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[Intervention Review]

Exercise for women receiving adjuvant therapy for breast cancer

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ABSTRACT

Background

A huge clinical research database on adjuvant cancer treatment has verified improvements in breast cancer outcomes such as recurrence and mortality rates. On the other hand, adjuvant and neoadjuvant therapy with chemotherapy and radiotherapy impacts on quality of life due to substantial short- and long-term side effects. A number of studies have evaluated the effect of exercise interventions on those side effects. This is an updated version of the original Cochrane review published in 2006. The original review identified some benefits of physical activity on physical fitness and the resulting capacity for performing activities of daily life. It also identified a lack of evidence for other outcomes, providing clear justification for an updated review.

Objectives

To assess the effect of aerobic or resistance exercise interventions during adjuvant treatment for breast cancer on treatment-related side effects such as physical deterioration, fatigue, diminished quality of life, depression, and cognitive dysfunction.

Search methods

We carried out an updated search in the Cochrane Breast Cancer Group Specialised Register (30 March 2015), the Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 2, 2015), MEDLINE (1966 to 30 March 2015), and EMBASE (1966 to 30 March 2015). We did not update the original searches in CINAHL (1982 to 2004), SPORTDiscus (1975 to 2004), PsycINFO (1872 to 2003), SIGLE (1880 to 2004), and ProQuest Digital Dissertations (1861 to 2004). We searched the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) and ClinicalTrials.gov for ongoing trials on 30 March 2015. We screened references in relevant reviews and published clinical trials.

Selection criteria

We included randomised controlled trials that examined aerobic or resistance exercise or both in women undergoing adjuvant treatment for breast cancer. Published and unpublished trials were eligible.

Data collection and analysis

Two review authors independently performed data extraction, assessed trials, and graded the methodological quality using Cochrane's 'Risk of bias' tool. Any disagreements were resolved through discussion or by consulting the third review author. We entered data into Review Manager for analysis. For outcomes assessed with a variety of instruments, we used the standardised mean difference (SMD) as a summary statistic for meta-analysis; for those assessed with the same instrument, we used the mean difference (MD).

Main results

For this 2015 update we included a total of 32 studies with 2626 randomised women, 8 studies from the original search and 24 studies from the updated search. We found evidence that physical exercise during adjuvant treatment for breast cancer probably improves physical fitness (SMD 0.42, 95% confidence interval (CI) 0.25 to 0.59; 15 studies; 1310 women; moderate-quality evidence) and slightly reduces fatigue (SMD -0.28, 95% CI -0.41 to -0.16; 19 studies; 1698 women; moderate-quality evidence). Exercise may lead to little or no improvement in health-related quality of life (MD 1.10, 95% CI -5.28 to 7.48; 1 study; 68 women; low-quality evidence), a slight improvement in cancer site-specific quality of life (MD 4.24, 95% CI -1.81 to 10.29; 4 studies; 262 women; low-quality evidence), and an improvement in cognitive function (MD -11.55, 95% CI -22.06 to -1.05; 2 studies; 213 women; low-quality evidence). Exercise probably leads to little or no difference in cancer-specific quality of life (SMD 0.12, 95% CI 0.00 to 0.25; 12 studies; 1012 women; moderate-quality evidence) and little or no difference in depression (SMD -0.15, 95% CI -0.30 to 0.01; 5 studies; 674 women; moderate-quality evidence). Evidence for other outcomes ranged from low to moderate quality. Seven trials reported a very small number of adverse events.

Authors' conclusions

Exercise during adjuvant treatment for breast cancer can be regarded as a supportive self care intervention that probably results in less fatigue, improved physical fitness, and little or no difference in cancer-specific quality of life and depression. Exercise may also slightly improve cancer site-specific quality of life and cognitive function, while it may result in little or no difference in health-related quality of life. This review is based on trials with a considerable degree of clinical heterogeneity regarding adjuvant cancer treatments and exercise interventions. Due to the difficulty of blinding exercise trials, all included trials were at high risk for performance bias. Furthermore, the majority of trials were at high risk for detection bias, largely due to most outcomes being self reported.

The findings of the updated review have enabled us to make a more precise conclusion that both aerobic and resistance exercise can be regarded as beneficial for individuals with adjuvant therapy-related side effects. Further research is required to determine the optimal type, intensity, and timing of an exercise intervention. Furthermore, long-term evaluation is required due to possible long-term side effects of adjuvant treatment.

PLAIN LANGUAGE SUMMARY

Exercise for women receiving chemotherapy or radiation therapy or both (adjuvant therapy) for breast cancer

What is the issue?

In the past, women receiving cancer treatment were usually advised to rest and avoid physical activity. But, we now know that too much rest and too little physical activity can lead to muscle wasting. This reduces women's physical fitness level and may limit their regular activities. Women also often have other side effects that can affect their daily lives, such as extreme tiredness (fatigue), depression, and reduced mental functioning, for example being able to remember things or keep focused.

Why does it matter?

The side effects of breast cancer treatment can interfere with daily activities and return to work. It is important to learn of ways to reduce these side effects.

We asked if physical exercise during chemotherapy or radiation therapy or both helped to reduce treatment side effects. Side effects studied included tiredness, depression, and reduced physical fitness and mental functioning. We also studied general effects such as health-related, cancer-specific, and cancer site-specific quality of life. Questionnaires for cancer-specific quality of life ask questions that are important for patients with cancer in general, for example about pain or nausea. Cancer site-specific quality of life is measured with questionnaires that ask women with breast cancer about topics that are especially important to them, for example about breast symptoms or body image. We only included questionnaires that have been shown to be reliable.

We found 32 studies involving 2626 women. The included studies were published up through March 2015. Not all studies considered all of these potential side effects. Combining the results of these studies suggests that physical exercise probably improves physical fitness and slightly lessens fatigue. These studies also suggest that physical exercise probably results in little or no improvement in cancer-specific quality of life and depression. Exercise may improve mental function and slightly improve cancer site-specific quality of life, although the quality of the evidence was low for both of these outcomes. It may result in little or no improvement in health-related quality of life, however the quality of evidence was low for this outcome. The quality of evidence may have been low because many of the studies did not have enough participants to observe small differences and because results may be biased due to people assessing the outcomes knowing which participants were in the control group.

Importantly, physical exercise did not harm most women. Very few women experienced discomfort or pain in their arms or legs.

What does this mean?

It appears that exercise during cancer treatment can help lessen fatigue and improve physical fitness. It probably results in little or no improvement in cancer-specific quality of life and depression. It is unknown whether it helps for other side effects. At least nine current studies will help to answer the question if and how much exercise helps with the mentioned side effects and other side effects.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Exercise compared with control for women receiving adjuvant therapy for breast cancer

Exercise compared with control for women receiving adjuvant therapy for breast cancer

Population: women receiving adjuvant therapy (chemo- or radiotherapy or both) for breast cancer

Settings: supervised or home based

Intervention: aerobic or resistance exercise or a combination of both

Comparison: control intervention (usual care or intervention that was not exercise, such as stretching)

Outcomes	Relative effects* (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Exercise vs control			
Physical fitness assessed with: 6- or 12-minute walk test, peak oxygen uptake, and other scales (follow-up: 18 weeks to 6 months)	The mean physical fitness in the intervention group was **0.42 standard deviations higher** (0.25 to 0.59 higher)	1310 (15 RCTs)	⊕⊕⊕⊖ **moderate** [1]	SMD 0.42 (95% CI 0.25 to 0.59)
Fatigue assessed with: FACIT-F scale, (revised) Piper Fatigue Scale, Multidimensional Fatigue Inventory and other scales (follow-up: 18 weeks to 6 months)	The mean fatigue in the intervention group was **0.28 standard deviations lower** (0.41 lower to 0.16 lower)	1698 (19 RCTs)	⊕⊕⊕⊖ **moderate** [2]	SMD -0.28 (95% CI -0.41 to -0.16)
Cancer-specific quality of life assessed with: FACT-G, EORTC QLQ-C30 and other scales (follow-up: 12 weeks to 6 months)	The mean cancer-specific quality of life in the intervention group was **0.12 standard deviations higher** (0.00 to 0.25 higher)	1012 (12 RCTs)	⊕⊕⊕⊖ **moderate** [3]	SMD 0.12 (95% CI 0.00 to 0.25)
Health-related quality of life assessed with EQ-5D visual analogue scale (higher scores indicate higher quality of life, score range from 0 to 100) MID: 7 points (follow-up: end of intervention)	The mean health-related quality of life in the intervention group was **1.10 points higher** (5.28 lower to 7.48 higher)	68 (1 RCT)	⊕⊕⊖⊖ **low** [4,5]	MD 1.10 (95% CI -5.28 to 7.48)
Cancer site-specific quality of life assessed with: FACT-B (higher scores indicate better quality of life, score range from 0 to 144) MID: 7 to 8 points (follow-up: end of intervention)	The mean cancer site-specific quality of life in the intervention group was **4.24 points higher** (1.81 lower to 10.29 points higher)	262 (4 RCTs)	⊕⊕⊖⊖ **low** [6,7]	MD 4.24 (95% CI -1.81 to 10.29)

Depression assessed with: BDI, CES-D (follow-up: 6 months)	The mean depression in the intervention group was **0.15 standard deviations lower** (0.30 lower to 0.01 higher)	674 (5 RCTs)	⊕⊕⊕⊖ **moderate** [8]	SMD -0.15 (95% CI -0.30 to 0.01)
Cognitive function assessed with: Trail Making Test (less time in seconds needed for completing the test means less cognitive dysfunction) (follow-up: end of intervention)	The mean time needed for completing the test in the intervention group was **11.55 seconds less** (22.06 seconds less to 1.05 seconds less)	213 (2 RCTs)	⊕⊕⊖⊖ **low** [9,10]	MD -11.55 (95% CI -22.06 to -1.05)
Lymphoedema assessed with: volumetric arm measurements and bioimpedance spectroscopy (follow-up: 8 weeks)	Assumed risk[11]: 85 per 1000 Corresponding risk: 60 per 1000 (30 to 123)	436 (2 RCTs)	⊕⊕⊖⊖ **low** [12,13]	RR 0.71 (95% CI 0.35 to 1.45)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
BDI: Beck Depression Inventory; **CES-D:** Center for Epidemiological Studies-Depression Scale; **CI:** confidence interval; **FACIT-F:** Functional Assessment of Chronic Illness Therapy-Fatigue Scale; **FACT-B:** Functional Assessment of Cancer Therapy-Breast; **FACT-G:** Functional Assessment of Cancer Therapy-General; **MD:** mean difference; **MID:** minimally important difference; **RCT:** randomised controlled trial; **RR:** risk ratio; **SMD:** standardised mean difference

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Lack of blinding, low adherence and high or unclear contamination, several randomisation and many allocation concealment procedures were unclear, therefore we downgraded by one level.
[2]Lack of blinding, low adherence and high or unclear amount of contamination, many allocation concealment procedures were unclear, therefore we downgraded by one level.
[3]Lack of blinding, low adherence and high or unclear amount of contamination, and a high rate of incomplete outcome data, therefore we downgraded by one level.
[4]Lack of blinding, low adherence and high amount of contamination, high rate of incomplete outcome data, and group similarity at baseline was at high risk, therefore we downgraded by one level.
[5]Small number of participants and null effect and appreciable benefit included in the confidence interval for the mean difference: imprecision, therefore we further downgraded by one level.
[6]Lack of blinding, low adherence, a high or unclear amount of contamination in three of four trials in the meta-analysis, two of four allocation concealment procedures were unclear, therefore we downgraded by one level.
[7]Small number of participants, wide confidence intervals for two of the four trials, and null effect and appreciable benefit included in the confidence interval for the mean difference: imprecision, therefore we further downgraded by one level.
[8]Lack of blinding, low adherence and unclear or high contamination, two published studies could not contribute to the meta-analysis, and in one of those there were no changes in the depression scores in any of the groups, therefore we downgraded by one level.
[9]Lack of blinding, low and unclear adherence and unclear contamination, group similarity at baseline for one study was at high risk of bias, therefore we downgraded by one level.
[10]Small number of participants: imprecision, therefore we further downgraded by one level.
[11]Assumed risk based on the mean control group risk in the included studies.

[12]Lack of blinding, low adherence and unclear or high contamination, one of two allocation procedures was unclear, group similarity at baseline was at high risk of bias for one study, therefore we downgraded by one level.
[13]Small number of participants and null effect and appreciable harm and benefit included in the confidence interval for the risk ratio: imprecision, therefore we further downgraded by one level.

BACKGROUND

Description of the condition

Breast cancer detection and management have undergone dramatic changes over the past three decades. Women are increasingly diagnosed with early-stage disease, leaving them with treatment choices ranging from breast-conserving options to mastectomy (Newman 2003). With the majority of breast cancers diagnosed at an early stage, treatment is focused on cure and the prevention of relapse due to micrometastatic disease. The mainstay of care is local therapy, consisting of mostly breast-conserving surgery followed by radiotherapy. Adjuvant systemic therapy includes chemotherapy (cytotoxic agents) when there is an increased risk for systemic relapse and hormonal and/or antibody therapy (trastuzumab), depending on the expression of hormone and HER2/neu receptors.

Besides these major advances in managing both early and locally advanced breast cancer, women still have to deal with severe side effects and psychological distress during adjuvant therapy. This has a substantial impact on their quality of life. Side effects that appear with adjuvant cancer treatment differ depending on the mode of treatment, that is radiotherapy, chemotherapy, hormonal, or antibody therapy.

Radiotherapy is frequently associated with short-term side effects such as fatigue and skin reactions, and relatively rare long-term side effects including lymphoedema, cardiac and pulmonary toxicities, and secondary malignancy (Brown 2015). Chemotherapy is associated with short-term side effects such as nausea, emesis, stomatitis, alopecia, myelosuppression, thromboembolism, myalgias, neuropathy, and fatigue. Long-term side effects of chemotherapy are premature menopause, weight gain, fatigue, cardiac dysfunction, and cognitive dysfunction (Partridge 2001). Furthermore, people receiving radiotherapy or chemotherapy report anxiety and depression prior to, during, and after therapy due to treatment side effects (Spiegel 1997). Adjuvant hormonal therapy produces symptoms secondary to oestrogen withdrawal, such as hot flushes, bone demineralisation, and psychosexual effects (Rutqvist 2004). A particular concern with antibody therapy in combination with anthracycline chemotherapy is cardiac toxicity (Rayson 2008).

Description of the intervention

Although research is producing increasingly hopeful insights into the causes and cures for cancer, efforts to manage the side effects of adjuvant therapy have not kept apace (Patrick 2003). Exercise interventions may be effective in managing some of these side effects, such as fatigue, depression, and cognitive dysfunction.

How the intervention might work

Evidence concerning the natural progression of physical activity suggests that women with breast cancer significantly decrease physical activity and exercise from pre-diagnosis to postdiagnosis (Irwin 2003). These decreases are associated with adjuvant cancer treatment; observed decreases in physical activity were greater among women who were treated with radiation and chemotherapy (50% decrease) compared with women who underwent surgery only (24% decrease) or who were treated with surgery and radiation only (23% decrease) (Irwin 2003).

The National Comprehensive Cancer Network defines cancer-related fatigue as a "persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning" (NCCN 2004). Fatigue results in substantial physical, psychosocial, cognitive, and socioeconomic consequences (Holley 2000). During and after adjuvant chemotherapy and radiotherapy the prevalence of fatigue is high and fluctuating (de Jong 2002; Jereczek-Fossa 2001). Fatigue is also associated with factors such as depression, impaired quality of sleep, or pain (de Jong 2002).

The rationale supporting exercise interventions for cancer-related fatigue is based on the proposition that the combined effects of a toxic treatment and a decreased level of activity during treatment result in a reduction in the capacity for physical performance. Patients must in turn use greater effort and expend more energy to perform daily activities, which leads to fatigue (NCCN 2004). Physical exercise training programmes may increase functional capacity, leading to reduced effort and decreased fatigue.

Women treated for breast cancer frequently experience higher levels of emotional distress than the general population (Spiegel 1997). The rationale for considering exercise as an intervention to reduce distress in women receiving adjuvant therapy for breast cancer is based upon literature that has demonstrated ameliorating effects of exercise on these problems. Results of studies with non-cancer populations indicate that aerobic exercise training has antidepressant and anxiolytic effects and protects against harmful consequences of stress (Salmon 2001). There is evidence that cognitive dysfunction may also occur in women receiving adjuvant chemotherapy for breast cancer (O'Shaughnessy 2003; Rugo 2003; Tchen 2003). A meta-analytic study conducted to examine the hypothesis that aerobic fitness training enhances the cognitive vitality of healthy but sedentary older adults indicated that fitness training has robust benefits for cognition (Colcombe 2003).

Why it is important to do this review

The majority of research focused on rehabilitation and health promotion in women who had completed cancer treatment. This review aims to evaluate the role of exercise in managing common side effects of adjuvant and neoadjuvant therapy for breast cancer. We conducted this review update to incorporate and analyse the increasing number of studies in women undergoing adjuvant treatment.

OBJECTIVES

To assess the effect of aerobic or resistance exercise interventions during adjuvant treatment for breast cancer on treatment-related side effects such as physical deterioration, fatigue, diminished quality of life, depression, and cognitive dysfunction.

METHODS

Criteria for considering studies for this review

Types of studies

We considered randomised controlled trials of exercise training during adjuvant (including neoadjuvant) treatment (radiotherapy, chemotherapy) for women with non-metastatic breast cancer.

Types of participants

We included studies involving women who were diagnosed with breast cancer stages I, II, and III and who were undergoing adjuvant (including neoadjuvant) chemotherapy, radiotherapy, or a combination concurrently with an exercise intervention in the active group.

Types of interventions

We included studies that assessed the effects of all forms of repeatedly performed aerobic or resistance exercise or both with programme duration of at least six weeks. To be included in this review, the exercise intervention had to coincide with the adjuvant treatment regimen rather than follow it. We excluded studies where the exercise intervention was part of a complex intervention (for example complete decongestive lymphatic therapy). We also excluded trials with interventions restricted to local muscular endurance (for example training of shoulders, back, or legs only) instead of including all major muscle groups or restricted to stretching exercises.

We included trials making the following comparisons:

- exercise versus no exercise;
- exercise versus other interventions (e.g. psychosocial interventions).

Types of outcome measures

Primary outcomes

1. physical fitness: objective tests measuring VO_2 max or distance walked per time
2. fatigue: using a validated questionnaire such as Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)
3. quality of life (cancer-specific quality of life, health-related quality of life, cancer site-specific quality of life): using a validated questionnaire such as Functional Assessment of Cancer Therapy-General (FACT-G), European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 36 (EORTC QLQ-C30), Functional Assessment of Cancer Therapy-Breast (FACT-B)
4. depression: using a validated questionnaire such as Beck Depression Inventory (BDI)
5. cognitive function: using a validated test such as the Trail Making Test

Secondary outcomes

1. strength
2. other psychological distress outcomes
3. physical activity behaviour
4. multidimensional outcomes (e.g. pain)
5. harms

Search methods for identification of studies

Electronic searches

- We searched the Cochrane Breast Cancer Group Specialised Register on 30 March 2015 (details of search strategies used by the group for the identification of studies and the procedure used to code references are outlined in the group's module at www.mrw.interscience.wiley.com/cochrane/clabout/articles/BREASTCA/frame.html). We extracted studies including the text words 'early', 'locally advanced', local recurrence', 'locoregional', 'exercise', and 'exercise therapy' on the Specialised Register for consideration.
- Cochrane Central Register of Controlled Trials (CENTRAL) (via the Cochrane Library, Issue 2, 2015). See Appendix 1.
- MEDLINE (via OvidSP) from 1966 until 30 March 2015. See Appendix 2.
- EMBASE (via Embase.com) from 1966 until 30 March 2015. See Appendix 3.
- The World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch/Default.aspx) for all prospectively registered and ongoing trials on 30 March 2015. See Appendix 4.
- ClinicalTrials.gov (clinicaltrials.gov/ct2/home) until 30 March 2015. See Appendix 5.

We did not update the searches in the original review in the following databases:

- CINAHL (1982 to 2004)
- SPORTDiscus (1975 to 2004)
- PsycINFO (1872 to 2003)
- SIGLE (1880 to 2004)
- ProQuest Digital Dissertations (1861 to 2004)

Searching other resources

References from published studies

We screened references in relevant reviews and in published clinical trials for further trials.

Other

We consulted six experts in the field of cancer and exercise to identify additional trials. We applied no language restrictions.

Data collection and analysis

Selection of studies

Two review authors (either ACF and MHM or ACF and MM) independently reviewed the titles and abstracts of reports identified by the search and selected those that potentially fulfilled the inclusion criteria of this review. We retrieved these potentially relevant reports for more detailed evaluation. Both review authors then independently made a final selection of studies to be included in the review. A report was excluded according to the first criterion that it did not fulfil. We resolved disagreements by consensus, or if necessary by consulting a third person (MM or MHM) to reach a final decision.

