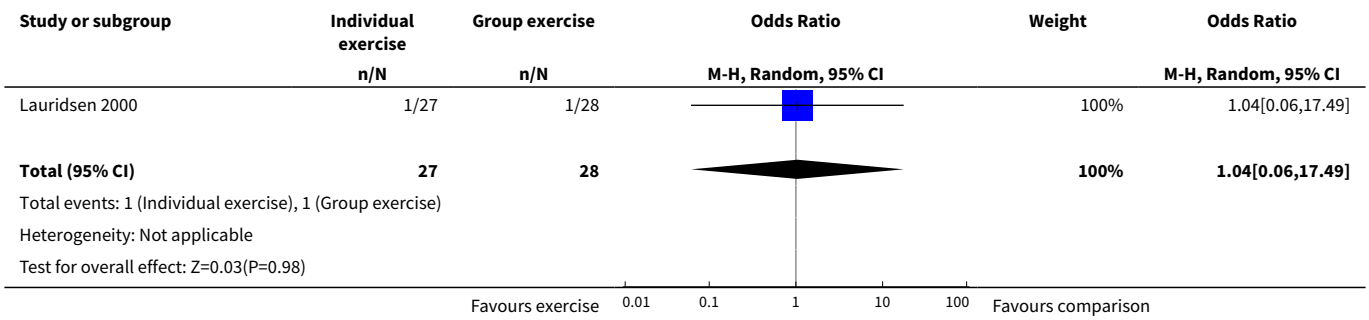
Analysis 4.4. Comparison 4 Post Cancer Treatment: Exercise versus Comparison/ control, Outcome 4 Shoulder Abduction ROM Post Intervention.



Analysis 4.5. Comparison 4 Post Cancer Treatment: Exercise versus Comparison/ control, Outcome 5 Upper-Extremity Strength.

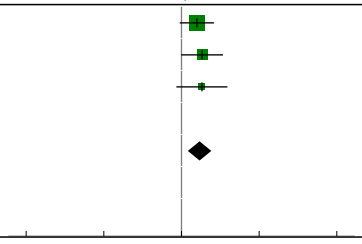


Analysis 4.6. Comparison 4 Post Cancer Treatment: Exercise versus Comparison/ control, Outcome 6 Incidence of Upper-Extremity Strength Impairment.



Analysis 4.7. Comparison 4 Post Cancer Treatment: Exercise versus Comparison/ control, Outcome 7 Quality of Life Post Intervention.

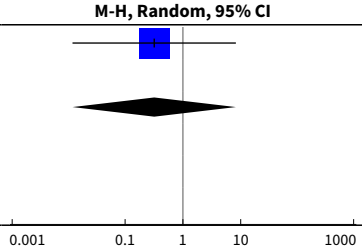
Study or subgroup	Exercise N	Exercise Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Ahmed 2006	40	2.3 (4.5)	41	0.6 (4)		47.26%	0.4[-0.04,0.84]
Cho 2006	28	7 (1.3)	27	6.3 (1.3)		31.55%	0.53[-0.01,1.07]
Sandel 2005	19	116.7 (16.9)	18	106.1 (22.3)		21.2%	0.53[-0.13,1.18]
Total ***	**87**		**86**			**100%**	**0.47[0.16,0.77]**
Heterogeneity: Tau^2=0; Chi^2=0.19, df=2(P=0.91); I^2=0%							
Test for overall effect: Z=3.02(P=0)							



Favours control — Favours exercise

Analysis 4.8. Comparison 4 Post Cancer Treatment: Exercise versus Comparison/ control, Outcome 8 Incidence of Lymphedema.

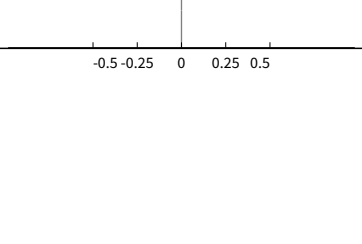
Study or subgroup	Exercise n/N	Control n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Ahmed 2006	0/23	1/23		100%	0.32[0.01,8.25]
Total (95% CI)	**23**	**23**		**100%**	**0.32[0.01,8.25]**
Total events: 0 (Exercise), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.69(P=0.49)					



Favours exercise — Favours control

Analysis 4.9. Comparison 4 Post Cancer Treatment: Exercise versus Comparison/ control, Outcome 9 Arm Circumference.

Study or subgroup	Exercise N	Exercise Mean(SD)	Comparison N	Comparison Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Sandel 2005	19	0 (9.7)	18	0.8 (9)		100%	-0.08[-0.73,0.56]
Total ***	**19**		**18**			**100%**	**-0.08[-0.73,0.56]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.25(P=0.8)							



Favours exercise — Favours Usual Care

APPENDICES

Appendix 1. MEDLINE search strategy

1. exp Breast Neoplasms/
2. (breast cancer$ or breast tumor$ or breast tumour$ or breast neoplasm$ or axillary dissection).tw.
3. (breast carcinoma$ or breast adenocarcinoma$ or breast sarcoma$).mp
4. exp mastectomy/
5. *Lymph node excision/
6. (axill$ adj3 lymph node dissection).mp