Data extraction and management

Two review authors (ACF, MHM) independently extracted data (including study characteristics, study results, and point estimates together with measures of variability for selected outcome variables). We reviewed all discrepancies and achieved consensus through discussion, if necessary consulting a third person (MM) to reach a final decision. Where we found more than one publication for a study, we extracted data from all available publications if applicable. When a design publication and a results publication

were available, we considered the results publication to be the primary reference. In cases where a doctoral dissertation was available, we considered this to be the primary reference for the study. In other cases, we considered the publication with the most relevant reported information for the review, especially regarding results, to be the primary reference.

Assessment of risk of bias in included studies

In the original version of the review, we assessed the included studies for quality using van Tulder methodological quality criteria. In the updated review, we used the Cochrane 'Risk of bias' tool (Higgins 2011). Two review authors (either ACF and MM or ACF and MHM) assessed the risk of bias of all included studies. This included assessment of sequence generation, allocation concealment, masking or blinding (of participants, researchers/healthcare providers, and outcome assessors), methods of addressing incomplete outcome data, selective reporting of outcomes, and other possible sources of bias including attrition from the exercise intervention. We graded each risk of bias parameter as high risk, low risk, or unclear risk based on recommendations for judging risk of bias provided in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). For attrition bias, we judged studies to be at high risk when more than 20% of data were missing for short-term follow-up and more than 30% for long-term follow-up, as these are commonly used thresholds. We resolved disagreement through consensus, if necessary consulting a third review author (MHM or MM) for a final decision.

We used the last two rows in the 'Risk of bias' assessment tables to document reporting and amount of adherence and contamination in the exercise and control groups. If participants allocated to the exercise group do not exercise (non-adherence), and at the same time participants allocated to the control group do exercise (contamination), the originally intended study groups are distorted into groups with participants who exercise and those who do not (moreover in unknown proportions). Effects may be underestimated as a result.

There are several bias issues inherent to exercise studies, that is blinding of participants and exercise supervising personnel is difficult or impossible, leading to high risk of performance bias in every study. It is therefore important to point out that the bias assessment for those items does not reflect a low quality of study design as such, but expresses the inevitable bias introduced by lack of blinding. Nevertheless, exercise intervention studies should be subjected to the same 'Risk of bias' assessment as other studies, for example drug intervention studies. A similar challenge applies to adherence and contamination in exercise studies. It is difficult to maximise exercise adherence, especially in a participant cohort with cancer, and a certain amount of contamination and imperfect adherence is to be expected. Confidence in the results might therefore be lowered, even if studies are well planned and reported.

When high risk of bias for a study was due to lack of blinding, contamination, and/or non-adherence, we did not downgrade the quality of evidence for this alone. We only downgraded the evidence one level for risk of bias when other factors such as unclear allocation procedures or high attrition rates were present.

'Risk of bias' tables for each study are presented in the Characteristics of included studies table and a summary of the risk of bias is presented.

Measures of treatment effect

Outcome measurements were presented as continuous data across included studies. As the first step, we extracted data on outcomes in the format in which they were reported. For selected outcomes we extracted group means for final values and change scores with the corresponding measures of variability such as standard deviations (SD) or confidence intervals (CI) and the number of participants on whom the outcome was assessed per group.

As a summary statistic for meta-analysis of continuous outcomes, we either used the standardised mean difference (SMD) or the weighted mean difference (WMD). We chose the SMD in cases where different assessment instruments measuring the same construct were used across studies (for example for fatigue and physical fitness outcomes). We did not combine final values and change scores in meta-analyses since the difference in standard deviation does not reflect "differences in measurement scale, but differences in the reliability of the measurements" (Deeks 2005).

We did not include data for outcomes assessed with subscales of questionnaires (for example physical functioning subscale of the 36-Item Short Form Health Survey (SF-36) or vitality subscale of the SF-36, nausea item of the Symptom Checklist-90 (SCL-90)), because we only wanted to assess the respective full construct in this review as well as only include validated questionnaires, which often is not the case for subscales.

As a summary statistic for dichotomous outcomes we chose the risk ratio (RR). Lymphoedema was the only outcome that was analysed as a dichotomous outcome: two studies reported the number of participants with lymphoedema (Courneya 2007: Courneya 2007 AET and Courneya 2007 RET; Hayes 2013: Hayes 2013 FtF and Hayes 2013 Tel). For those outcomes with data available from only one study, we calculated and presented a summary statistic for this particular study.

Unit of analysis issues

Five studies were three-arm trials (Courneya 2007 split into Courneya 2007 AET and Courneya 2007 RET; Hayes 2013: Hayes 2013 FtF and Hayes 2013 Tel; Schwartz 2007: Schwartz 2007 AET and Schwartz 2007 RET; Segal 2001: Segal 2001 SD and Segal 2001 SU; van Waart 2014: van Waart 2014 high and van Waart 2014 low), and they contributed to the meta-analysis of physical fitness with two exercise groups. For all five studies, we incorporated both exercise arms into the meta-analysis and allocated a control group to each of them (that is by halving the number of participants and events observed in the control group).

Dealing with missing data

Whenever possible, we tried to contact the investigators or sponsors of studies with missing data.

Assessment of heterogeneity

We used the random-effects model to obtain the average effect of exercise because, in addition to the presence of random error, differences between exercise studies during adjuvant cancer treatment can also result from real differences between study

populations, adjuvant cancer treatment, and the training stimulus. The random-effects model considers these additional sources of between-study variability as well as within-study variability.

We evaluated inconsistency of results across studies using the I^2 statistic, which describes the percentage of variability in the point estimates that is due to heterogeneity rather than sampling error (Higgins 2002). Following Higgins (Higgins 2003), we considered I^2 values of 25% as indicating low heterogeneity, I^2 values of 50% moderate heterogeneity, and I^2 values of 75% large heterogeneity.

We also used visual assessment of forest plots; if no or small overlap of CIs for the results of individual studies was present, we assumed statistical heterogeneity.

Assessment of reporting biases

If we identified a sufficient number of studies (that is more than 10), we prepared funnel plots and visually examined them for signs of asymmetry to detect publication bias.

Data synthesis

We used the random-effects model to obtain the average effect of exercise because, in addition to the presence of random error, differences between exercise studies during adjuvant cancer treatment can also result from real differences between study populations, adjuvant cancer treatment, and the training stimulus. The random-effects model considers these additional sources of between-study variability as well as within-study variability.

We used the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach to assess the quality of the evidence, grading the following main outcomes for quality: physical fitness, fatigue, cancer-specific quality of life, health-related quality of life, cancer site-specific quality of life, depression, cognitive function, and lymphoedema. We used GRADEproGDT software to develop the 'Summary of findings' table, and two review authors (either ACF and MM or ACF and MHM) graded the quality of the evidence for each outcome. We resolved disagreement by consensus, if necessary consulting a third review author (MHM or MM) for a final decision.

As blinding of participants and exercise supervising personnel is difficult or impossible, and as self reported outcomes inherently carry a high risk of detection bias, those items were assessed with a high risk of bias, but did not lead to downgrading unless there were additional high risks of bias (for example sequence generation and allocation concealment).

Subgroup analysis and investigation of heterogeneity

We did not conduct subgroup analyses.

If possible, in future updates we will consider conducting the following subgroup analyses: adjuvant treatment received, chemo- and radiotherapy or radiotherapy only, type of exercise intervention (aerobic or resistance exercise, self directed or supervised exercise).

Sensitivity analysis

Where important statistical inconsistency existed as measured by the I^2 statistic, we conducted sensitivity analyses to assess the robustness of the review results by removing those studies that seemed to be estimating a different effect.

RESULTS

Description of studies

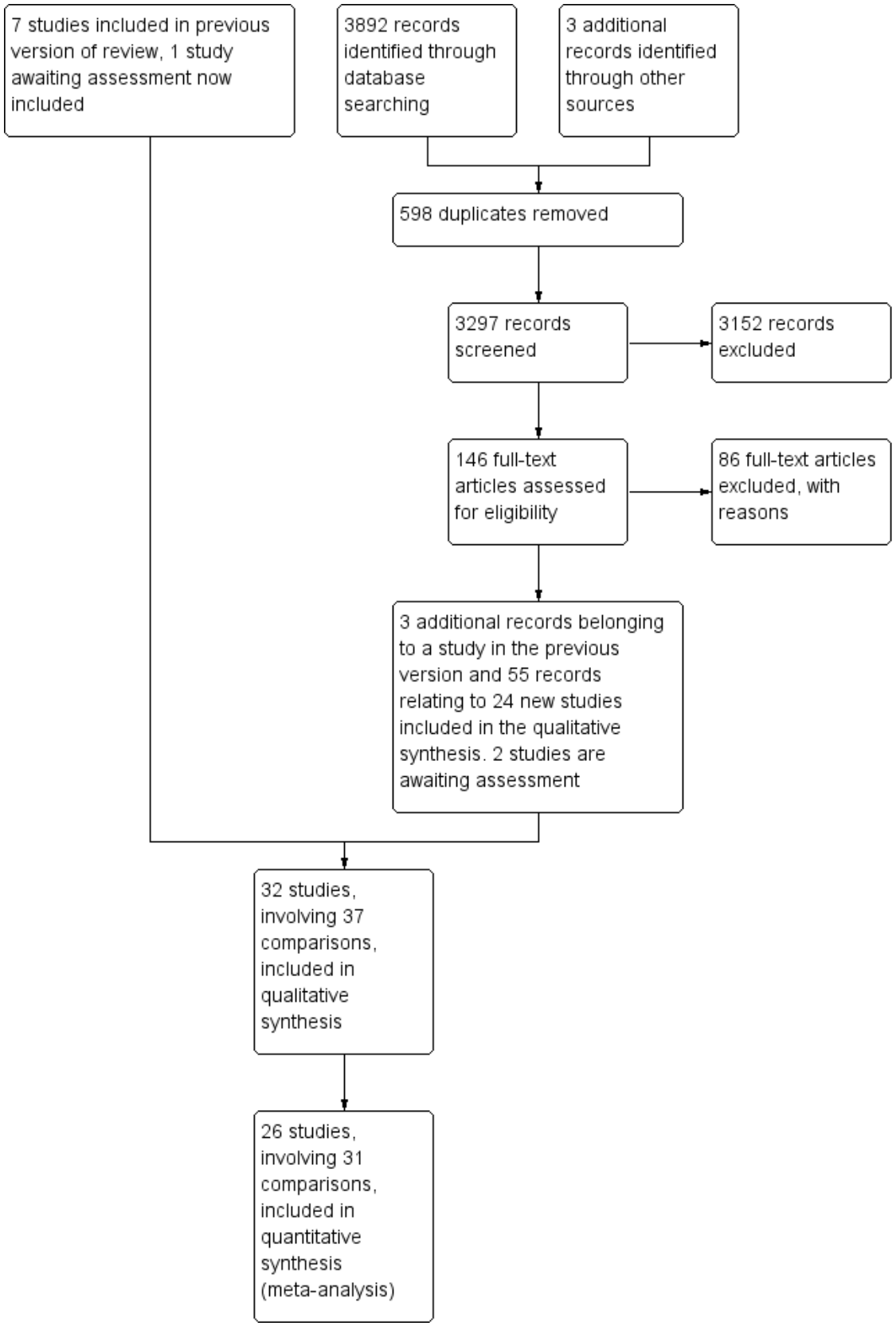
Results of the search

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.

In the original review published in 2006, we retrieved 32 full-text references for more detailed evaluation after screening of 1612 potentially relevant references. From the 32 full-text references, 22 publications were excluded, one trial was awaiting assessment (pending publication), and nine trials were included. We considered seven of the nine trials to be appropriate for inclusion in this updated review (Campbell 2005; Crowley 2003; Drouin 2002; MacVicar 1989; Mock 2004; Segal (Segal 2001 SD & Segal 2001 SU); Winningham 1988). We excluded two of these in this updated review because they were not randomised controlled trials (MacVicar 1986; Mock 1997). We included the trial that was awaiting assessment in the original review in this updated review (Battaglini 2004).

In this updated review, we retrieved a further 146 full-text references following screening of 3297 titles and abstracts. From these 146 full-text references we excluded 86 and identified 60 records as appropriate for inclusion in this review. Three records belonged to a study that had been included in the first version of this review, and 55 records related to 24 new studies. One study is awaiting assessment due to pending publication (Petrella 2012), and another study was due to be published after our analyses were finished (Lotzke 2016). For further details see Figure 1.

Figure 1. Study flow diagram.



Included studies

The eight studies from the original review and the 24 new studies amounted to a total of 32 studies (2626 participants) for inclusion in the review. Trial characteristics and outcomes are found in the Characteristics of included studies tables. We included only randomised controlled trials in this updated version of the review. Five of the included studies incorporated two separate exercise groups and are therefore entered twice for the purposes of statistical analysis (Courneya 2007: Courneya 2007 AET and Courneya 2007 RET; Hayes 2013: Hayes 2013 FtF and Hayes 2013 Tel; Schwartz 2007: Schwartz 2007 AET and Schwartz 2007 RET; Segal 2001: Segal 2001 SD and Segal 2001 SU; van Waart 2014: van Waart 2014 high and van Waart 2014 low).

Characteristics of participants

Women obtained different regimens of adjuvant treatment across these 32 exercise intervention studies: they received either chemotherapy or radiotherapy in one trial (Mock 2004); either chemotherapy or radiotherapy or a combination of the two in another 10 trials (Battaglini 2004; Cadmus 2007; Caldwell 2009; Campbell 2005; Eakin 2012; Haines 2010; Hayes 2013: Hayes 2013 FtF and Hayes 2013 Tel; Mutrie 2007; Perna 2010; Segal 2001: Segal 2001 SD and Segal 2001 SU), sequential chemo- and radiotherapy in one trial (Cornette 2013), chemotherapy only in nine trials (Courneya 2007: Courneya 2007 AET and Courneya 2007 RET; Crowley 2003; Ingram 2010; MacVicar 1989; Moros 2010; Schmidt 2014; Visovsky 2014; Winningham 1988; Yang 2011); neoadjuvant chemotherapy in two trials (Hornsby 2014; Rao 2012), neoadjuvant and adjuvant chemotherapy in one trial (Gokal 2013), and radiotherapy only in three trials (Drouin 2002; Reis 2013; Steindorf 2014). Five trials included women who were scheduled for chemotherapy, some of whom underwent radiation therapy as well (Dodd 2010; Husebo 2014; Schwartz 2007: Schwartz 2007 AET and Schwartz 2007 RET; Travier 2015; van Waart 2014: van Waart 2014 high and van Waart 2014 low).

Characteristics of the intervention

Mode of exercise differed across trials. Thirteen trials (Cadmus 2007; Dodd 2010; Drouin 2002; Gokal 2013; Hornsby 2014; Husebo 2014; MacVicar 1989; Mock 2004; Moros 2010; Reis 2013; Segal 2001: Segal 2001 SD and Segal 2001 SU; Winningham 1988; Yang 2011), and one of two intervention arms in two studies (Courneya 2007: Courneya 2007 AET; Schwartz 2007: Schwartz 2007 AET) tested aerobic exercise interventions, with three studies using cycle ergometer interval training (Hornsby 2014; MacVicar 1989; Winningham 1988), and six studies offering walking programmes (Drouin 2002; Gokal 2013; Husebo 2014; Mock 2004; Segal 2001: Segal 2001 SD and Segal 2001 SU; Yang 2011). Aerobic exercise also consisted of Nia exercise, in Reis 2013, and aerobic exercise self chosen by the participants in two studies, Cadmus 2007 and Dodd 2010, and in one intervention arm of one study (Schwartz 2007: Schwartz 2007 AET). Fifteen studies (Battaglini 2004; Caldwell 2009; Campbell 2005; Cornette 2013; Crowley 2003; Eakin 2012; Haines 2010; Hayes 2013: Hayes 2013 FtF and Hayes 2013 Tel; Husebo 2014; Ingram 2010; Moros 2010; Mutrie 2007; Perna 2010; Rao 2012; Travier 2015), and one of two intervention arms in one study (van Waart 2014: van Waart 2014 high) applied a combined aerobic-resistance programme. Exercise was implemented as a supervised group exercise programme in seven studies (Battaglini 2004; Campbell 2005; Courneya 2007: Courneya 2007 AET and Courneya 2007 RET; MacVicar 1989; Mutrie 2007; Travier 2015; Winningham 1988), and in one of two intervention arms in two studies (Segal 2001: Segal 2001 SU; van Waart 2014: van Waart 2014 high). Two studies tested resistance exercise interventions (Schmidt 2014; Steindorf 2014), as well as one intervention arm of two further studies (Courneya 2007: Courneya 2007 RET; Schwartz 2007: Schwartz 2007 RET). One study started with supervised resistance training at the hospital, followed by a combined self directed aerobic-resistance programme (Cornette 2013).

Four studies used a stretching intervention as a comparison arm (Drouin 2002; Haines 2010; MacVicar 1989; Winningham 1988), two studies used progressive muscle relaxation as the comparison arm (Schmidt 2014; Steindorf 2014), and the remaining 26 studies compared an exercise intervention with no intervention.

Exercise interventions lasted six to seven weeks for women undergoing radiation treatment in two trials (Drouin 2002; Mock 2004), 10 weeks in two trials for women undergoing chemotherapy (MacVicar 1989; Winningham 1988), and 12 to 13 weeks in 11 trials (Caldwell 2009; Campbell 2005; Crowley 2003; Gokal 2013; Hornsby 2014; Mutrie 2007; Reis 2013; Schmidt 2014; Steindorf 2014; Visovsky 2014; Yang 2011). In nine trials, the exercise intervention lasted 18 to 32 weeks (Battaglini 2004; Cadmus 2007; Cornette 2013; Eakin 2012; Hayes 2013: Hayes 2013 FtF and Hayes 2013 Tel; Ingram 2010; Schwartz 2007: Schwartz 2007 AET and Schwartz 2007 RET; Segal 2001: Segal 2001 SD and Segal 2001 SU; Travier 2015).The longest intervention period was 52 weeks, in two trials (Dodd 2010; Haines 2010). Trials with shorter intervention periods (six to seven weeks) were those in which women received radiation treatment, which is of shorter duration than chemotherapy. In five trials (Courneya 2007: Courneya 2007 AET and Courneya 2007 RET; Husebo 2014; Mock 2004; Moros 2010; van Waart 2014: van Waart 2014 high and van Waart 2014 low), the exercise intervention was implemented to span the period of time from initiation to cessation of the woman's adjuvant therapy, and subsequently the intervention periods of women in the intervention arm of the trial varied in length (either six weeks with radiation treatment or three to six months with chemotherapy).

In 12 trials (Battaglini 2004; Campbell 2005; Courneya 2007: Courneya 2007 AET and Courneya 2007 RET; Hornsby 2014; MacVicar 1989; Moros 2010; Mutrie 2007; Rao 2012; Schmidt 2014; Steindorf 2014; Travier 2015; Winningham 1988), and in one of the two intervention arms in three trials (Hayes 2013: Hayes 2013 FtF; Segal 2001: Segal 2001 SU; van Waart 2014: van Waart 2014 low), the exercise intervention was supervised. Women's exercise was self directed in 15 trials (Cadmus 2007; Caldwell 2009; Crowley 2003; Dodd 2010; Drouin 2002; Eakin 2012; Gokal 2013; Haines 2010; Husebo 2014; Ingram 2010; Mock 2004; Reis 2013; Schwartz 2007: Schwartz 2007 AET and Schwartz 2007 RET; Visovsky 2014; Yang 2011), and in the second intervention arm of Hayes 2013 (Hayes 2013 Tel), Segal 2001 (Segal 2001 SD), and van Waart 2014 (van Waart 2014 low). Two studies started with supervised sessions, which were followed by self directed sessions in the home (Cornette 2013; Perna 2010). Two trials applied supervised, one-on-one sessions, Rao 2012 home based and Hornsby 2014 at the clinical institution.

Characteristics of the outcome measures

The most frequently assessed outcomes were physical fitness and fatigue, with 22 studies measuring physical fitness (Battaglini 2004; Caldwell 2009; Campbell 2005; Cornette 2013; Courneya

2007: Courneya 2007 AET and Courneya 2007 RET; Crowley 2003; Dodd 2010; Drouin 2002; Haines 2010; Hayes 2013: Hayes 2013 FtF and Hayes 2013 Tel; Hornsby 2014; Husebo 2014; MacVicar 1989; Mock 2004; Mutrie 2007; Reis 2013; Schmidt 2014; Schwartz 2007: Schwartz 2007 AET and Schwartz 2007 RET; Segal 2001: Segal 2001 SD and Segal 2001 SU; Steindorf 2014; Travier 2015; van Waart 2014: van Waart 2014 high and van Waart 2014 low), and 21 studies measuring fatigue (Battaglini 2004; Caldwell 2009; Campbell 2005; Cornette 2013; Courneya 2007: Courneya 2007 AET and Courneya 2007 RET; Crowley 2003; Dodd 2010; Drouin 2002; Eakin 2012; Gokal 2013; Haines 2010; Hayes 2013: Hayes 2013 FtF and Hayes 2013 Tel; Hornsby 2014; Husebo 2014; Mock 2004; Mutrie 2007; Reis 2013; Schmidt 2014; Steindorf 2014; Travier 2015; van Waart 2014: van Waart 2014 high and van Waart 2014 low). Other outcomes assessed were quality of life, strength, depression, anxiety, cognitive function, self esteem, mood disturbances, physical activity level, gait and balance, subjective upper body function, neuropathy symptoms, chemotherapy completion, shoulder mobility, arm morbidity, nausea relief, sleep disturbances, endocrine symptoms, and adverse effects. For detailed information on outcome measures see the Characteristics of included studies table.

Other study characteristics

Small sample size was common among the included studies. Sixteen studies randomised fewer than 50 women. Ten of the 32 studies randomised more than 50 women per group (Courneya 2007: Courneya 2007 AET and Courneya 2007 RET; Dodd 2010; Eakin 2012; Hayes 2013: Hayes 2013 FtF and Hayes 2013 Tel; Mock 2004; Mutrie 2007; Segal 2001: Segal 2001 SD and Segal 2001 SU; Steindorf 2014; Travier 2015; van Waart 2014: van Waart 2014 high and van Waart 2014 low). Sample sizes ranged from 10 to 242 women. The median sample size was 50 women, interquartile range (IQR) 22 to 124. Sample size was reported to be based on power calculations in 14 studies, and 12 of the 14 studies reached the target sample size.

Excluded studies

In the majority of cases, we excluded studies because the exercise intervention took place after the adjuvant treatment period. Other reasons were that studies were not randomised controlled trials, exercise was part of a complex intervention or no exercise intervention was implemented, the majority of participants were not women with breast cancer, or the exercise intervention had a duration of less than six weeks. Furthermore, we excluded studies assessing yoga or qigong because we regard both as a complex intervention. Some studies could not be characterised as controlled trials (they were study protocols or reviews). For a detailed description of the reasons for exclusion, see the Characteristics of excluded studies table. Note that this table contains not only clinical studies but also review articles that were part of our full-text retrieval to confirm our decision to exclude studies when abstracts were ambiguous.

Risk of bias in included studies

We assessed the risk of bias for each included study and reported the judgements for the individual 'Risk of bias' domains in the 'Risk of bias' table. We have presented these in the 'Risk of bias' summary in Figure 2.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

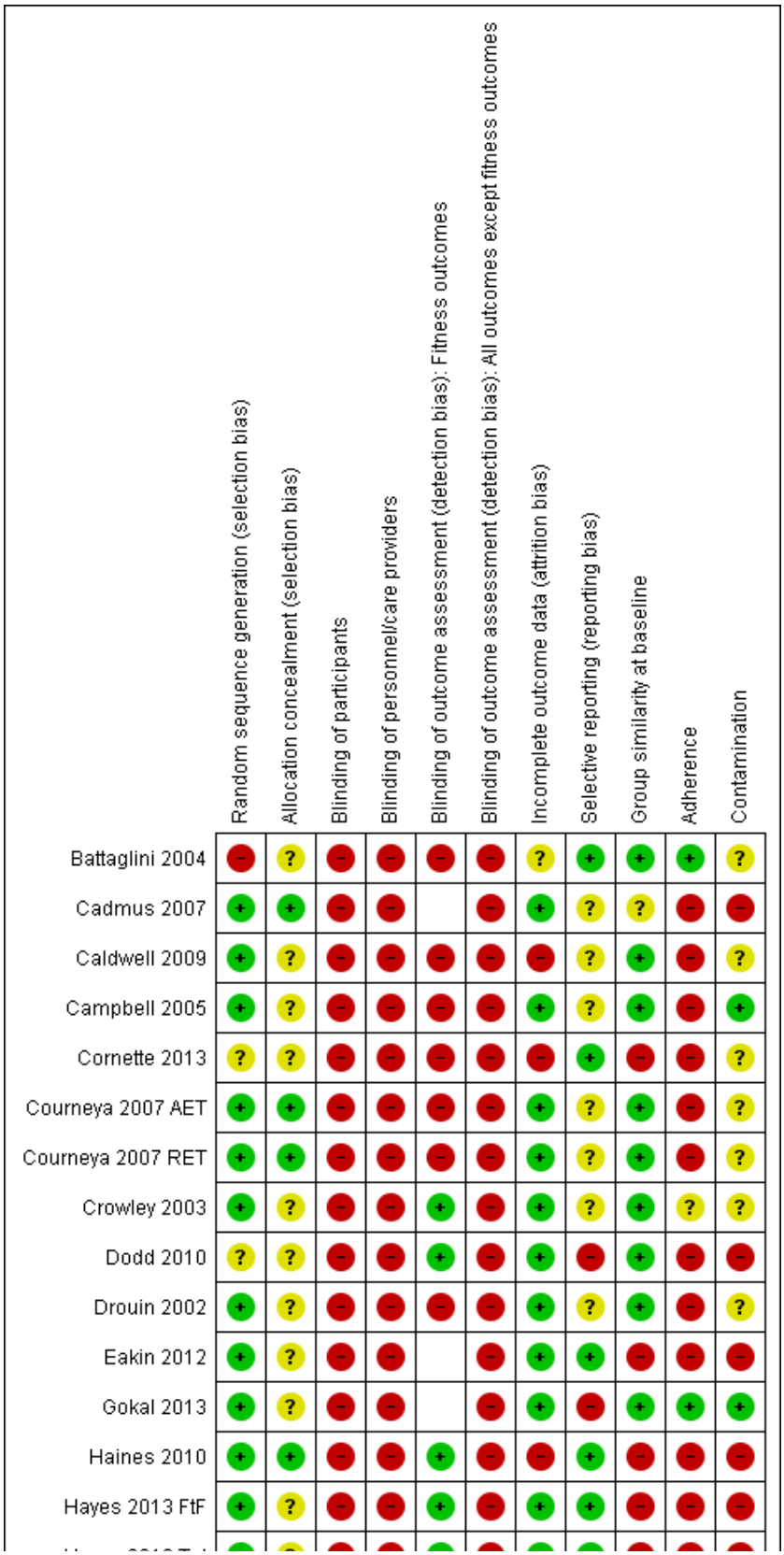
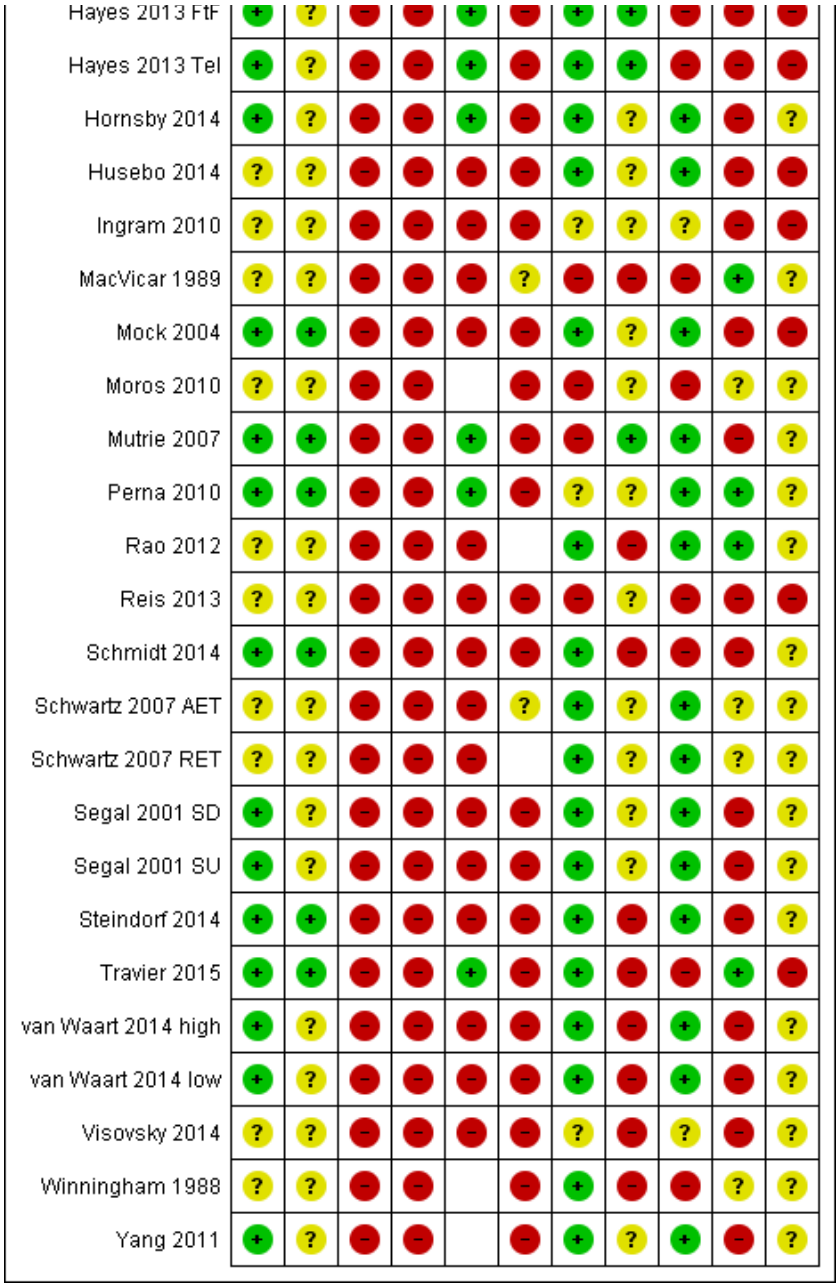


Figure 2. (Continued)



Allocation

Random sequence generation

Twenty trials were at a low risk of selection bias as they reported to have adequately generated their randomised sequence with a random component. One trial used a non-random component to generate the sequence (Battaglini 2004), and was thus judged to be at a high risk of selection bias. We considered 11 trials to have an unclear risk of selection bias, largely because the generation of the random sequence was not described.

Allocation concealment

Nine trials adequately concealed allocation to the intervention so that participants and investigators could not foresee assignment to the study groups, and were thus judged to be at low risk of selection bias. Twenty-three trials did not describe the method of allocation concealment or did not describe it in detail enough to allow for a definitive judgement, and were considered to have an unclear risk of selection bias.

Blinding

Blinding of participants and personnel

All trials included in this review were at high risk for performance bias because, owing to the nature of the intervention (exercise), it was not possible to blind the participants and the study personnel. Three studies mentioned a placebo group (Haines 2010; MacVicar 1989; Winningham 1988), in which women were instructed to do stretching in a similar setting to the exercise groups. But as

knowledge about the difference between physical exercise and stretching is usually present in the population, we cannot assume that participants and personnel were unaware of being in the exercise or the stretching group.

Blinding of outcome assessors (detection bias)

Eight studies reported blinding of outcome assessors (Crowley 2003; Dodd 2010; Haines 2010; Hayes 2013: Hayes 2013 FtF and Hayes 2013 Tel; Hornsby 2014; Mutrie 2007; Perna 2010; Travier 2015). Blinding was performed for assessment of fitness outcomes, as well as for lymphoedema in one study (Hayes 2013), and for upper limb swelling and shoulder range of motion in another study (Haines 2010), with a low risk of bias for these outcomes, but not for the remaining self reported outcomes, for which risk of bias was high. Perna 2010 did not report the assessed fitness outcomes. In the remaining 24 studies, no information was given on blinding of outcome assessors, which we judged as lack of blinding and therefore high risk of bias for this item for all outcomes. In cases where no fitness outcomes or no self reported outcomes were measured in a trial, this appears as unclear risk of bias in the tables and as an empty cell in the 'Risk of bias' summary.

Incomplete outcome data

Twenty-three of the 32 studies reported to have analysed data according to the intention-to-treat (ITT) principle. Twenty of these 23 studies had low drop-out rates or less than 20% missing data and were thus judged to be at low risk of attrition bias. Of the remaining three studies, one reported imbalanced drop-out rates between the exercise group and the control group (Mutrie 2007), with almost twice as many dropped-out participants in the intervention group (19 of 101) than in the control group (10 of 102); we therefore judged this study to be at high risk of attrition bias. The second study had more than 30% missing data (Cornette 2013). In spite of the trial authors undertaking an ITT analysis with imputation of missing data, we judged this study to be at high risk of attrition bias due to the amount of missing data. It remained unclear if there had been missing data in the third study, leading to a judgement of unclear risk of attrition bias (Visovsky 2014).

Five studies did not report if data were analysed by intention to treat. Three of these studies had more than 20% dropouts or missing data and were thus judged to be at high risk of attrition bias (Caldwell 2009; Haines 2010; Moros 2010). Another study did not report if there were missing data (Battaglini 2004), and was thus judged to be at an unclear risk of attrition bias. The remaining study had a low drop-out rate (4 of 44 women) and was judged to be at low risk of attrition bias (Yang 2011).

We judged one study to be at high risk of attrition bias (Reis 2013), because it only reported a per-protocol analysis of participants that adhered to the exercise intervention (12 of 22 women). In one study (Perna 2010), the numbers randomised to each arm as well as completion rates were unclear. The authors reported that they used regression modelling to impute missing values to conduct the analyses. We thus judged risk of attrition bias for this study as unclear and extracted no data. One study reported no outcome data as the study was closed early due to changes in the chemotherapy protocol (Ingram 2010); we judged this study to be at unclear risk of attrition bias. MacVicar 1989 undertook an analysis of 45 of 62 women; nine of the excluded women were reclassified to more advanced stages of disease than stage II during participation and not analysed for that reason. We judged this study to be at high risk of attrition bias.

Selective reporting

Six studies were at a low risk of reporting bias, as the studies had been registered prospectively or study protocols had been published and the prospectively registered outcomes were in line with the published ones. We considered 10 studies to be at high risk of reporting bias, because reporting of assessed outcomes in the final paper differed from entries in trial registries or study protocols, and no explanation was given. We considered 16 studies to be at an unclear risk for reporting bias, as no study protocol or design paper was available, and no trial registration had taken place; the information was therefore insufficient to judge this item for those studies.

Other potential sources of bias

Nineteen studies were at low risk of selection bias owing to adequate group similarity at baseline, three studies were at unclear risk for selection bias, and 10 studies were at high risk for selection bias, because group similarity at baseline was inadequate.

Adherence and contamination

Different approaches were used among the included studies to measure adherence, that is the level of exercise participation achieved once the woman had agreed to undertake it. Fifteen studies reported exercise levels in non-exercising control groups (contamination) (Cadmus 2007; Courneya 2007: Courneya 2007 AET and Courneya 2007 RET; Crowley 2003; Dodd 2010; Eakin 2012; Gokal 2013; Haines 2010; Hayes 2013: Hayes 2013 FtF and Hayes 2013 Tel; Hornsby 2014; Husebo 2014; Mock 2004; Perna 2010; Reis 2013; Travier 2015; van Waart 2014: van Waart 2014 high and van Waart 2014 low). A high percentage of women (up to 70% in Dodd 2010) in the control groups reported to be regularly exercising or had a high level of activity. In a study with two exercise groups (Hayes 2013: Hayes 2013 FtF and Hayes 2013 Tel), the usual-care group was more active than one of the exercise groups and as active as the other exercise group, according to the survey used.

In six studies, women adhered adequately to the exercise intervention, and in four studies this was unclear. In the remaining 22 studies, adherence to the exercise intervention was so low that we judged it to cause a high risk of bias. The amount of contamination was low in two studies, high in 10 studies, and unclear in the remaining 20 studies.

Effects of interventions

See: **Summary of findings for the main comparison** Exercise compared with control for women receiving adjuvant therapy for breast cancer

Effectiveness of exercise programmes

Most trial authors reported study results as follow-up values, which we pooled. When outcomes were assessed with different instruments, follow-up values and change scores could not be pooled. We performed meta-analyses for physical fitness, fatigue, cancer-specific quality of life, cancer site-specific quality of life, depression, cognitive function, strength, subjective upper body function, arm morbidity, anxiety, mood disturbance, self esteem, physical activity, gait and balance, and lymphoedema.

Studies that were included in the meta-analysis for physical fitness predominantly either measured performance, for example distance walked in a given time, or maximum oxygen uptake. Studies that were included in the meta-analysis for fatigue predominantly applied the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale. Studies that were included in the meta-analysis for cancer-specific quality of life either used the Functional Assessment of Cancer Therapy-General (FACT-G) or the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 36 (EORTC QLQ-C30) questionnaires. Studies that were included in the meta-analysis for cancer site-specific quality of life all used the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire. Studies that were included in the meta-analysis for depression predominantly used the Center for Epidemiological Studies-Depression scale (CES-D). The two studies that were included in the meta-analysis for cognitive function both used the Trail Making Test.

Primary outcomes

Physical fitness

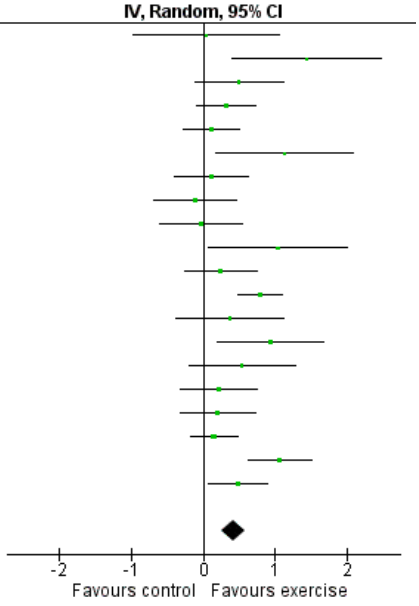
Twelve studies applied tests of cardiorespiratory fitness (Battaglini 2004; Cornette 2013; Courneya 2007 (Courneya 2007 AET and Courneya 2007 RET); Crowley 2003; Dodd 2010; Drouin 2002; Hornsby 2014; MacVicar 1989; Schmidt 2014; Segal 2001 (Segal 2001 SD and Segal 2001 SU); Steindorf 2014; Travier 2015), eight studies assessed physical performance via timed walking distances (Caldwell 2009; Campbell 2005; Haines 2010; Husebo 2014; Mock 2004; Mutrie 2007; Reis 2013; Schwartz 2007 (Schwartz 2007 AET and Schwartz 2007 RET)), and two studies used other physical performance tests (Hayes 2013 (Hayes 2013 FtF and Hayes 2013 Tel); van Waart 2014 (van Waart 2014 high and van Waart 2014 low)). Hayes 2013 assessed heart rate at the end of test completion, and van Waart 2014 assessed endurance time in minutes.

Meta-analysis was feasible for 15 of those 22 studies (1310 women) yielding 20 comparisons (Caldwell 2009; Campbell 2005; Cornette 2013; Courneya 2007 (Courneya 2007 AET and Courneya 2007 RET); Drouin 2002; Haines 2010; Hayes 2013 (Hayes 2013 FtF and Hayes 2013 Tel); Hornsby 2014; Husebo 2014; Mutrie 2007; Reis 2013; Schwartz 2007 (Schwartz 2007 AET and Schwartz 2007 RET); Segal 2001 (Segal 2001 SD and Segal 2001 SU); Travier 2015; van Waart 2014 (van Waart 2014 high and van Waart 2014 low)). The standardised mean difference (SMD) for the pooled data was 0.42 (95% confidence interval (CI) 0.25 to 0.59; I^2 = 49%; Analysis 1.1; Figure 3). There was moderate heterogeneity with an I^2 of 49%, which could be explained by the wide range of exercise interventions and outcome assessment protocols in the different studies.

Figure 3. Forest plot of comparison: 1 Exercise versus control, outcome: 1.1 Physical fitness.