7. (sentinel node dissection).mp
8. or/1-7
9. exp ARM/
10. exp SHOULDER JOINT/ or exp SHOULDER/ or exp SHOULDER PAIN/
11. *Pain/
12. Limit 11 to yr=1966-1998
13. (arm$ or shoulder$ or upper limb$ or upper extremit$).tw.
14. adhesive capsulitis.mp.
15. axillary web syndrome.mp.
16. cording.mp.
17. or/9-16
18. 8 and 17
19. exp REHABILITATION/
20. exp Physical Therapy Techniques/ or Physical Therapy Specialty/
21. exp EXERCISE/ or exp EXERCISE THERAPY/ or exp EXERCISE MOVEMENT TECHNIQUES/
22. *Exertion/
23. Limit 22 to yr=1966-1988
24. *Physical fitness/
25. Limit 24 to yr=1966-1988
26. Musculoskeletal manipulations/
27. (rehabilitat$ or physiotherap$ or manual therap$ or exercise$ or mobili$).mp.
28. exp Activities of Daily Living/
29. exp Occupational Therapy/
30. or/19-29
31. 18 and 30
32. randomized controlled trial.pt
33. controlled clinical trial.pt
34. randomized controlled trials.sh.
35. random allocation.sh
36. double-blind method.sh.
37. single-blind method.sh.
38. or/32-37
39. clinical trial.pt
40. exp clinical trials/
41. (clin$ adj25 trial$).ti,ab.
42. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
43. placebos.sh.
44. placebo$.ti,ab.
45. random$.ti,ab.
46. research design.sh.
47. or/39-46
48. 38 or 47
49. 31 and 48
50. (animals not human).sh.
51. 49 not 50

Appendix 2. EMBASE search strategy

1. exp Breast Tumor/
2. (breast cancer$ or breast tumor$ or breast tumour$ or breast neoplasm$).tw.
3. or/1-2
4. exp SHOULDER PAIN/ or exp SHOULDER/ or exp SHOULDER GIRDLE/
5. exp ARM/
6. (arm$ or shoulder$ or upper limb$ or upper extremit$).tw.
7. (arm$ or shoulder$ or upper limb$ or upper extremit$).tw.
8. adhesive capsulitis.mp. or exp Humeroscapular Periarthritis/
9. cording.mp.
10. or/4-9
11. 3 and 10
12. exp CANCER REHABILITATION/ or exp REHABILITATION/ or exp REHABILITATION MEDICINE/

13.physical therapy.mp. or exp Physiotherapy/
14.exp EXERCISE/
15.(rehabilitat$ or physiotherap$ or manual therap$ or exercise$ or mobili$).mp.
16.exp Daily Life Activity/
17.exp Occupational Therapy/
18.or/12-17
19.11 and 18
20.Clinical Trial/
21.19 and 20

Appendix 3. PEDro search strategy

Therapy: 1) stretching, mobilisation; 2) strength training

Problem: 1) muscle shortening, reduced joint compliance; 2) muscle weakness; 3) oedema; 4) pain

Body part: 1) upper arm, shoulder or shoulder girdle

Subdiscipline: 1) women's health; 2) musculoskeletal

Method: 1) clinical trial

Appendix 4. LILACs search strategy

Combinations of condition/ treatment and body part:

1. breast neoplasms/ cancer; breast tumor; axillary dissection

2. mastectomy

3. physical Therapy/ exercise/ exercise therapy

4. shoulder, arm, upper-extremity, upper limb

CONTRIBUTIONS OF AUTHORS

Contributions:
Margaret McNeely: conceived project, developed protocol, conducted searches, coordinated reviewers, data collection and extraction, quality assessment, and manuscript preparation.
Kristin Campbell: conceived project, contributed to protocol, selection of articles, data collection and extraction, quality assessment and manuscript preparation and review.
Maria Ospina: selection of articles, data collection and extraction, quality assessment, manuscript preparation and review.
Brian Rowe: methodological expert, contributed to protocol, manuscript preparation and review.
Terry Klassen: methodological expert, contributed to protocol, and manuscript review.
John Mackey: clinical and content expert, contributed to protocol, and manuscript review.
Kelly Dabbs: clinical and content expert, contributed to protocol, and manuscript review.
Kerry Courneya: content expert, contributed to protocol, and manuscript review.

DECLARATIONS OF INTEREST

The authors declare no conflicts, financial or otherwise. Drs Courneya and Mackey were investigators of one of the included studies.

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- No sources of support supplied

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- Canadian Institutes of Health Research (CIHR; BR), Canada.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We were not able to perform subgroup analyses for all outcomes as there were insufficient numbers of studies in the comparison groups. Furthermore, few studies reported results by patient demographic and treatment variables to allow for examination of benefit for varying age groups or surgical procedures.

INDEX TERMS

Medical Subject Headings (MeSH)

*Shoulder Joint [physiology]; Breast Neoplasms [drug therapy] [radiotherapy] [*surgery]; Exercise Therapy [adverse effects] [*methods]; Joint Diseases [etiology] [*rehabilitation]; Lymphedema [etiology]; Postoperative Complications [*rehabilitation]; Randomized Controlled Trials as Topic; Range of Motion, Articular; Recovery of Function [physiology]; Time Factors; Upper Extremity

MeSH check words

Female; Humans