Study or Subgroup	Exercise Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Caldwell 2009	1,761.87	343.7	7	1,749	245.47	8	2.3%	0.04 [-0.97, 1.06]
Campbell 2005	1,423	261	10	1,083	176	9	2.2%	1.44 [0.41, 2.48]
Cornette 2013	549	53	20	517.5	69.3	22	4.6%	0.50 [-0.12, 1.11]
Courneya 2007 AET	25.7	7.4	71	23.5	5.4	36	6.9%	0.32 [-0.08, 0.72]
Courneya 2007 RET	24.2	6.1	77	23.5	5.4	37	7.1%	0.12 [-0.27, 0.51]
Drouin 2002	22.6	6.2	13	16.6	2.2	8	2.5%	1.13 [0.17, 2.09]
Haines 2010	545	83	27	535	88	30	5.5%	0.12 [-0.41, 0.64]
Hayes 2013 FtF	-123.2	15.36	38	-121.3	19.17	16	4.9%	-0.11 [-0.70, 0.47]
Hayes 2013 Tel	-121.7	14.92	42	-121.3	19.17	16	5.0%	-0.02 [-0.60, 0.55]
Hornsby 2014	22.1	7	9	16	4	10	2.4%	1.04 [0.06, 2.01]
Husebo 2014	644.02	63.3	29	628.33	60.44	31	5.7%	0.25 [-0.26, 0.76]
Mutrie 2007	1,135	143	82	984	221	92	8.2%	0.80 [0.49, 1.11]
Reis 2013	1,568	259.8	12	1,433	398.4	17	3.6%	0.38 [-0.37, 1.12]
Schwartz 2007 AET	1,228	322	22	944	241	12	3.6%	0.93 [0.19, 1.68]
Schwartz 2007 RET	1,055	177	21	944	241	11	3.6%	0.54 [-0.20, 1.28]
Segal 2001 SD	26.3	5.3	40	25.1	6.1	20	5.3%	0.21 [-0.33, 0.75]
Segal 2001 SU	26.2	5.1	42	25.1	6.1	21	5.5%	0.20 [-0.33, 0.72]
Travier 2015	21.51	5.52	83	20.71	4.9	63	8.0%	0.15 [-0.18, 0.48]
van Waart 2014 high	13.7	9	71	5.1	5.4	33	6.5%	1.06 [0.62, 1.50]
van Waart 2014 low	9	9	69	5.1	5.4	33	6.7%	0.48 [0.06, 0.90]
Total (95% CI)			**785**			**525**	**100.0%**	**0.42 [0.25, 0.59]**

Heterogeneity: Tau² = 0.07; Chi² = 37.53, df = 19 (P = 0.007); I² = 49%
Test for overall effect: Z = 4.81 (P < 0.00001)



We could not transform data from two studies for meta-analysis requirements (Crowley 2003; MacVicar 1989). Both studies reported small but statistically significant improvements. Another study reported no group differences in the ITT analysis for the 12-minute walk test but presented no data for the ITT analysis (Mock 2004). Four studies reported neither data nor descriptive results for cardiorespiratory fitness. One study provided only a comparison of means without standard deviations for cardiorespiratory fitness data (Battaglini 2004).

We rated the result of a statistically significant improvement in physical fitness as moderate-quality evidence due to lack of blinding, low adherence, and high or unclear contamination in most of the studies and because many randomisation and allocation procedures were unclear. Furthermore, there was a considerable number of women (390 in 4 studies) for whom no data were reported. There was no indication of publication bias from examination of the funnel plot for this outcome. See Summary of findings for the main comparison.

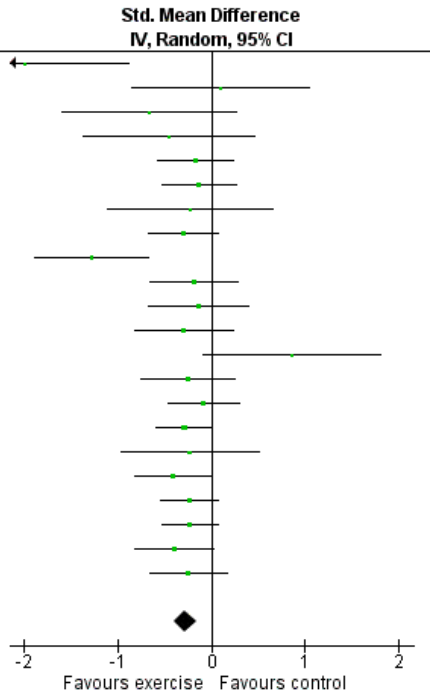
Fatigue

Meta-analysis was possible for 19 studies (1698 women) yielding 22 comparisons (Battaglini 2004; Caldwell 2009; Campbell 2005; Cornette 2013; Courneya 2007 (Courneya 2007 AET and Courneya 2007 RET); Drouin 2002; Eakin 2012; Gokal 2013; Haines 2010; Hayes 2013 (Hayes 2013 FtF and Hayes 2013 Tel); Hornsby 2014; Husebo 2014; Mock 2004; Mutrie 2007; Reis 2013; Schmidt 2014; Steindorf 2014; Travier 2015; van Waart 2014 (van Waart 2014 high and van Waart 2014 low)). Several tools were used to measure fatigue: the FACIT-F scale, the (revised) Piper Fatigue Scale, the Multidimensional Fatigue Inventory, the Schwartz Cancer Fatigue Scale, and the Fatigue Assessment Questionnaire and the Fatigue Quality List. The SMD between intervention and control was -0.28 (95% CI -0.41 to -0.16; I^2 = 29%; Analysis 1.2; Figure 4), favouring the exercise group. Two studies did not report data for fatigue (Crowley 2003; Dodd 2010). Both studies reported that there were no statistically significant group differences. We assumed that their results would not have substantially influenced the pooled result because they involved only 22 and 119 women, respectively. We rated the result as moderate-quality evidence due to lack of blinding, low adherence, and high or unclear contamination and because the allocation concealment procedures in many studies were unclear. The funnel plot was asymmetrical when Battaglini 2004 was included; otherwise there was no indication of publication bias from examination of the funnel plot for this outcome, and we did not downgrade for publication bias. See Summary of findings for the main comparison.

Figure 4. Forest plot of comparison: 1 Exercise versus control, outcome: 1.2 Fatigue.

Study or Subgroup	Exercise Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Battaglini 2004	0.84	1.13	10	3.23	1.16	10	1.1%	-2.00 [-3.12, -0.88]
Caldwell 2009	10.5	6.41	8	10	2.6	9	1.5%	0.10 [-0.85, 1.05]
Campbell 2005	2.43	1.94	10	4.35	3.48	9	1.6%	-0.66 [-1.59, 0.27]
Cornette 2013	41.9	14.8	10	49.8	18.4	9	1.6%	-0.45 [-1.37, 0.46]
Courneya 2007 AET	-36.8	10.4	74	-34.9	12.5	36	6.1%	-0.17 [-0.57, 0.23]
Courneya 2007 RET	-36.3	9.4	76	-34.9	12.5	37	6.2%	-0.13 [-0.53, 0.26]
Drouin 2002	3.4	1.9	13	3.9	2.4	8	1.7%	-0.23 [-1.11, 0.66]
Eakin 2012	-36.95	11.05	58	-33.7	10.77	53	6.6%	-0.30 [-0.67, 0.08]
Gokal 2013	26.04	3.8	25	33.6	7.29	25	3.3%	-1.28 [-1.89, -0.67]
Haines 2010	11.1	4.2	36	11.9	4.5	34	4.9%	-0.18 [-0.65, 0.29]
Hayes 2013 FtF	-36	11.65	45	-34.4	11.26	19	4.0%	-0.14 [-0.67, 0.40]
Hayes 2013 Tel	-37.3	8.99	45	-34.4	11.26	20	4.1%	-0.29 [-0.82, 0.23]
Hornsby 2014	-32.8	14.8	9	-42.2	3.4	10	1.5%	0.86 [-0.09, 1.81]
Husebo 2014	12.01	4.38	29	13.13	4.47	31	4.4%	-0.25 [-0.76, 0.26]
Mock 2004	3.5	2.4	54	3.7	2.6	54	6.5%	-0.08 [-0.46, 0.30]
Mutrie 2007	-120.8	26.7	82	-113.3	25	92	8.5%	-0.29 [-0.59, 0.01]
Reis 2013	-136.8	15.67	12	-132.9	16.85	17	2.4%	-0.23 [-0.97, 0.51]
Schmidt 2014	36.1	20.6	49	44.8	21	46	5.9%	-0.41 [-0.82, -0.01]
Steindorf 2014	5.4	2.3	77	5.9	1.9	78	8.0%	-0.24 [-0.55, 0.08]
Travier 2015	11.82	4.23	91	12.74	3.69	82	8.5%	-0.23 [-0.53, 0.07]
van Waart 2014 high	13.1	3.9	71	14.7	4.2	33	5.8%	-0.40 [-0.81, 0.02]
van Waart 2014 low	13.7	3.9	69	14.7	4.2	33	5.8%	-0.25 [-0.66, 0.17]
Total (95% CI)			**953**			**745**	**100.0%**	**-0.28 [-0.41, -0.16]**

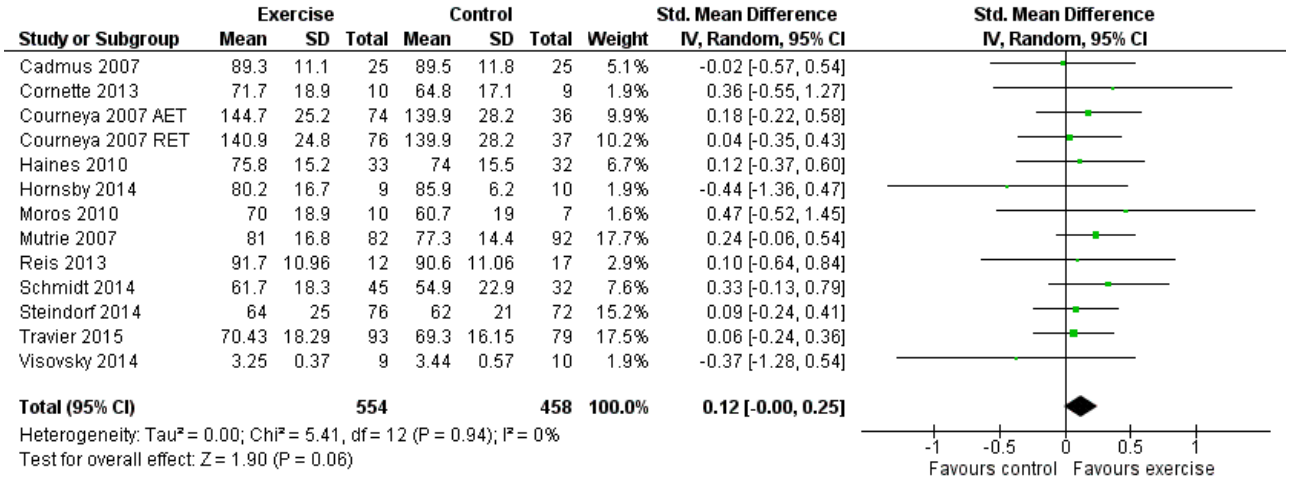
Heterogeneity: Tau² = 0.02; Chi² = 29.57, df = 21 (P = 0.10); I² = 29%
Test for overall effect: Z = 4.50 (P < 0.00001)



Cancer-specific quality of life

Sixteen studies examined effects of exercise on cancer-specific quality of life (Cadmus 2007; Campbell 2005; Cornette 2013; Courneya 2007 (Courneya 2007 AET and Courneya 2007 RET); Dodd 2010; Haines 2010; Hornsby 2014; Moros 2010; Mutrie 2007; Reis 2013; Schmidt 2014; Segal 2001 (Segal 2001 SD and Segal 2001 SU); Steindorf 2014; Travier 2015; van Waart 2014 (van Waart 2014 high and van Waart 2014 low); Visovsky 2014). Cancer-specific quality of life was measured with either the FACT-G scale or the EORTC QLQ-C30 questionnaire. Twelve studies (1012 women) reported final values, and one study reported change scores for this outcome (Campbell 2005). Meta-analysis of the 12 studies reporting final values showed a SMD of 0.12 (95% CI 0.00 to 0.25; I^2 = 0%; Analysis 1.3; Figure 5) (Cadmus 2007; Cornette 2013; Courneya 2007 (Courneya 2007 AET and Courneya 2007 RET); Haines 2010; Hornsby 2014; Moros 2010; Mutrie 2007; Reis 2013; Schmidt 2014; Steindorf 2014; Travier 2015; Visovsky 2014). The study reporting change scores found statistically significant differences between groups, favouring the exercise group, in cancer-specific quality of life, using the FACT-G (Campbell 2005).

Figure 5. Forest plot of comparison: 1 Exercise versus control, outcome: 1.3 Cancer-specific quality of life.



Segal 2001 (Segal 2001 SD and Segal 2001 SU) reported no significant differences between groups for cancer-specific quality of life measured with FACT-G, but reported no data. van Waart 2014 (van Waart 2014 high and van Waart 2014 low) assessed cancer-specific quality of life with the EORTC QLQ-C30, but reported no summary score and no score for global health, therefore we did not use data in the meta-analysis. Results for the subscales were all in favour of the exercise groups, some reaching statistical significance and some not. One publication related to another study reported assessment of cancer-specific quality of life with the Multidimensional Quality of Life scale, Cancer version (MQOLS-Ca) (Dodd 2010), but neither data nor descriptive results were reported. Taken together, the reported results of studies that could not be included in the meta-analysis seem to be in line with the pooled result. Results that were not reported concerned less than 10% of all women. We rated the result as moderate-quality evidence due to lack of blinding, low adherence and unclear or high contamination, and a high rate of incomplete outcome data. We did not detect an indication of publication bias from the funnel plot. See Summary of findings for the main comparison.

Health-related quality of life

Four studies examined generic health-related quality of life (assessed via MOS 36-Item Short Form Health Survey (MOS SF-36)) (Cadmus 2007; Crowley 2003; Segal 2001 (Segal 2001 SD and Segal 2001 SU); Travier 2015). We did not perform a meta-analysis because only data for subscales, but no data for physical and mental health summary measures, were presented. The studies did not find statistically significant differences between groups. Another study assessed generic health-related quality of life via the EQ-5D VAS (score range 0 to 100) and did not find statistically significant differences between groups: mean difference (MD) 1.10 (95% CI -5.28 to 7.48; Analysis 1.4) (Haines 2010). We rated this result as low-quality evidence due to lack of blinding, low adherence and high contamination, a high rate of incomplete outcome data, and high risk of bias for group similarity at baseline. Additionally, we further downgraded for imprecision because of a small number of participants and because the null effect and an appreciable benefit were included in the confidence interval for the mean difference. With only one study extracted for the analysis, examination of the funnel plot for publication bias was not possible. We did not downgrade for publication bias. See Summary of findings for the main comparison.

Cancer site-specific quality of life

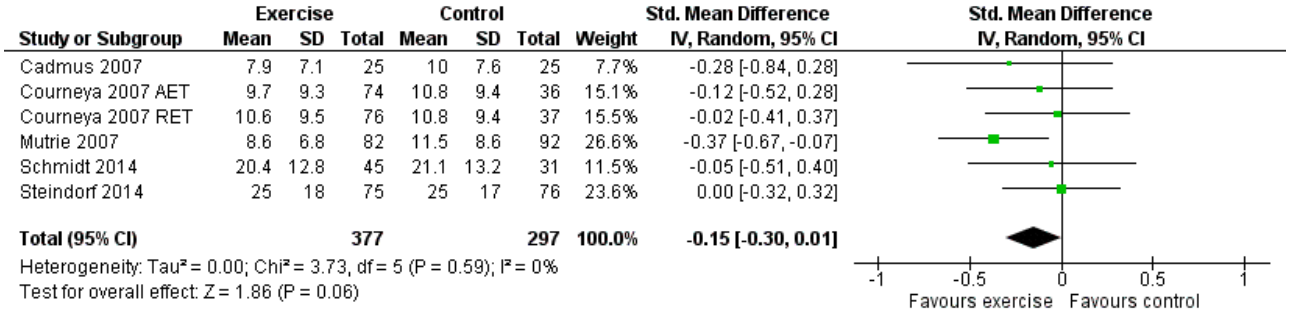
Ten studies examined the effects of exercise on cancer site-specific quality of life (Cadmus 2007; Campbell 2005; Eakin 2012; Haines 2010; Hayes 2013 (Hayes 2013 FtF and Hayes 2013 Tel); Hornsby 2014; Mutrie 2007; Schmidt 2014; Segal 2001 (Segal 2001 SD and Segal 2001 SU); Steindorf 2014). We could extract data for meta-analysis from four studies (262 women) (Cadmus 2007; Campbell 2005; Hornsby 2014; Mutrie 2007), which had all used the FACT-B questionnaire (score range 0 to 144): MD 4.24 (95% CI -1.81 to 10.29; I^2 = 25%; Analysis 1.5). Three studies did not report a summary score of the EORTC QLQ-BR23 questionnaire and were therefore not included in the meta-analysis (Haines 2010; Schmidt 2014; Steindorf 2014). Segal 2001 (Segal 2001 SD and Segal 2001 SU - 123 women) reported finding no significant differences between groups for cancer site-specific quality of life measured with the FACT-B questionnaire, but reported no data. We rated the result for cancer site-specific quality of life as low-quality evidence due to lack of blinding, low adherence, an unclear or high amount of contamination in three of the four studies in the meta-analysis, and because two of four allocation concealment procedures were unclear. Furthermore, the number of women included in the meta-analysis was small (n = 262), and the null effect as well as an appreciable benefit were included in the confidence interval for the mean difference, leading to further downgrading for imprecision. The four studies in the meta-analysis were not sufficient for the examination of publication bias in the funnel plot, as at least 10 studies were considered a sufficient number. We did not downgrade for publication bias. See Summary of findings for the main comparison.

Depression

Seven studies examined group differences for depression (Cadmus 2007; Courneya 2007: Courneya 2007 AET and Courneya 2007 RET; Dodd 2010; Mutrie 2007; Perna 2010; Schmidt 2014; Steindorf 2014). Meta-analysis was possible for five studies (674 women) yielding six comparisons. Depression was assessed either with the Beck Depression Inventory (BDI) or with the Center for Epidemiological Studies-Depression scale (CES-D). The SMD between intervention

and control was -0.15 (95% CI -0.30 to 0.01; I^2 = 0%; Analysis 1.6; Figure 6). Two studies involving 51 and 119 women (Dodd 2010 and Perna 2010, respectively) did not report their data for depression, or it was not possible to extract data due to lack of information. Being borderline significant, their reported results might not necessarily alter that of the meta-analysis, but they might contribute to a more or less clear inclusion of the null effect: one study reported finding a statistically significant effect in favour of the exercise group (Perna 2010), and the second study reported that depression scores did not change in any of the groups (Dodd 2010). We rated the result as moderate-quality evidence due to lack of blinding, low adherence, and unclear or high contamination. The five studies in the meta-analysis were not sufficient for the examination of publication bias in the funnel plot, as at least 10 studies were considered a sufficient number. We did not downgrade for publication bias. See Summary of findings for the main comparison.

Figure 6. Forest plot of comparison: 1 Exercise versus control, outcome: 1.6 Depression.



Cognitive function

Two studies including a total of 213 women examined the effects of exercise on cognitive function with the Trail Making Test (Schmidt 2014; Steindorf 2014). The MD between intervention and control was -11.55 (95% CI -22.06 to -1.05; I^2 = 0%; Analysis 1.7). Another study reported in their published study protocol that it aimed to assess cognitive function besides psychosocial well-being, but the results paper did not mention the cognitive function outcome (Gokal 2013). Crowley 2003 reported having assessed attention performance with the Attention Functional Index, finding no statistically significant difference between groups. Data could not be extracted. Considering the relatively small number of women in the meta-analysis, and missing data or no evidence of a difference for another 72 women outside the meta-analysis, we can make a conclusion on the effect only under reservation. We rated the result as low-quality evidence due to lack of blinding, low and unclear adherence and unclear contamination, and because group similarity at baseline for Schmidt 2014 was at high risk of bias. Schmidt 2014 reported a higher number of participants with depression, which often leads to impairment of cognitive function, in the control group. Our confidence in the result was lowered further because of imprecision (a small number of women). The two studies in the meta-analysis were not sufficient for the examination of publication bias in the funnel plot as at least 10 studies were considered a sufficient number. We did not downgrade for publication bias. See Summary of findings for the main comparison.

Secondary outcomes

Strength

Fourteen studies reported assessment of changes in muscular strength (Battaglini 2004; Cornette 2013; Courneya 2007 (Courneya 2007 AET and Courneya 2007 RET); Crowley 2003; Drouin 2002; Haines 2010; Hayes 2013 (Hayes 2013 FtF and Hayes 2013 Tel); Ingram 2010; Schmidt 2014; Schwartz 2007 (Schwartz 2007 AET and Schwartz 2007 RET); Steindorf 2014; Travier 2015; van Waart 2014 (van Waart 2014 high and van Waart 2014 low); Visovsky 2014). We could extract data from nine studies yielding 13 comparisons for the meta-analysis (Battaglini 2004; Cornette 2013; Courneya 2007 (Courneya 2007 AET and Courneya 2007 RET); Drouin 2002; Haines 2010; Hayes 2013 (Hayes 2013 FtF and Hayes 2013 Tel); Schwartz 2007 (Schwartz 2007 AET and Schwartz 2007 RET); Travier 2015; van Waart 2014 (van Waart 2014 high and van Waart 2014 low)), which showed a SMD of 0.27 (95% CI 0.04 to 0.50; I^2 = 59%; 912 women; Analysis 1.8). The heterogeneity could be explained by a wide range of interventions and outcome assessment protocols.

Two studies reported significant improvements in muscle strength (Schmidt 2014; Steindorf 2014), but did not report data for the results. One study reported finding no significant change in upper or lower body strength between the two groups across the study period (Crowley 2003), but did not report data for the results. One study measuring strength was finished early with no reported results (Ingram 2010), while another study did not report results about strength (Visovsky 2014).

We rated the result of a statistically significant improvement in strength as moderate-quality evidence due to lack of blinding, low adherence and mostly unclear amount of contamination, and because many allocation procedures were unclear. We did not detect an indication of publication bias from the funnel plot.

The studies used different assessment protocols to measure muscular strength. Extracted data for the studies in the meta-analysis is from the following assessment protocols: leg press strength (Cornette 2013; Haines 2010), grip strength (Drouin 2002; Travier 2015 - right hand; van Waart 2014), overhead press, chest (Courneya 2007: Courneya 2007 AET and Courneya 2007 RET; Schwartz 2007: Schwartz 2007 AET and Schwartz 2007 RET), overall muscular strength (Battaglini 2004), and upper body function (strength and endurance) (Hayes 2013: Hayes 2013 FtF and Hayes 2013 Tel).

Subjective upper body function

Furthermore, two studies reported subjective upper body function measured with the Disability of Arm, Shoulder and Hand

Questionnaire (DASH) (Eakin 2012; Hayes 2013: Hayes 2013 FtF and Hayes 2013 Tel). There was no statistically significant difference between groups in the meta-analysis: MD -0.52 (95% -4.45 to 3.41; 231 women; Analysis 1.9). We rated the result as low-quality evidence due to lack of blinding, low adherence and high contamination, and because the allocation concealment procedures were unclear. The group similarity at baseline was at high risk of bias as well. Furthermore, the number of participants was small, and confidence intervals were wide, raising concerns about imprecision, which further lowered our confidence in the result.

Shoulder mobility

Two studies measured shoulder range of motion (Haines 2010; Reis 2013), and one study reported a shoulder mobility score (Mutrie 2007). We could only extract data for the shoulder mobility score, and found a statistically significant difference between groups: MD 3.10 (95% CI 1.54 to 4.66; 174 women; 1 study; Analysis 1.10). Two further studies reported assessment of shoulder range of motion in their respective design papers, but did not mention the outcome in the final publications (Schmidt 2014; Steindorf 2014). We rated the result as low-quality evidence due to lack of blinding, low adherence, and an unclear amount of contamination in the one study that reported results. The small number of participants and the lack of data reporting in four of five studies further lowered our confidence in the result.

Arm morbidity

Two studies used the FACT-B + 4 questionnaire, which for cancer site-specific quality of life includes four questions in addition to the FACT-B about arm morbidity and lymphoedema (higher scores mean less upper extremity impairment) (Eakin 2012; Hayes 2013: Hayes 2013 FtF and Hayes 2013 Tel). Meta-analysis of the two studies yielding three comparisons showed a MD between groups of 1.11 (95% CI -4.07 to 6.29; I^2 = 0%; 240 women; Analysis 1.11). We rated the result as low-quality evidence due to lack of blinding, unclear allocation concealment, low adherence and high contamination, and imprecision (small number of participants).

Other psychological distress outcomes

Anxiety

Three studies assessed anxiety using the State-Trait Anxiety Inventory (STAI) (Cadmus 2007; Courneya 2007: Courneya 2007 AET and Courneya 2007 RET; Eakin 2012); Eakin 2012 used the short form of the questionnaire, and Cadmus 2007 reported that they only used the state anxiety and not the trait anxiety scale. Cadmus 2007 found a small, not statistically significant effect. Meta-analysis of the two studies using the whole questionnaire yielding three comparisons found no statistically significant difference between groups: MD -1.45 (95% CI -4.36 to 1.46; 331 women; Analysis 1.12) (Courneya 2007: Courneya 2007 AET and Courneya 2007 RET; Eakin 2012). We rated the result as low-quality evidence due to lack of blinding, low adherence, and high or unclear contamination. The rather small number of participants further lowered our confidence in the results.

Mood disturbances

Meta-analysis of data from three small studies assessing mood disturbances showed a SMD of -1.00 (95% CI -1.40 to -0.60; I^2 = 0%; 111 women; Analysis 1.13) (Drouin 2002; Gokal 2013; Yang 2011). One study used the long version of the Profile of Mood States (POMS) questionnaire (Drouin 2002), whereas the other two studies used the short form of the questionnaire (Gokal 2013; Yang 2011). We rated the statistically significant result of diminished mood disturbances as low-quality evidence due to lack of blinding, low adherence and unclear contamination in two of the three studies, and because the allocation concealment procedures of the three studies were unclear. The small number of participants (n = 111) further lowered our confidence in the results.

Psychological distress

Another study used the General Health Questionnaire to assess psychological distress and did not find a statistically significant difference between groups: MD -1.47 (95% CI -9.38 to 6.44) (Moros 2010). One study measured negative and positive affects with the Positive and Negative Affect Schedule and found a statistically significant difference for positive affects but not for negative affects (positive affects: MD 4.10, 95% CI 1.38 to 6.82; negative affects: MD -2.10, 95% CI -4.18 to -0.02) (Mutrie 2007). Cadmus 2007 reported perceived stress and happiness; in this one study stress did not show a statistically significant difference (MD -3.10; 95% CI -6.63 to 0.43), and neither did happiness (MD -0.90; 95% CI -9.92 to 8.12).

Anxiety and Depression

Four studies used the Hospital Anxiety and Depression Scale to examine symptoms of depression and anxiety in one questionnaire (Cornette 2013; Gokal 2013; Travier 2015; van Waart 2014: van Waart 2014 high and van Waart 2014 low). Cornette 2013 reported final values for the summary score and found a statistically significant difference between groups: MD -6.10 (95% CI -9.65 to -2.55; 20 women; Analysis 1.14). The other three studies reported finding no statistically significant differences between groups for the summary score. van Waart 2014 did not report any data. Travier 2015 and Gokal 2013 additionally reported final values for the depression and anxiety subscales.

Due to the differences of the outcome assessment instruments and the differing utilisation of summary scores and subscales, we did not pool the data from the studies, apart from those using the POMS. We rated the results from the single studies as low-quality evidence due to the high risk of bias in all of the studies and the small numbers of participants.

Sleep disturbances

Dodd 2010 and van Waart 2014 (van Waart 2014 high and van Waart 2014 low) reported sleep quality as an outcome, measured with the General Sleep Disturbance Scale and the Pittsburgh Sleep Quality Index respectively, but did not report results. Dodd 2010 reported only that no group differences were detected over time.

Self esteem

Three studies examined the effects of exercise on self esteem with the Rosenberg self-esteem scale (Cadmus 2007; Courneya 2007: Courneya 2007 AET and Courneya 2007 RET; Gokal 2013). We found no statistically significant difference in the meta-analysis: MD 1.69 (95% CI -0.01 to 3.39; 323 women; Analysis 1.15). The heterogeneity of 57% was introduced by Gokal 2013. Removal of Gokal 2013 in a sensitivity analysis lowered the heterogeneity to 0% with a MD of 0.97 (95% CI -0.28 to 2.21). We rated the result as low-quality evidence due to lack of blinding, low adherence and high or unclear contamination in two studies, and unexplained heterogeneity.

Physical activity behaviour

Meta-analysis of seven studies showed a SMD of 0.29 (95% CI 0.12 to 0.47; 549 women; Analysis 1.16) (Caldwell 2009; Cornette 2013; Eakin 2012; Hayes 2013: Hayes 2013 FtF and Hayes 2013 Tel; Husebo 2014; Mutrie 2007; Yang 2011). Six further studies also examined the effects of exercise on physical activity, but they did not report data that could be used for meta-analysis (Cadmus 2007; Gokal 2013; Hornsby 2014; Mock 2004; Perna 2010; van Waart 2014: van Waart 2014 high and van Waart 2014 low). However, three of these studies reported that there were no statistically significant group differences for physical activity (Hornsby 2014; Mock 2004; van Waart 2014: van Waart 2014 high and van Waart 2014 low). On the other hand, Perna 2010 reported that there were significantly higher LTEQ (leisure time exercise questionnaire) scores in the intervention group than in controls.

We rated the result as moderate-quality evidence due to lack of blinding, low adherence and high or unclear contamination, and because many (six of seven) allocation concealment procedures were unclear.

Multidimensional outcomes

Self efficacy

One study reported that confidence to exercise (self efficacy) increased significantly more in the intervention group than in the control group (Eakin 2012). We could not extract data. A second study reported that there were no statistically significant differences between groups for physical self efficacy (Crowley 2003). Another study reported assessment of self efficacy regarding the performance of physical activity in the design paper, but did not mention the outcome in the publication of study results (Travier 2015).

Functioning in daily life and return to work

One study reported that there were no statistically significant differences for functioning in daily life for either of the two exercise groups (van Waart 2014: van Waart 2014 high and van Waart 2014 low). Functioning in daily life was measured with the Impact on Participation and Autonomy (IPA) instrument. Another study reported assessment of perceived impact of the disease on participation and autonomy assessed with the same instrument (IPA) in the study design paper, but did not mention the outcome in the final publication (Travier 2015). The first study, van Waart 2014 (van Waart 2014 high and van Waart 2014 low), additionally used the study-specific "Return to work questionnaire", and reported that at the end of the intervention a significantly greater number of participants in the exercise groups were working than in the usual-care group, and that at follow-up the intervention groups had significantly higher return-to-work rates than the usual-care group and worked a significantly higher percentage of the pre-illness hours on the job. We could not extract data.

Symptom severity and symptom interference

One small study used the Taiwanese version of the MD Anderson Symptom Inventory (MDASI-T) to assess symptom severity and symptom interference with daily life and reached statistically significant results for both outcomes: symptom severity MD -1.49 (95% CI -2.36 to -0.62) and symptom interference MD -1.10 (95% CI -1.89 to -0.31) (Yang 2011). Another study used the Symptom Experience Scale, but did not report results (Visovsky 2014). We rated the results as low-quality evidence due to lack of blinding, low adherence and unclear amount contamination, and because the allocation concealment procedure was unclear. The small number of participants (n = 40) further lowered our confidence in the results.

One study reported finding no statistically significant differences between groups for satisfaction with life (Campbell 2005). Another study developed a study-specific functional wellness questionnaire, and did not find a statistically significant difference between groups (Crowley 2003).

Chemotherapy completion

Two studies assessed chemotherapy completion rates, but different outcome measures did not allow for meta-analysis (Courneya 2007: Courneya 2007 AET and Courneya 2007 RET; van Waart 2014: van Waart 2014 high and van Waart 2014 low). van Waart 2014 (van Waart 2014 high and van Waart 2014 low) reported how many women in each group required a dose adjustment of the chemotherapy and the average dose reduction among these women. Statistically significantly fewer women required a dose adjustment for the high-intensity exercise group compared to the low-intensity exercise and the control groups. There was also a statistically significant difference in the average dose reduction between the two exercise groups and the control group.

Courneya 2007 (Courneya 2007 AET and Courneya 2007 RET) assessed chemotherapy completion rate as the "average relative dose-intensity (RDI) for the originally planned regimen based on standard formulas". The study reported the percentage of women in each group that received at least 85% of their planned RDI, and found no statistically significant differences between groups.

Other side effects relating to adjuvant cancer treatment: neuropathy symptoms, endocrine symptoms, pain, gait and balance, nausea

Neuropathic pain was measured with the neuropathic pain scale in one study (Hayes 2013: Hayes 2013 FtF and Hayes 2013 Tel), while another study, Visovsky 2014, measured neuropathy symptoms with the FACT-Taxane scale in women treated with taxanes. Neither study reached statistically significant results: neuropathic pain (Hayes 2013: Hayes 2013 FtF and Hayes 2013 Tel): MD 3.64 (95% CI -1.32 to 8.60; 130 women; Analysis 1.17) and neuropathy symptoms (Visovsky 2014): MD -0.21 (95% CI -0.75 to 0.33; 19 women; Analysis 1.18). We rated these results as low-quality evidence due to lack of blinding, unclear allocation concealment procedures, low or unclear adherence, and high or unclear contamination. Group similarity at baseline was unclear or at high risk of bias as well. Imprecision due to a small number of participants and wide confidence intervals further lowered our confidence in the results. Visovsky 2014 also reported assessment of cold thermal sensation and vibratory sensation in the trial registration, but did not report these outcomes in the results paper.

Hayes 2013 (Hayes 2013 FtF and Hayes 2013 Tel) measured menopausal symptoms with the Greene Climacteric Scale and found no group differences. No summary score was presented. Mutrie 2007 assessed endocrine symptoms with the FACT for endocrine symptoms (FACT-ES): MD 1.30 (95% CI -1.49 to 4.09; 174 women; Analysis 1.19). We rated the result as low-quality evidence due to lack of blinding, low adherence, and unclear contamination. The small number of participants in this one study reporting a summary score further lowered our confidence in the results.

Dodd 2010 reported pain measured with the Worst Pain Intensity Scale and found no statistically significant differences between groups. No data were reported.

Gait and balance was measured with the Timed Get-up-and-Go Test in two studies (Caldwell 2009; Visovsky 2014), and with a step test in one study (Haines 2010). There was no statistically significant difference between groups in the meta-analysis: SMD 0.10 (95% CI -0.25 to 0.46; 122 women; Analysis 1.20). We rated the result as low-quality evidence due to lack of blinding, low and unclear adherence, and unclear and high contamination. Allocation concealment procedures were unclear in two studies. The small number of participants further lowered our confidence in the result.

Two studies reported nausea as an outcome (Dodd 2010; Winningham 1988). Winningham 1988 assessed nausea with the Symptom Checklist-90 (SCL-90) item for nausea, whereas Dodd 2010 assessed nausea intensity with a subscale of a symptom checklist of 25 commonly experienced symptoms. We did not consider either of these to be valid methods of assessment and therefore did not report data here.

Harms

Twenty-one studies assessed adverse effects due to exercise (Battaglini 2004; Cadmus 2007; Campbell 2005; Cornette 2013; Courneya 2007: Courneya 2007 AET and Courneya 2007 RET; Crowley 2003; Dodd 2010; Drouin 2002; Eakin 2012; Haines 2010; Hornsby 2014; Husebo 2014; Mock 2004; Moros 2010; Schmidt 2014; Schwartz 2007: Schwartz 2007 AET and Schwartz 2007 RET; Segal 2001: Segal 2001 SD and Segal 2001 SU; Steindorf 2014; Travier 2015; Visovsky 2014; Yang 2011). Seven studies observed adverse effects (Crowley 2003; Dodd 2010; Drouin 2002; Eakin 2012; Haines 2010; Hornsby 2014; Husebo 2014). Details of these adverse effects can be found in the Characteristics of included studies table. In general, adverse effects concerned only a very small number of women.

Seven studies described how relevant information on adverse effects was collected. In two studies this was done by the exercise trainers who supervised the intervention (Courneya 2007: Courneya 2007 AET and Courneya 2007 RET; Hornsby 2014). In one of these studies (Hornsby 2014), safety of the supervised aerobic exercise intervention was the primary outcome, and all adverse effects during aerobic training were monitored and reported on the participant case report forms. In one study with a telephone group (Eakin 2012), exercise physiologists recorded adverse effects after each call in case management folders; Husebo 2014 used biweekly telephone calls to monitor adverse effects. The participants in Haines 2010 were told to document adverse effects and accidental falls in a log book. Two studies used standardised questionnaires where participants recorded adverse effects (Schmidt 2014; Steindorf 2014). In one of these two studies (Steindorf 2014), adverse effects reported spontaneously by the participant or observed by therapists were also recorded. Many of the studies did not describe how relevant information was collected or whether surveillance of adverse effects was passive (spontaneously reported by participants) or active (based on structured questionnaires or interviews).

Lymphoedema

Two studies (Courneya 2007: Courneya 2007 AET and Courneya 2007 RET; Hayes 2013: Hayes 2013 FtF and Hayes 2013 Tel) systematically assessed the incidence of lymphoedema. Hayes 2013 (Hayes 2013 FtF and Hayes 2013 Tel) reported four objectively measured cases each in both exercise groups (face to face: n = 67 and telephone: n = 67) and six cases in the usual-care group (n = 60). These numbers reported for Hayes 2013 (Hayes 2013 FtF and Hayes 2013 Tel) were for all women and not only women who exercised concurrently with their adjuvant treatment. Meta-analysis of the two studies yielding four comparisons showed a risk ratio for lymphoedema of 0.71 (95% CI 0.35 to 1.45; 436 women; Analysis 1.21). Crowley 2003 reported lymphoedema as an adverse effect in one woman. Haines 2010 measured the circumference of upper limb segments and reported that changes in the circumference of upper limb segments favoured the intervention group.

We rated the results as low-quality evidence due to lack of blinding, low adherence and a high or unclear amount of contamination, the allocation concealment procedure was unclear in one of the two studies, and group similarity at baseline was at high risk of bias for one study. Furthermore, the null effect and appreciable harm and benefit were included in the confidence interval for the risk ratio. The two studies in the meta-analysis were not sufficient for the examination of publication bias in the funnel plot as at least 10 studies were considered to be a sufficient number. We did not downgrade for publication bias. See Summary of findings for the main comparison.

Effectiveness and adverse effects during follow-up

Several studies assessed effectiveness of exercise during adjuvant therapy after a follow-up period of several months.

Five studies measured physical fitness 18 weeks, in Travier 2015, to six months after the intervention: SMD 0.26 (95% CI -0.06 to 0.57; 612 women; Analysis 2.1) (Cornette 2013; Husebo 2014; Mutrie 2007; Travier 2015; van Waart 2014: van Waart 2014 high and van Waart 2014 low). We rated the result as low-quality evidence due to lack of blinding, low adherence, and unclear or high contamination. Additionally, randomisation and allocation concealment procedures were unclear in several studies. Heterogeneity with an I^2 of 70% could be only partly explained by introduction of Travier 2015, which was the only study with a follow-up period shorter than six months. Removal of the study in the sensitivity analysis still resulted in an I^2 of 40% and a SMD of 0.38 (95% CI 0.121 to 0.63). It remained unclear why a shorter follow-up period would result in a smaller effect for cardiorespiratory fitness. With regard to all of these studies, the large variation in effect and confidence intervals that did not overlap raised concerns about inconsistency, which further lowered our confidence in the result.

Six studies assessed fatigue 18 weeks, in Travier 2015, to six months after the intervention period: SMD -0.21 (95% CI -0.35 to -0.07; 814 women; Analysis 2.2) (Cornette 2013; Courneya 2007: Courneya 2007 AET and Courneya 2007 RET; Husebo 2014; Mutrie 2007; Travier 2015; van Waart 2014: van Waart 2014 high and van Waart 2014 low). We rated the result as moderate-quality evidence due to lack of blinding, low adherence, and unclear or high contamination. Furthermore, randomisation and allocation concealment procedures were unclear in several studies. A sensitivity analysis including only the five studies with a six-month follow-up period also showed a SMD between intervention and control of -0.21 (95% CI -0.37 to -0.05).

Six studies assessed cancer-specific quality of life 12 weeks, in Visovsky 2014, to six months after the intervention: SMD 0.18 (95% CI 0.01 to 0.35; 583 women; Analysis 2.3) (Cornette 2013; Courneya 2007: Courneya 2007 AET and Courneya 2007 RET; Mutrie 2007; Travier 2015; van Waart 2014: van Waart 2014 high and van Waart 2014 low; Visovsky 2014). van Waart 2014 (van Waart 2014 high and van Waart 2014 low) only presented data for subscales and no summary score. We rated the result as moderate-quality evidence due to lack of blinding, low adherence and unclear or high contamination, and because risk of attrition bias was high in two of the five studies in the meta-analysis. Furthermore, randomisation and allocation concealment procedures were unclear in two studies. A sensitivity analysis including only the three studies with a six-month follow-up period showed a SMD between intervention and control of 0.25 (95% CI 0.04 to 0.45) (Cornette 2013; Courneya 2007: Courneya 2007 AET and Courneya 2007 RET; Mutrie 2007).

Two studies assessed depression six months after the intervention period: SMD -0.27 (95% CI -0.48 to -0.06; 378 women; Analysis 2.4) (Courneya 2007: Courneya 2007 AET and Courneya 2007 RET; Mutrie 2007). We rated the result as moderate-quality evidence due to lack of blinding, low adherence, and unclear contamination.

Three studies assessed strength at six months' follow-up: SMD 0.00 (95% CI -0.30 to 0.30; 386 women; Analysis 2.5) (Cornette 2013; Travier 2015; van Waart 2014: van Waart 2014 high and van Waart 2014 low). The heterogeneity, with an I^2 of 49%, was introduced by the high-intensity group (resistance training) of van Waart 2014 high and was reduced to 0% when this study was removed in a sensitivity analysis (SMD -0.11; 95% CI -0.35 to 0.13); thus heterogeneity could be explained. We rated the result as low-quality evidence due to lack of blinding, low adherence and unclear or high contamination, and because there was a high risk of selection bias in two of three studies. Furthermore, allocation concealment procedures were unclear in two studies. The wide confidence interval introduced uncertainty about the magnitude of the effect, and thus confidence in the result was lowered further.

Three studies assessed physical activity at six months' follow-up: SMD 0.28 (95% CI -0.05 to 0.61; 261 women; Analysis 2.6) (Cornette 2013; Husebo 2014; Mutrie 2007). We rated the result as low-quality evidence due to lack of blinding, low adherence, and unclear or high contamination. Additionally, randomisation and allocation concealment procedures were unclear in two of the three studies and there was attrition bias in two studies. Furthermore, imprecision (rather small number of participants and null effect and appreciable benefit included in confidence interval for SMD) further lowered our confidence in the result.

Courneya 2007 (Courneya 2007 AET and Courneya 2007 RET) also reported results for anxiety (MD -3.61; 95% CI -7.24 to 0.03; 201 women; Analysis 2.7) and self esteem (MD 1.20; 95% CI -0.41 to 2.81; 201 women; Analysis 2.8) six months after the intervention, and Mutrie 2007 reported results for endocrine symptoms (MD 1.30; 95% CI -1.65 to 4.25; 177 women; Analysis 2.9) and positive affects (MD -0.59; 95% CI -1.63 to 0.45) and negative affects (MD -1.70; 95% CI -3.62 to 0.22). One study also assessed neuropathy symptoms (MD -0.45; 95% CI -0.98 to 0.08; 19 women; Analysis 2.10) and gait and balance (MD -0.59; 95% CI -1.63 to 0.45; 19 women; Analysis 2.11) 12 weeks after the end of the intervention (Visovsky 2014). We rated all these results as low-quality evidence due to the small number of women in the single studies, lack of blinding, low adherence, and unclear contamination. All 'Risk of bias' items for Visovsky 2014 were at high or unclear risk of bias.

One study with an intervention period of one year reported no significant differences for any outcome after one year, but did not report data (Dodd 2010).

One study reported long-term follow-up data for 18 months and five years in an additional paper from 2012 (Mutrie 2007), which was the longest follow-up period of the included studies. For both follow-up periods, less than 70% of the original participants were included in the analysis, therefore we did not present data here.

Lymphoedema

One study reported lymphoedema incidence eight weeks after the intervention (Hayes 2013: Hayes 2013 FtF and Hayes 2013 Tel). The numbers reported were for all women and not only women who exercised concurrently with their adjuvant treatment (risk ratio 0.79; 95% CI 0.37 to 1.69; 194 women; Analysis 2.12). Otherwise, harms or adverse effects were not reported after a follow-up period.

DISCUSSION

Summary of main results

Exercise during adjuvant treatment for breast cancer improves physical fitness and probably slightly reduces fatigue. It likely leads to little or no difference in depression and cancer-specific quality of life. Women with breast cancer may benefit from exercise during adjuvant cancer treatment through improved cognitive function and slightly improved cancer site-specific quality of life. Exercise may lead to little or no improvement in health-related quality of life and may lower the risk of lymphoedema.

Exercise also probably slightly improves muscular strength and leads to a slightly higher amount of physical activity. Women with breast cancer who exercise during adjuvant treatment may experience fewer mood disturbances, and their shoulder mobility might be slightly improved. For other outcomes such as self esteem, exercise may lead to little or no difference. For some of the outcomes not all studies could be included in the meta-analyses, therefore the results do not reflect the body of evidence as a whole. An improvement for several other outcomes is uncertain, mostly due to scarcity or lack of data.

Overall completeness and applicability of evidence

This review is based on studies with a considerable degree of clinical heterogeneity regarding adjuvant cancer treatment and exercise interventions. It remains to be explored whether differences in adjuvant cancer treatment and exercise intervention actually affect results. In spite of our comprehensive attempts to identify all relevant studies, we retrieved predominantly English language studies for inclusion in this review. This may reflect selective publication of English language studies with statistically significant findings. In addition, most of the included studies were primarily conducted among white women in high-income countries, which makes generalisation of the results to different ethnic groups and countries questionable.

Type of intervention

Exercise interventions varied widely regarding implementation of aerobic or resistance exercise or a combination of both, supervised

or home-based, frequency, duration, and intensity. Furthermore, the reporting of the exercise intervention differed, and details were not always available.

As exercise as such can be seen as a complex intervention, the evaluation of exercise interventions is prone to the diverse challenges associated with evaluating complex interventions.

Key features of complex interventions (according to Craig 2008: the Medical Research Council guidance on complex interventions) applicable to exercise are the:

- number of interacting components, e.g. exercise in a group versus alone; aerobic or resistance exercise; or the empathy of an exercise instructor;
- number and difficulty of behaviours required by those delivering or receiving the intervention, e.g. adherence to the prescribed intensity of exercise or challenging participants to exercise at a higher heart rate;
- number and variability of outcomes, e.g. fatigue, depression, anxiety with a range of scales to assess;
- degree of flexibility or tailoring of the intervention permitted (non-standardisation/reproducibility), e.g. tailoring the exercise intervention according to the motivation level of the group or to the current physical condition of the woman with breast cancer.

The aim of this review was to answer quite a broad review question, namely to assess the effect of exercise per se on several patient-relevant outcomes for women undergoing adjuvant treatment for breast cancer, which is why we included exercise interventions delivered at diverse levels and with a variety of components. Based on this evidence, further steps could be taken to identify and differentiate all the interacting components of exercise interventions.

Type of control

Most studies reported usual care as the control intervention, but they often did not describe this in detail. As studies were conducted in different settings, home-based or at the treatment clinic, and with different types of adjuvant treatment, variation in usual care in the included studies should be taken into account. Some studies offered control interventions in order to establish similar circumstances with regards to time and attention and, if applicable, group interaction.

Type of adjuvant treatment

Women were treated in some studies with radiation treatment only, chemotherapy only, or a combination of the two, resulting in large variation in the duration and frequency of adjuvant treatment as well as differences in possible side effects. We included studies with the latest treatment protocols as well as studies from the 1980s onward, meaning that not only treatment protocols but also drugs to treat side effects were used in many different ways in the included studies. Details on treatment protocols were provided in some, but not all studies, whereas drug treatment of side effects was most often not described.

Timing of outcome assessment and follow-up

As it has been shown that, for example psychological distress of women, diminishes with time after diagnosis, timing of measuring outcomes can make a difference in the magnitude and direction of the effect of the intervention. The same may apply to other outcomes assessed in our review. Timing of outcome assessments was very heterogeneous in the included studies, which should be kept in mind when comparing different studies and interpreting results. Follow-up ranged from no follow-up to five years in one study. Analyses were only possible for a few studies with a maximum follow-up period of six months, as either data reporting was poor or attrition rates were too high for studies with longer follow-up periods. Apart from lymphoedema, which was reported after a short follow-up period in one study, harms or adverse effects were not reported after a follow-up period.

Reporting of outcome measures

A wide range of outcome measures was assessed across the studies, making it difficult to combine outcomes in meta-analysis. Moreover, data reporting was often poor and did not provide estimates of effect size that could be pooled. Assessment and reporting of harms-related data from exercise intervention studies during adjuvant cancer treatment also needs improvement. Future studies should apply so-called core outcome sets to facilitate comparison and meta-analysis (Gargon 2014).

Quality of the evidence

Quality of studies

Due to the nature of exercise as an intervention, blinding of participants and exercise supervisors is not possible. The precise effect of the absence of blinding on the magnitude and direction of the treatment effect is unclear, but constitutes a high risk for performance bias. Furthermore, many outcomes were self reported, which leads to a high inherent risk of detection bias, when blinding of participants is not possible. We decided not to downgrade studies for those 'Risk of bias' items alone. However, reasons for assigning studies a high risk of bias was never due only to lack of blinding, contamination, and/or non-adherence, because other factors such as unclear allocation procedures or high attrition rates were present as well, leading to downgrading of the evidence one level for risk of bias. We included only randomised controlled studies in this version of the review, but 11 studies reported insufficient details on random sequence generation, and 23 provided insufficient details on allocation concealment.

Statistical power

Benefits of exercise interventions may be relatively small. Subsequently, the number of included participants should be great enough to allow for the detection of small differences between groups. The sample sizes in the included studies ranged from 5 to 91 in the intervention group.

Initial fitness level

The individual's level of fitness is an important factor to consider before determining the level of exercise intensity (ACSM 2000). According to the American College of Sports Medicine (ACSM 2000), deconditioned individuals may demonstrate increases in their cardiorespiratory fitness with exercise intensities at the lower end of the intensity continuum, whereas more fit individuals need to work at the higher end of the intensity continuum to improve fitness. A small number of studies limited participation to sedentary women; however, definitions of sedentary varied.

Adherence and contamination

For sedentary individuals, a change in personal health behaviour is required in order to take up regular exercise. Thus, any exercise intervention can additionally be evaluated according to the degree of behavioural change achieved in the intervention group; a lack of adherence can compromise the training stimulus as well as the sustainability of exercise behaviour. According to the American College of Sports Medicine (ACSM 2000), the art of exercise prescription is the "successful integration of exercise science with behavioral techniques that result in long-term program compliance". Some studies applied theory-based methods focused on changing behaviour. Adherence problems do not only arise in terms of participation in exercise sessions and frequency of sessions, but also in terms of the training intensity and duration actually achieved during each exercise session. Insufficient exercise intensity or duration may compromise the training stimulus as a whole. However, these two facets of the training stimulus were poorly evaluated and reported in many of the included studies.

Besides adherence, the extent to which the control group performs exercise (contamination) is a second critical component in exercise studies. Exercise contamination is rarely reported and often only when the exercise programme is home-based. Furthermore, reports of adherence and contamination most often rely on self report by participants, which can lead to over-reporting of adherence but also contamination.

Potential biases in the review process

Despite a well-established methodology for conducting systematic reviews, subjective judgement is inevitable throughout the process. The main limitation of this review was the lack of sufficient information or data in many studies to make a clear judgement in various bias domains. Other limitations were the heterogeneity in the intervention delivered, adjuvant treatment, timing of outcome measurement, and the assessment and reporting of outcome measures with a wide range of outcome measures.

We did not systematically evaluate assessment instruments with regards to their strengths and weaknesses. However, we noted that for the outcome physical activity, the reported activity levels of women with breast cancer were surprisingly high in some studies. Three of seven studies in the meta-analysis for physical activity used the International Physical Activity Questionnaire (IPAQ) (Caldwell 2009; Cornette 2013; Husebo 2014), which has been reported to lead to over-reporting of physical activity (Lee 2011).

Mostly due to limited resources, we did not systematically assess the training stimulus in this version of the review as well as the baseline activity and fitness levels of participants and the application of behaviour change theories in the studies.

Agreements and disagreements with other studies or reviews

Another Cochrane systematic review assessed the effect of exercise during adjuvant therapy for cancer on quality of life (Mishra 2012), and another on fatigue (Cramp 2012). Both reviews included adults with different cancer diagnoses, not only breast cancer. Cramp 2012 also included studies evaluating the effect of exercise after adjuvant therapy, and Mishra 2012 included 10 studies with participants both during and after adjuvant therapy. Both reviews identified benefits on fatigue for participants with breast cancer, which is in agreement with the results of our review. Mishra 2012 reported that exercise interventions resulted in improvements in overall quality of life for all participants, but found no statistically significant difference for women with breast cancer. We did not perform a meta-analysis for overall quality of life because only one study presented a summary measure, whereas the others only reported data for subscales. The single studies reporting that outcome did not result in a significant difference between groups.

Meneses-Echavez 2015 reviewed the effect of supervised exercise during or after adjuvant therapy for breast cancer on cancer-related fatigue, and found benefits as well.

Bourke 2014 published another Cochrane systematic review with the main goal of assessing the effects of interventions to promote exercise behaviour in sedentary people living with and beyond cancer. Eleven of 14 studies were conducted in women with breast cancer, but mostly in women who had finished adjuvant treatment. Interventions resulted in improvements in aerobic exercise tolerance at 8 to 12 weeks in intervention participants compared with controls. Aerobic exercise tolerance was also improved at six months. These findings are in agreement with our review, but participants differed with regard to cancer diagnosis and treatment status.

One systematic review assessed depression and anxiety in addition to fatigue and cancer-specific quality of life in women with breast cancer undergoing adjuvant therapy (Carayol 2013). The authors reported that the exercise intervention led to statistically significant improvements for fatigue, cancer-specific quality of life, and depression, while the decrease in anxiety was "borderline significant". Our results for both cancer-specific quality of life and depression were close to showing a statistically significant difference between groups, favouring exercise, with a lower respectively upper limit of the confidence interval of 0.00 and 0.01. In three of the 17 included studies in the review by Carayol 2013, the intervention was yoga, which we excluded, regarding it as a complex intervention. For depression and anxiety, the authors pooled data from the Hamilton Anxiety and Depression Score with data from the Beck Depression Inventory and Center for Epidemiological Studies-Depression scale, which we did not. Keeping in mind the similar but not identical inclusion criteria, the findings of this review are thus mostly in line with our review.

AUTHORS' CONCLUSIONS

Implications for practice

Exercising while receiving adjuvant treatment for breast cancer is a feasible, supportive self care intervention. Based on current evidence, exercise probably slightly reduces fatigue and improves physical fitness. It likely leads to little or no difference in depression and cancer-specific quality of life. Women with breast cancer may benefit from exercise during adjuvant cancer treatment through improved cognitive function and slightly improved cancer site-specific quality of life. Exercise may lead to little or no improvement in health-related quality of life. Muscular strength and physical activity are probably improved by exercising. Several further outcomes such as shoulder mobility showed slight improvements, and several such as self esteem showed little or no difference, but the quality of the evidence was low.

Exercise adherence during cancer treatment constitutes a challenge, and thus attempts to foster exercise participation might enhance effectiveness. For behaviour changes to occur (the adoption of regular exercise in this instance), it is essential that intervention programmes focus on underlying principles from theories about why people change their behaviours. The social cognitive theory appears to be a promising theoretical framework for promoting exercise behaviour in women with breast cancer (Pinto 2002; Rogers 2004; Rogers 2005). The key construct in the social cognitive theory is self efficacy. Exercise self efficacy can be described either as the confidence to overcome barriers to exercise or as confidence in the ability to perform certain exercise tasks. Self efficacy has proven to be an important correlate of exercise among women with breast cancer. Exercise self efficacy among women with breast cancer during cancer treatment is reported to be lowest when women are nauseated, tired, not interested, lacking time, and lacking exercise enjoyment (Rogers 2006).

Future exercise interventions should target the exercise barriers. Exercise enjoyment, for example, may be addressed through picking up recent trends in the field of fitness, such as Pilates, Nordic walking, Tai Chi, step aerobics, and dancing, of course adequately adjusted to the needs and limitations of the target group. Group exercise or partner-assisted exercises may also increase exercise enjoyment. Time management may be addressed by exercise classes taking place in different locations, choosing venues that are accessible by public transport, and by scheduling classes at various times in the day and evening.

Implications for research

At this stage there is still a lack of evidence for several relevant potential benefits of exercise as well as for harms. The increasing number of studies assessing the benefits and harms of exercise during adjuvant therapy is promising, but while study quality and reporting of studies have certainly improved since the first studies assessing this question, the quality of the evidence is still low for many outcomes. This is due in part to the difficulty of blinding participants and supervising personnel in studies with exercise as an intervention. For other factors that diminish the quality of evidence, such as lack of outcome assessor blinding, or the reporting of methodology and data, an improvement is feasible.

As described above, the actual training stimulus may substantially deviate from the assigned exercise regimen. In efficacy trials investigators need to ensure adherence to the intervention to determine whether exercise interventions in this population work. Exercise programmes should be designed to address exercise facilitators such as exercise enjoyment; this may be achieved by offering a variety of alternating exercise modes that assure an adequate training stimulus. Inclusion of sedentary participants only may be a way to deal with contamination issues, utilising the observation that physical activity and exercise decline during cancer treatment (Irwin 2003). While efforts can and should be made to maximise adherence and to minimise contamination, imperfect adherence and an amount of contamination is even to be expected in efficacy studies, lowering the confidence in the results. In effectiveness trials, we recommend that both adherence and contamination are reported as an outcome measure because poor adherence can render an efficacious intervention ineffective. To date, effectiveness trials are rare, but would be of additional value for this field of research.

Consensus of researchers on outcome measures for exercise studies involving women with breast cancer receiving adjuvant treatment is needed in order to facilitate interpretation and comparison of results across various interventions. The long-term follow-up of exercise interventions also requires attention because some side effects of adjuvant cancer treatment are long term, such as fatigue or deconditioning, and the effects of exercise themselves might have a long-term component. Besides health-related outcome measures, adherence and contamination as well as potential harms should be assessed and reported systematically. Reporting standards for harms should help to inform practitioners and the public on potential harms of exercise interventions during adjuvant cancer treatment (Ioannidis 2004).

Regarding recruitment difficulties and thus the problem of small sample sizes, multisite trials are advisable.

The seven ongoing studies and the two studies awaiting assessment identified during our search also have small sample sizes and assess a wide variety of outcomes with different outcome measures. The majority include interventions with aerobic exercise of moderate intensity and compare exercise to usual care, apart from one study awaiting assessment in which yoga is the control intervention (Lotzke 2016). One study is notable for its rather long intervention period of 12 months, a large estimated number of enrolment of 600 participants, and a planned follow-up of 10 years, including relapse of breast cancer disease, breast cancer-specific mortality, and overall mortality as secondary outcomes (NCT02240836).

Once the effectiveness of exercise - even in widely varying frequency and intensity - for women with breast cancer during adjuvant therapy for different outcomes has been established, the next step is to assess which frequency, intensity, and type of exercise (aerobic, resistance, combination) is most effective for which outcome. There are ongoing and published studies comparing different dose regimens to each other, but which we could not include in our review because they had no usual care or non-exercising control group. The number of studies comparing exercise to not exercising is still much higher, and there are even still feasibility studies underway or currently being published, although feasibility of exercise studies has certainly been proven. The comparison of different dosages of exercise for different outcomes might be a question for several reviews of their own.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Battaglini 2004

Methods	RCT, 2 groups Study start and stop dates: not reported Length of intervention: 15 weeks Length of follow-up: 5 to 7 weeks after the intervention
Participants	20 breast cancer patients due to receive adjuvant therapy
Interventions	Intervention (n = 10): Aerobic and resistance training at 40% to 60% maximum exercise capacity and stretching; 2/week, up to 60 minutes per session Control (n = 10): usual care
Outcomes	• Fatigue: Revised Piper Fatigue Scale • Cardiovascular endurance: Modified Bruce treadmill protocol • Dynamic muscular endurance: Submaximal muscle endurance protocol after Kuramoto and Payne • Body composition: lean body mass (LBM in %), body fat (BF in %) • Total caloric intake: 3-day food diary Outcomes were measured at baseline and postintervention and at 3 time points during treatment

Battaglini 2004 *(Continued)*

	Adverse events: "No cases of injury or any cancer treatment complications impeded subjects in the exercise group from completing the exercise protocol two times a week."
Notes	Funding: Grants obtained through the University of Northern Colorado (Dissertation), University of Northern Colorado, Sponsored Programs and Academic Research Center (2007) Conflicts of interest: The authors declared there was no potential conflict of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Drawing of numbers (1 to 20) by the participants. Participants who drew even numbers were placed into the experimental group, while participants who drew odd numbers were placed into the control group
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants All outcomes	High risk	Not done
Blinding of personnel/care providers All outcomes	High risk	Not reported. Comment: probably not done
Blinding of outcome assessment (detection bias) Fitness outcomes	High risk	Not reported. Comment: probably not done
Blinding of outcome assessment (detection bias) All outcomes except fitness outcomes	High risk	Self reported items
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was no description of missing outcome data or attrition from the trial
Selective reporting (reporting bias)	Low risk	Dissertation with all assessed outcomes available
Group similarity at baseline	Low risk	No significant differences for weight, age, body fat, fitness (cardiorespiratory and strength)
Adherence	Low risk	"The adherence rate among all the subjects was 100%." All study participants completed the study protocol. One participant missed 1 week of exercise for reasons unrelated to the study
Contamination	Unclear risk	Not reported

Cadmus 2007

Methods	RCT, 2 groups Study start and stop dates: March 2004 to July 2006 Length of intervention: 6 months

Cadmus 2007 *(Continued)*

	Length of follow-up: to end of the intervention
Participants	50 newly diagnosed breast cancer patients, aged 35 to 75, who had not yet begun or had only recently begun adjuvant treatment (completed fewer than 2 weeks of radiation or 2 cycles of chemotherapy)
Interventions	Intervention (n = 25): home-based exercise program, type of exercise up to the women's choice, weekly telephone calls, information, heart monitor, activity logs, 60% to 80% of predicted maximal heart rate, 5 days per week, 30 minutes, 120 sessions Control (n = 25): usual care
Outcomes	• happiness: 2-item Fordyce Happiness Measure • self esteem: Rosenberg self-esteem scale • depression: CES-D • anxiety: Spielberger State-Trait Anxiety Inventory (STAI) • stress: Cohen's 10-item Perceived Stress Scale • cancer site-specific quality of life: FACT-B • cancer-specific quality of life: FACT-G • health-related quality of life: MOS SF-36 • body composition: weight change and body fat • physical activity: 7-Day PAL and 7-day pedometer log Outcomes were measured at baseline and 6 months Adverse events: none reported
Notes	Funding: Lance Armstrong Foundation, American Cancer Society, Susan G. Komen, National Institutes of Health Conflict of interest: None reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer program randomly assigned each study participant with equal probability to the exercise group or the usual-care group
Allocation concealment (selection bias)	Low risk	The randomisation code for each participant was obtained by the principal investigator (who was not involved in recruitment or data collection) only after baseline measures for that woman had been completed, and staff conducting clinic visits did not have access to the randomisations program
Blinding of participants All outcomes	High risk	Not done
Blinding of personnel/care providers All outcomes	High risk	Not reported. Comment: probably not done
Blinding of outcome assessment (detection bias) All outcomes except fitness outcomes	High risk	Self reported items
Incomplete outcome data (attrition bias) All outcomes	Low risk	5 women (10%) had missing 6-month data (3 exercisers and 2 usual-care group participants).

Cadmus 2007 *(Continued)*

		All analyses were conducted according to the intention-to-treat principle. Baseline QoL values were carried forward for the 5 IMPACT study participants who had missing 6-month data. Not reported for other outcomes
Selective reporting (reporting bias)	Unclear risk	Study protocol not published prospectively
Group similarity at baseline	Unclear risk	"No differences between exercise and usual care groups at baseline. Exception: exercisers were more likely to receive lumpectomy than usual care group participants ($P < 0.05$)."
Adherence	High risk	Participants performed 144 (SD = 75) minutes of activity per week throughout the 6 months (range: 0 to 253). 64% met the goal of 150 min per week
Contamination	High risk	Women didn't have to be sedentary at baseline. 36% of IMPACT study control group participants reported no sports/recreational physical activity at 6-month follow-up; the remaining 64% of controls reported between 35 and 378 min/week of activity, with a median of 181 minutes. Obese cohort (mean BMI > 30 kg/m^2)

Caldwell 2009

Methods	RCT, 2 groups Study start and stop dates: not reported Length of intervention: 12 weeks Length of follow-up: 2 weeks after last chemotherapy Study was discontinued due to peripheral neuropathy
Participants	25 breast cancer patients undergoing neoadjuvant or adjuvant chemotherapy treatment
Interventions	Intervention (n = 13): home-based, low-intensity level strength training and functional endurance regimen (strength training combined with walking) Control (n = 12): usual care
Outcomes	Primary outcome: • Fatigue: Schwartz Cancer Fatigue Scale (SCFS) Secondary outcomes: • Physical activity: IPAQ • Timed Get-up-and-Go Test (TGUG) • Cardiorespiratory fitness: 6-MWT Adverse events: Detailed adverse event data were not collected for participants in this study. Outcomes were measured at baseline and 2 weeks after the last chemotherapy treatment
Notes	Funding: None reported Conflict of interest: None reported

Caldwell 2009 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerised randomisation program
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants All outcomes	High risk	Not reported
Blinding of personnel/care providers All outcomes	High risk	Not reported. Comment: probably not done
Blinding of outcome assessment (detection bias) Fitness outcomes	High risk	Not reported. Comment: probably not done
Blinding of outcome assessment (detection bias) All outcomes except fitness outcomes	High risk	Self reported items
Incomplete outcome data (attrition bias) All outcomes	High risk	3 participants were not able to start the study owing to changes in treatment plan and were not included in any analysis. • exercise group: n = 13 at baseline, n = 8 at 6 months • control group: n = 12 at baseline, n = 9 at 6 months > 30% drop-out Treatment of missing data was not described
Selective reporting (reporting bias)	Unclear risk	No study protocol published
Group similarity at baseline	Low risk	No significant differences
Adherence	High risk	Once peripheral neuropathy developed, these participants (12 of 13) adopted a sporadic pattern of "walking only", which lasted for approximately 4 weeks before coming to an abrupt end. Participants in this study were not able to recall the times they exercised during the telephone contacts. The investigator was not able to measure adherence, which was defined as the number of sessions attended by each participant
Contamination	Unclear risk	Participants did not have to be sedentary

Campbell 2005

Methods	RCT, 2 groups

Campbell 2005 *(Continued)*

	Study start and stop dates: not reported Length of intervention: 12 weeks Length of follow-up: to end of the intervention
Participants	22 breast cancer patients, after surgery, receiving chemotherapy or radiotherapy
Interventions	Intervention (n = 12): supervised group exercise: aerobic and resistance training (walking, cycling, low-level aerobics, muscle-strengthening exercises, circuits), behaviour change communication, 60% to 75% HRmax, 10 to 20 min per session exercise, plus warm-up, cool-down, relaxation, 2 sessions per week Control (n = 10): no intervention
Outcomes	• quality of life (cancer-specific, cancer site-specific): FACT-G and FACT-B • fatigue: PFS • cardiorespiratory fitness: 12-minute walk test (12-MWT) • physical activity: Scottish Physical Activity Questionnaire (SPAQ) • perceived expectation of treatment: Perceived Expectations and Benefits of Total Care (study-specific questionnaire) • satisfaction with life: SWLS Outcomes were measured at baseline and 12 weeks. Adverse events: "There were no adverse reactions to taking part in the exercise intervention"
Notes	Funding: Greater Glasgow NHS Trust Conflicts of interest: None reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated numbers, stratification by adjuvant cancer treatment
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants All outcomes	High risk	Not done
Blinding of personnel/care providers All outcomes	High risk	Not reported. Comment: probably not done
Blinding of outcome assessment (detection bias) Fitness outcomes	High risk	Not reported. Comment: probably not done
Blinding of outcome assessment (detection bias) All outcomes except fitness outcomes	High risk	Self administered questionnaires were returned to researcher in sealed envelopes. Comment: high risk because items were self reported items
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-out: • Intervention group: 2/12 (16.7%) • Control group: 1/10 (10%)

Campbell 2005 *(Continued)*

		All participants: 3/22 (13.7%) No imputation of missing data
Selective reporting (reporting bias)	Unclear risk	No study protocol published
Group similarity at baseline	Low risk	Similarity for the most important prognostic indicators
Adherence	High risk	Adherence: 70% of all sessions
Contamination	Low risk	Control group more physically active at baseline than intervention group (421 min vs 330 min). Controls remained at baseline level, whereas intervention group increased level. The self reported levels of physical activity at baseline for both groups and at follow-up for the control group were similar to those found in sedentary populations

Cornette 2013

Methods	RCT, 2 groups Study start and stop dates: Recruitment between June 2011 and June 2012 Length of intervention: 27 weeks Length of follow-up: 27 weeks
Participants	44 outpatient breast cancer patients with HER2-negative status randomised, scheduled for adjuvant or neoadjuvant chemotherapy with 6 cycles (3FEC100+3 taxanes), followed by radiotherapy
Interventions	Intervention (n = 22): aerobic and resistance training, 9 supervised sessions of resistance training and 72 unsupervised home-based sessions (resistance and aerobic training): bicycle or walking 20 to 40 minutes 2/week, resistance training with resistance bands 1/week. Control (n = 22): adjuvant treatment only
Outcomes	Primary outcome: • Cardiorespiratory fitness: VO_2 peak at 27 weeks Secondary outcomes: • Cardiorespiratory fitness: 6-minute walk test (6-MWT) • Cancer-specific QoL: EORTC QLQ-C30 • Fatigue: MFI • Strength: leg press strength • Physical activity: IPAQ • Depression and anxiety: HADS • Body composition: lean body mass, % body fat, bone density, BMI, weight change Outcomes were measured at time point: before start of chemotherapy, after 27 weeks of treatment, and after 27 weeks of follow-up Adverse events: no adverse events were reported
Notes	Funding: Sponsored by Limoges University Hospital. Supported by a grant from the Ligue Contre le Cancer (19-87) and the ALAIR-AVD. Conflicts of interest: Not reported.

Cornette 2013 *(Continued)*

Study registration: NCT01322412

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Block randomisations with variable block size, 1:1, no stratification, further details not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants All outcomes	High risk	Open study
Blinding of personnel/care providers All outcomes	High risk	Open study
Blinding of outcome assessment (detection bias) Fitness outcomes	High risk	Open study
Blinding of outcome assessment (detection bias) All outcomes except fitness outcomes	High risk	Self reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Cardiorespiratory fitness and strength: 30/42 participants (68%) took part in all fitness evaluations. QoL, fatigue, psychological distress, physical activity: 19/42 (45.2%) participants in the analysis at the end of the intervention. ITT analysis for cardiorespiratory fitness (VO peak, 6-MWT) and strength with imputation for missing values. "Several methods were tested and last observation carried forward (LOCF) was used." Otherwise no imputation for missing data
Selective reporting (reporting bias)	Low risk	Trial prospectively registered
Group similarity at baseline	High risk	Significant baseline differences in cardiorespiratory fitness and BMI
Adherence	High risk	9 of 14 participants took part in more than 70% of the exercise program
Contamination	Unclear risk	The control group was not asked to abstain from physical activity

Courneya 2007 AET

Methods	RCT, 3 groups Study start and stop dates: 2003 and 2005 Length of intervention: Duration of the chemotherapy, median 17 weeks (9 to 24 weeks)

Courneya 2007 AET *(Continued)*

	Length of follow-up: 6 months for patient-reported outcomes, for objectively measured outcomes 3 to 4 weeks after chemotherapy
Participants	242 breast cancer patients initiating adjuvant chemotherapy
Interventions	**Intervention group 1 (n = 78): 'Courneya AET' aerobic - endurance exercise: cycle ergometer, treadmill, elliptical** Intervention group 2 (n = 82): 'Courneya RET' muscular endurance exercise: weight machines (set with 9 exercises) Control group (n = 82): Usual care; women were asked not to initiate an exercise programme
Outcomes	Primary outcome: • Cancer-specific quality of life: FACT-An Secondary outcomes: • Fatigue: FACT-An • Self esteem: Rosenberg self-esteem scale • Depression: CES-D • Anxiety: Spielberger State-Trait Anxiety Inventory (STAI) • Aerobic fitness: maximal incremental exercise protocol on a treadmill • Cardiorespiratory capacity: peak oxygen consumption • Strength: 8-repetition maximum on the horizontal bench press and leg extension. The maximum weight and number of repetitions were used to estimate the 1-repetition maximum. • Body composition (whole body fat, lean tissue): dual X-ray absorptiometry scan, weight • Lymphoedema: standard volumetric arm measurements based on water displacement. • Chemotherapy completion rate: assessed as the average relative dose intensity (RDI) for the originally planned regimen based on standard formulas. Patient-rated outcomes were assessed at baseline (1 to 2 weeks after starting chemotherapy), mid-point (middle of chemotherapy), after the intervention (3 to 4 weeks after chemotherapy), and at the 6-month follow-up. Objectively measured outcomes were assessed at baseline and after intervention. Adverse events: "exercise did not cause adverse events"
Notes	Study description for Courneya AET (aerobic exercise training) and Courneya RET (resistance exercise training) Funding: Canadian Breast Cancer Research Alliance; the Canada Research Chairs Program, Research Team Grant from the National Cancer Institute of Canada with funds from the Canadian Cancer Society (CCS) and the NCIC/CCS Sociobehavioral Cancer Research Network, New Investigator Award from the Heart and Stroke Foundation of Canada; a New Investigator Award from the Canadian Institutes of Health Research and a Health Scholar Award from the Alberta Heritage Foundation for Medical Research; Canada Graduate Scholarship from the Canadian Institutes of Health Research and an Incentive Award from the Alberta Heritage Foundation for Medical Research. Conflict of interest: Authors declared no potential conflict of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated program, stratification by centre and chemotherapy protocol

Courneya 2007 AET *(Continued)*

Allocation concealment (selection bias)	Low risk	"The allocation sequence was...concealed from the project directors at each site who assigned participants to groups"
Blinding of participants All outcomes	High risk	Not done
Blinding of personnel/care providers All outcomes	High risk	Not reported. Comment: probably not done
Blinding of outcome assessment (detection bias) Fitness outcomes	High risk	Not reported. Comment: probably not done
Blinding of outcome assessment (detection bias) All outcomes except fitness outcomes	High risk	Self reported items
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-out: • Intervention group 1 (aerobic): 5.1% (4/78) • Intervention group 2 (resistance): 7.3% (6/82) • Control group: 11% (9/82) All participants: 7.9% (19/242)
Selective reporting (reporting bias)	Unclear risk	No study protocol published
Group similarity at baseline	Low risk	No significant differences
Adherence	High risk	Aerobic exercise group: 72% sessions; 95.6% met duration; 87.2% met intensity Resistance exercise group: 68.2% sessions; 96.8% completed all 9 exercises; 96.9% completed 2 sets each; 94.5% completed 8 to 12 repetitions
Contamination	Unclear risk	Women were asked not to initiate an exercise programme. Otherwise not reported

Courneya 2007 RET

Methods	RCT, 3 groups Study start and stop dates: 2003 and 2005 Length of intervention: Duration of the chemotherapy, median 17 weeks (9 to 24 weeks) Length of follow-up: 6 months for patient-reported outcomes, for objectively measured outcomes 3 to 4 weeks after chemotherapy
Participants	242 breast cancer patients initiating adjuvant chemotherapy
Interventions	Intervention group 1 (n = 78): 'Courneya AET' aerobic - endurance exercise: cycle ergometer, treadmill, elliptical **Intervention group 2 (n = 82): 'Courneya RET' muscular endurance exercise: weight machines (set with 9 exercises)**

Courneya 2007 RET *(Continued)*

	Control group (n = 82): Usual care; women were asked not to initiate an exercise programme
Outcomes	Primary outcome: • Cancer-specific quality of life: FACT-An Secondary outcomes: • Fatigue: FACT-An • Self esteem: Rosenberg self-esteem scale • Depression: CES-D • Anxiety: Spielberger State-Trait Anxiety Inventory (STAI) • Aerobic fitness: maximal incremental exercise protocol on a treadmill • Cardiorespiratory capacity: peak oxygen consumption • Strength: 8-repetition maximum on the horizontal bench press and leg extension.The maximum weight and number of repetitions were used to estimate the 1-repetition maximum. • Body composition (whole body fat, lean tissue): dual X-ray absorptiometry scan, weight • Lymphoedema: standard volumetric arm measurements based on water displacement. • Chemotherapy completion rate: Chemotherapy completion rate was assessed as the average relative dose intensity (RDI) for the originally planned regimen based on standard formulas. Patient-rated outcomes were assessed at baseline (1 to 2 weeks after starting chemotherapy), mid-point (middle of chemotherapy), after the intervention (3 to 4 weeks after chemotherapy), and at the 6-month follow-up. Objectively measured outcomes were assessed at baseline and after intervention. Adverse events: "exercise did not cause adverse events"
Notes	Study description for Courneya AET (aerobic exercise training) and Courneya RET (resistance exercise training) Funding: Canadian Breast Cancer Research Alliance; the Canada Research Chairs Program, Research Team Grant from the National Cancer Institute of Canada with funds from the Canadian Cancer Society (CCS) and the NCIC/CCS Sociobehavioral Cancer Research Network, New Investigator Award from the Heart and Stroke Foundation of Canada; a New Investigator Award from the Canadian Institutes of Health Research and a Health Scholar Award from the Alberta Heritage Foundation for Medical Research; Canada Graduate Scholarship from the Canadian Institutes of Health Research and an Incentive Award from the Alberta Heritage Foundation for Medical Research. Conflict of interest: Authors declared no potential conflict of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated program, stratification by centre and chemotherapy protocol
Allocation concealment (selection bias)	Low risk	“The allocation sequence was...concealed from the project directors at each site who assigned participants to groups”
Blinding of participants All outcomes	High risk	Not done
Blinding of personnel/care providers All outcomes	High risk	Not reported. Comment: probably not done

Courneya 2007 RET *(Continued)*

Blinding of outcome assessment (detection bias) Fitness outcomes	High risk	Not reported. Comment: probably not done
Blinding of outcome assessment (detection bias) All outcomes except fitness outcomes	High risk	Self reported items
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-out: • Intervention group 1 (aerobic): 5.1% (4/78) • Intervention group 2 (resistance): 7.3% (6/82) • Control group: 11% (9/82) All participants: 7.9% (19/242)
Selective reporting (reporting bias)	Unclear risk	No study protocol published
Group similarity at baseline	Low risk	No significant differences
Adherence	High risk	Aerobic exercise group: 72% sessions; 95.6% met duration; 87.2% met intensity Resistance exercise group: 68.2% sessions; 96.8% completed all 9 exercises; 96.9% completed 2 sets each; 94.5% completed 8 to 12 repetitions
Contamination	Unclear risk	Women were asked not to initiate an exercise programme. Otherwise not reported

Crowley 2003

Methods	RCT, 2 groups Study start and stop dates: not reported Length of intervention: 13 weeks Length of follow-up: to the end of the intervention
Participants	22 breast cancer patients, stage I, II; after surgery, receiving adjuvant chemotherapy (doxorubicin (Adriamycin), cyclophosphamide (Cytoxan)), radiation therapy excluded
Interventions	Intervention (n = 13): Aerobic training (walking) and resistance training (tubing), self directed, 60% of HRmax, 20 to 60 min per session, 3 to 5 d/week. Resistance training: 12 to 15 repetitions, approximately 20 minutes, 1 to 2 sets, 2 to 3 d/week, 13 weeks. Control (n = 9): Usual care, the same scheduled contact with the nurse researcher as the intervention group during weeks 1, 4, 7, 10, and 13, activity log
Outcomes	• cardiorespiratory fitness: VO_2 max/kg - symptom-limited graded exercise test (GXT), Cornell Treadmill Protocol • muscular fitness: 1-repetition maximum (1-RM) chest press and leg press • fatigue: revised PFS • physical self efficacy: items from the Self-Efficacy to Perform Self-Management Behaviors and the Self-Efficacy to Achieve Outcomes scales • attention performance: Attentional Functional Index (AFI)

Crowley 2003 *(Continued)*

- functional wellness: investigator-developed Functional Wellness Questionnaire on perceptions of physical function, wellness, and health
- physical activity: activity log

Outcomes were measured at:

- physical performance (endurance and strength) week 1 (prior to initiation of the first chemotherapy treatment) and week 13 (3 weeks after the last chemotherapy treatment)
- fatigue, attention performance, physical self efficacy, functional wellness: week 1, week 7 (midpoint of the treatment cycles), week 13

Adverse events: lymphoedema in 1 participant

Notes	Funding: Not reported Conflicts of interest: Not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A random numbers table was utilised prior to the initiation of the study to randomise participants to 1 of the 2 groups. Consecutive numbers on the table were used with numbers ending in an even integer assigned to the exercise group, and numbers ending in an odd integer assigned to the comparison group. Each number was placed in an envelope that was then sealed. The outside of the envelope was then numbered in consecutive order
Allocation concealment (selection bias)	Unclear risk	Sealed envelope. Comment: it was not mentioned if the envelope was opaque
Blinding of participants All outcomes	High risk	Not done
Blinding of personnel/care providers All outcomes	High risk	Not reported. Comment: probably not done
Blinding of outcome assessment (detection bias) Fitness outcomes	Low risk	"The study participant's group assignment was blinded to the exercise physiologists performing the fitness testing at the week 13 appointment. Study participants were requested to not disclose which study group they had been randomized to."
Blinding of outcome assessment (detection bias) All outcomes except fitness outcomes	High risk	Self reported items
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were reported for 2 participants for strength assessment. "A second strength was the adherence by both groups in maintaining activity logs and completing all study measures."
Selective reporting (reporting bias)	Unclear risk	Detailed results only available for cardiorespiratory fitness
Group similarity at baseline	Low risk	"The groups were balanced in terms of demographic and disease characteristics."

Crowley 2003 *(Continued)*

Adherence	Unclear risk	The nurse researcher used the logs of both groups to assess adherence to the structured exercise program. Adherence defined as completion of 80% of the individualised targeted endurance and strength exercise, frequency, duration, and intensity. The intervention group walked a mean of 113 minutes per week, as compared to 53 minutes by the comparison group. "The intervention group also demonstrated commitment to following the exercise intervention across the study period."
Contamination	Unclear risk	The intervention group walked a mean of 113 minutes per week, as compared to 53 minutes by the comparison group. Thus the intervention group was considered to be performing at a moderate level of activity per week, while the comparison group had a low level of activity over the study period. Study participants were asked to commit to not initiating participation in a formal exercise program during the study period. Continuation of an ongoing exercise regimen was acceptable

Dodd 2010

Methods	RCT, 3 groups Study start and stop dates: 1999 to 2006 Length of intervention: 1 year Length of follow-up: end of intervention
Participants	119 participants randomised, majority with breast cancer (n = 112), but people with ovarian and colorectal cancer also included, undergoing chemotherapy, Karnofsky score > = 60. Excluded if they were having concurrent radiation therapy, and if pain intensity score greater than 3
Interventions	1. intervention group: cardiovascular/aerobic exercise, e.g. walking, jogging, or bicycling during chemotherapy (n = 44); home-based for 1 year, 3 to 5 times/week, 20- to 30-minute/session at 60% to 80% VO_2 peak or 12 to 14 on Borg scale 2. intervention group: cardiovascular/aerobic exercise, e.g. walking, jogging, or bicycling postchemotherapy (n = 36); home-based for 6 to 8 months, otherwise as group 1 3. control group (n = 39): usual care, no exercise prescription. Telephoned weekly to inquire about health and general response to cancer treatment
Outcomes	Primary outcomes: • Fatigue: PFS • Sleep disturbance: General Sleep Disturbance Scale • Depression: CES-D • Pain: Worst Pain Intensity Scale Secondary outcomes: • MQOLS-CA: reported in 1 related publication • Cardiorespiratory fitness: peak VO_2 • Nutritional symptoms • Body composition: % body fat, lean body mass (kg) (DEXA), BMI, weight • Nausea: Nausea intensity was measured using a 0 to 10 numeric scale (participants were asked how much nausea they were experiencing at the time of data collection). The nausea intensity scale was derived from a symptom checklist of 25 commonly experienced symptoms.

Dodd 2010 *(Continued)*

	Outcomes were measured at time point: baseline (T1: the week before the second chemotherapy treatment), at the end of cancer treatment (T2: 4 to 6 months after T1), and at the end of the study (T3: approximately 1 year after the start of T1). Adverse events: hip pain, sciatica (n = 16), arm discomfort (n = 4), knee discomfort (n = 10), ankle discomfort (n = 3), and foot discomfort (n = 8)
Notes	Funding: National Cancer Institute (CA83316), and the Clinical Translational Research Institute, Clinical Research Center (CTSI-CRC) (Dodd 2010) Conflicts of interest: The authors declared no potential conflicts of interest in 2 related publications

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reported as randomised, but method not described
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants All outcomes	High risk	Not done
Blinding of personnel/care providers All outcomes	High risk	Not reported. Comment: probably not done
Blinding of outcome assessment (detection bias) Fitness outcomes	Low risk	Cardiopulmonary exercise testing was performed in the exercise physiology lab by laboratory staff blinded to the participant's group assignment
Blinding of outcome assessment (detection bias) All outcomes except fitness outcomes	High risk	Not reported for other outcomes. Comment: probably not done or self reported items
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-out: • Early intervention during adjuvant treatment 7/44 (15.9%) • Late intervention after adjuvant treatment 4/36 (11.1%) • Usual-care group 2/39 (5%) • Late intervention and usual care: 6/75 (8%) • All participants: 13/119 (10.9%) ITT, no imputation
Selective reporting (reporting bias)	High risk	Cardiopulmonary fitness was tested but not reported as an outcome. It was unclear if cardiorespiratory fitness was a predefined outcome or only measured to individualise the exercise prescription. In 1 of 5 related publications, a quality of life questionnaire was mentioned (MQOLS-CA), but no results were reported in any publication. Outcomes were not reported completely, and could not be extracted for use in a meta-analysis

Dodd 2010 *(Continued)*

Group similarity at baseline	Low risk	"The three groups of patients did not differ significantly in any of the demographic, disease, or treatment characteristics on entry into the study"
Adherence	High risk	Group 1 (exercise during and after adjuvant treatment) reported an adherence rate of 73% at T2 and 75.7% at T3
Contamination	High risk	44% of group 2 (exercise after adjuvant treatment) reported meeting ACSM 1998 guidelines (aerobic activities 3x/week, for 20-minute duration, and at a moderate intensity) at T1, by T2 group 2 had decreased to 27%. 34% of group 3 (no exercise) reported meeting minimum criteria at T1, this decreased to 31% at T2.

Drouin 2002

Methods	RCT, 2 groups Study start and stop dates: not reported Length of intervention: 7 weeks Length of follow-up: end of intervention
Participants	23 breast cancer patients, stages 0 to III; after surgery, receiving radiotherapy, sedentary
Interventions	Intervention (n = 13): aerobic training (walking), self directed, 50% to 70% HRmax, 20 to 45 min per session, 3 to 5/week Control (n = 10): stretching, 3 to 5/week
Outcomes	• fatigue: PFS • cardiorespiratory fitness: peak aerobic capacity • muscular fitness: grip tests, handgrip testing using a Jamar Dynamometer • mood: POMS • body composition: skin caliper technique, body mass, BMI, waist-to-hip ratio • immune function (CD4+/CD8+ ratio, natural killer cytotoxic activity) • oxidative stress (8-isoprostane) Outcomes were measured within 1 week prior to and within 1 week following a 7-week radiation regimen. Adverse events: shoulder tendonitis and decreases in strength due to overtraining in 1 participant
Notes	Funding: grants from the Elsa U. Pardee Foundation in Midland, MI, USA, and the Max and Victoria Dreyfus Foundation in White Plains, NY, USA Conflict of interest: None reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants	High risk	Not reported

Drouin 2002 *(Continued)*

All outcomes		
Blinding of personnel/care providers All outcomes	High risk	Not reported Comment: probably not done
Blinding of outcome assessment (detection bias) Fitness outcomes	High risk	Not reported Comment: probably not done
Blinding of outcome assessment (detection bias) All outcomes except fitness outcomes	High risk	Self reported items
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-out: • Intervention group: 0/13 (0%) • Control group: 2/10 (20%) All participants: 2/23 (8.7%)
Selective reporting (reporting bias)	Unclear risk	No study protocol published
Group similarity at baseline	Low risk	Similarity for the most important prognostic indicators
Adherence	High risk	Adherence defined as 21 minimum sessions out of 35 possible sessions Adherence per group: • Intervention group: mean 25.8 sessions, SD = 10.1 (73.7%) • Control group: mean 29.2 sessions, SD = 7.7 (83.4%)
Contamination	Unclear risk	Obese cohort (mean BMI > 30 kg/m^2). Otherwise not reported

Eakin 2012

Methods	RCT, 2 groups Study start and stop dates: data were collected from April 2007 to April 2009 Length of intervention: 8 months Length of follow-up: 8 weeks after end of the intervention
Participants	142 non-urban-dwelling breast cancer patients, 111 underwent adjuvant therapy (chemotherapy, radiotherapy, or a combination) during the study intervention (unpublished data for these participants used in the analyses of this review)
Interventions	Intervention (n = 58): home-based, telephone-delivered mixed (aerobic and resistance training) exercise Control (n = 53): usual care; did not receive any study exercise intervention-related material until study completion
Outcomes	Primary outcomes: • Physical Activity (minutes per week): Active Australia Survey

Eakin 2012 *(Continued)*

	• Strength training (sessions per week): CHAMPS (Community Healthy Activities Models Programs for Seniors) Secondary outcomes: • QoL: Functional Assessment of Cancer Therapy-Breast questionnaire - for patients with breast cancer and lymphoedema (FACT-B+4) • Fatigue: FACIT-F • State anxiety: State-Trait Anxiety Inventory (STAI) • Upper body function: DASH Outcomes measures at 6 and 12 months Adverse events: muscle soreness in 2 participants and musculoskeletal injury in 1 participant
Notes	Funding: The National Breast Cancer Foundation (NBCF, Australia) and a Queensland Health Core Infrastructure grant funded the trial. EGE is supported by a National Health and Medical Research Council Senior Research Fellowship. SCH is supported by an Early Career Research Fellowship from the NBCF. Conflict of interest: The authors have no conflict of interest to disclose. Registered at: ACTRN12609000809235

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated, unblocked sequence of random numbers
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants All outcomes	High risk	Not done
Blinding of personnel/care providers All outcomes	High risk	Not reported. Comment: probably not done
Blinding of outcome assessment (detection bias) All outcomes except fitness outcomes	High risk	Self reported items
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-out all participants: • Intervention: 5/73 (6.8%) • Control: 1/70 (1.4%) Retention was 97% at 6 months and 96% at 12 months. No imputation of missing data
Selective reporting (reporting bias)	Low risk	Registered prospectively
Group similarity at baseline	High risk	For 111 participants during adjuvant treatment: more with chemotherapy in the treatment group: 47/58 (81%) vs 36/53 (68%)

Eakin 2012 *(Continued)*

		For all participants: "There was no evidence of failure of randomization (i.e. all baseline group differences were P > 0.05), however there were some notable group differences (>=10%) in terms of income (<$52,000 per annum), receipt of radiotherapy at baseline, overall receipt of chemotherapy, surgery type and lymph node status."
Adherence	High risk	41.2% at 6 months' postsurgery and 52.2% at 12 months' postsurgery met the criteria for aerobic activity. 45.6% at 6 months' postsurgery and 40.3% at 12 months' postsurgery met the criteria for strength.
Contamination	High risk	30% to 40% of control group were active during the study period. They started out as being as active

Gokal 2013

Methods	RCT, 2 groups Study start and stop dates: not reported Length of intervention: 12 weeks Length of follow-up: end of intervention
Participants	50 sedentary (< 30 minutes of moderate-intensity exercise 5 times a week) breast cancer patients (stage I to III) during adjuvant or neoadjuvant chemotherapy. Recruited from outpatient clinics
Interventions	Intervention (n = 25): home-based, moderate-intensity walking intervention (defined as walking at brisk pace) after 2 cycles of chemotherapy. 30 minutes of moderate-intensity walking 5 times a week, encouraged to gradually increase walking duration from 10- to 30-minute bouts through the course of the intervention. Control group (n = 25): usual care
Outcomes	Primary: • Anxiety and depression: HADS • Fatigue: FACT-F • Self esteem: Rosenberg self-esteem scale • Emotional distress: Profile of Mood States-Short Form Secondary: • Physical activity: General Practice Physical Activity Questionnaire Outcomes measured at: midway through chemotherapy (pre-intervention) and after the completion of chemotherapy (postintervention). All participants also completed outcome measures prior to receiving chemotherapy
Notes	Funding: Loughborough University as part of a PhD project. Conflict of interest: There were no conflicts of interest to report. Study registration: ISRCTN50709297

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Block randomisation using four blocks was used to allocate patients into one of two groups by the researcher. Within each group of four patients, two were

Gokal 2013 *(Continued)*

		allocated to the intervention group and two to the control group; the allocation of groups within each block was random."
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants All outcomes	High risk	There is no masking of participants or the research team
Blinding of personnel/care providers All outcomes	High risk	There is no masking of participants or the research team
Blinding of outcome assessment (detection bias) All outcomes except fitness outcomes	High risk	There is no masking of participants or the research team
Incomplete outcome data (attrition bias) All outcomes	Low risk	5 participants in the exercise group (20%) discontinued the intervention (4 due to hospitalisation and 1 due to medical difficulties), but completed all follow-up measures and were included in the analysis. ITT analysis, no imputation described
Selective reporting (reporting bias)	High risk	Measures of cognitive function (mentioned in the design paper and study registration) were not reported in the paper
Group similarity at baseline	Low risk	There were no significant differences between groups in sociodemographic or treatment-related variables. Using ITT, there were no significant between-group differences in baseline measures of anxiety, depression, fatigue, self esteem, mood, or subjective ratings of physical activity. There was a small difference between groups in 2 subscales of mood: vigour and confusion
Adherence	Low risk	20 (80%) out of the 25 participants randomised to the physical activity group adhered to the intervention and completed walking diaries. 5 participants discontinued participation within the first few weeks of the 12-week intervention
Contamination	Low risk	Sedentary patients at baseline. Self report of perceived physical activity for control group: 23/25 moderately inactive to inactive

Haines 2010

Methods	RCT, 2 groups Study start and stop dates: recruitment between May 2006 and September 2007 Length of intervention: 12 months Length of follow-up: end of intervention
Participants	89 breast cancer patients undergoing adjuvant therapy: chemotherapy, radiation, or a combination of both (more than 90% radiation)
Interventions	Intervention group (n = 46): home-based strength, balance, shoulder mobility, and cardiovascular endurance program. 36 minutes, of which 20 minutes were walking. Frequency not reported. Control group (n = 43): Static stretching, supine relaxation program following the Feldenkrais method

Haines 2010 *(Continued)*

Outcomes	Primary outcome measure: • health-related quality of life: EQ-5D • cancer-specific quality of life: EORTC C30 with BR23 supplement was also used to measure elements of disease-specific health-related quality of life that might explain changes in generic HRQoL • breast cancer-specific quality of life: EORTC C30 with BR23 supplement Secondary outcome measures: • upper limb swelling • cancer-related fatigue: MFI • balance: Functional Reach, Step Test • Strength: grip, leg press • cardiorespiratory fitness: 6-min walk test • shoulder range of motion (flexion, abduction, and external rotation, measured using plurimeter) • body composition (muscle mass %, body fat %) Outcomes were measured at baseline, 3, 6, and 12 months Adverse events: 9 participants with musculoskeletal pain, 3 of which reported pain whilst performing exercises as a part of the intervention program and 1 as a part of the control program. 8 participants with 1 fall each, 1 of which was the result of an intervention group participant tripping on a tree stump whilst undertaking the walking program
Notes	Funding: Project grant from the Princess Alexandra Hospital Cancer Collaborative Group, National Health and Medical Research Council Career Development Award (606732) Conflict of interest: No conflicts of interest declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised to intervention or control groups using a computer-generated randomisation sequence
Allocation concealment (selection bias)	Low risk	The randomisation sequence was entered into numbered, opaque, sealed envelopes by a study investigator and was held secure in an administration office separate from that of the investigators. Envelopes were only opened after completion of the initial assessment after which intervention or control programs were provided to participants according to the allocation sequence
Blinding of participants All outcomes	High risk	Sham intervention control group provided with what looked like an exercise program with an equivalent amount of supporting material. The video material was of similar content to that in the intervention program (though the actual exercises described differed). Comment: Participants would still have been aware if they were in the exercise group or the stretching group
Blinding of personnel/care providers All outcomes	High risk	Not reported. Comment: probably not done
Blinding of outcome assessment (detection bias) Fitness outcomes	Low risk	"blinded outcome assessment"

Haines 2010 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes except fitness outcomes	High risk	Self reported outcomes
Incomplete outcome data (attrition bias) All outcomes	High risk	Intervention group: more than 30% of outcome data was missing at 6 months Control group: more than 30% of outcome data was missing at 6 months Handling of dropouts and missing data not reported
Selective reporting (reporting bias)	Low risk	The trial was registered prospectively with the Australia New Zealand Clinical Trials Registry (ACTRN12606000047594)
Group similarity at baseline	High risk	"Control group participants also appeared to be healthier at baseline."
Adherence	High risk	Participants were to document adherence in log books on a weekly basis and were asked about adherence in the last 2 weeks of 12 months. At the 12-month review, 11 of 37 intervention group participants interviewed reported completing the strength/balance/shoulder mobility component of the program at least once in the past 2 weeks, whilst 7 reported completing it at least 3 times. The endurance component was completed at least once by 12, and at least 3 times by 7
Contamination	High risk	In addition to the program provided, 25 out of 37 intervention group participants and 21 out of 36 control group participants had commenced other forms of exercise (e.g. walking, dancing, gymnasium, and aerobics)

Hayes 2013 FtF

Methods	RCT, 3 groups Study start and stop dates: recruitment between October 2006 and June 2008 Length of intervention: 8 months Length of follow-up: 8 weeks after end of the intervention
Participants	194 breast cancer patients, of which 142 underwent adjuvant therapy concurrently with the exercise intervention (unpublished data for these patients used in the analyses of this review)
Interventions	Intervention group 1: 'Hayes 2013 Tel' Telephone (n = 50) - incorporating both aerobic and strength-based exercises **Intervention group 2: '**Hayes 2013**FtF' Face to face (n = 51) - incorporating both aerobic and strength-based exercises** Control group (n = 41): usual care
Outcomes	Primary outcome: • Cancer site-specific QoL: Functional Assessment of Cancer Therapy-Breast (FACT-B+4) - for patients with breast cancer and lymphoedema Secondary outcomes: • Subjective upper body function: DASH • Upper body function, clinically measured: strength and endurance test

Hayes 2013 FtF *(Continued)*

- Fatigue: FACIT-F
- Menopausal symptoms: Greene Climacteric Scale
- Neuropathic pain: Neuropathic Pain Scale
- Cardiorespiratory fitness: 3-min step test
- Lymphoedema status: bioimpedance spectroscopy (L-Dex score)
- Minutes of physical activity per week (Active Australia Survey)
- Body composition: BMI

Outcomes measured at: 6 months, 12 months

Notes	Funding: This research project was supported by the National Breast Cancer Foundation. The research positions of SH and EE are supported via an NBCF Early Career Research Fellowship and an NHMRC Senior Research Fellowship, respectively. Conflict of interest: Authors declare that they have no conflict of interest. Registered at ACTRN: 012606000233527

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Individually computer-generated non-blocked
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants All outcomes	High risk	Not done
Blinding of personnel/care providers All outcomes	High risk	Not reported Comment: probably not done
Blinding of outcome assessment (detection bias) Fitness outcomes	Low risk	"assessors blinded to group allocation"
Blinding of outcome assessment (detection bias) All outcomes except fitness outcomes	High risk	All outcomes except outcomes with clinical assessment: self reported items
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-out: all participants • Face-to-face intervention group: 6 • Telephone intervention group: 4 • Usual-care group: 4 All participants: 14/194 (7.2%) Comment: For the 142 participants undergoing adjuvant therapy: More than 20% drop-out for 3-min step test (cardiorespiratory fitness) High risk for cardiorespiratory fitness

Hayes 2013 FtF *(Continued)*

		ITT analysis, no imputation of data
Selective reporting (reporting bias)	Low risk	Registered prospectively
Group similarity at baseline	High risk	Slight imbalance in numbers, place of treatment (public vs private hospital), and rates of mastectomy between groups following randomisation. Rate of mastectomies higher in telephone group. This group has the biggest difference in QoL
Adherence	High risk	25% did not meet the intervention goal at mid- or postintervention and did not increase their total physical activity by 30+ min (a priori deemed clinically relevant) between baseline and mid- or postintervention
Contamination	High risk	The Active Australia Survey showed that the usual-care group was more active (more minutes per week) than the FtF group and as active as the Tel group at 6 months. At 12 months, the usual-care group was more active than the FtF group and less active than the Tel group

Hayes 2013 Tel

Methods	RCT, 3 groups Study start and stop dates: recruitment between October 2006 and June 2008 Length of intervention: 8 months Length of follow-up: 8 weeks after end of the intervention
Participants	194 breast cancer patients, of which 142 underwent adjuvant therapy concurrently with the exercise intervention (unpublished data for these patients used in the analyses of this review)
Interventions	**Intervention group 1: '**Hayes 2013**Tel' Telephone (n = 50) - incorporating both aerobic and strength-based exercises** Intervention group 2: 'Hayes 2013 FtF' Face to face (n = 51) - incorporating both aerobic and strength-based exercises Control group (n = 41): usual care
Outcomes	Primary outcome: • Cancer site-specific QoL: Functional Assessment of Cancer Therapy-Breast (FACT-B+4) - for patients with breast cancer and lymphoedema Secondary outcomes: • Subjective upper body function: DASH • Upper body function, clinically measured: strength and endurance test • Fatigue: FACIT-F • Menopausal symptoms: Greene Climacteric Scale • Neuropathic pain: Neuropathic Pain Scale • Cardiorespiratory fitness: 3-min step test • Lymphoedema status: bioimpedance spectroscopy (L-Dex score) • Minutes of physical activity per week (Active Australia Survey) • Body composition: BMI Outcomes measured at: 6 months, 12 months

Hayes 2013 Tel *(Continued)*

Notes	Funding: This research project was supported by the National Breast Cancer Foundation. The research positions of SH and EE are supported via an NBCF Early Career Research Fellowship and an NHMRC Senior Research Fellowship, respectively. Conflict of interest: Authors declare that they have no conflict of interest. Registered at ACTRN: 012606000233527

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Individually computer-generated non-blocked
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants All outcomes	High risk	Not done
Blinding of personnel/care providers All outcomes	High risk	Not reported Comment: probably not done
Blinding of outcome assessment (detection bias) Fitness outcomes	Low risk	"assessors blinded to group allocation"
Blinding of outcome assessment (detection bias) All outcomes except fitness outcomes	High risk	All outcomes except outcomes with clinical assessment: self reported items
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-out: all participants • Face-to-face intervention group: 6 • Telephone intervention group: 4 • Usual-care group: 4 All participants: 14/194 (7.2%) Comment: For the 142 participants undergoing adjuvant therapy: More than 20% drop-out for 3-min step test (cardiorespiratory fitness) High risk for cardiorespiratory fitness ITT analysis, no imputation of data
Selective reporting (reporting bias)	Low risk	Registered prospectively
Group similarity at baseline	High risk	Slight imbalance in numbers, place of treatment (public vs private hospital), and rates of mastectomy between groups following randomisation. Rate of mastectomies higher in telephone group. This group has the biggest difference in QoL

Hayes 2013 Tel *(Continued)*

Adherence	High risk	25% did not meet the intervention goal at mid- or postintervention and did not increase their total physical activity by 30+ min (a priori deemed clinically relevant) between baseline and mid- or postintervention
Contamination	High risk	The Active Australia Survey showed that the usual-care group was more active (more minutes per week) than the FtF group and as active as the Tel group at 6 months. At 12 months, the usual-care group was more active than the FtF group and less active than the Tel group

Hornsby 2014

Methods	RCT, 2 groups Study start and stop dates: recruitment between March 2007 and January 2010 Length of intervention: 12 weeks Length of follow-up: end of intervention
Participants	20 breast cancer patients, stage IIB to IIIC operable breast cancer, neoadjuvant chemotherapy consisted of 4 cycles of doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) every 3 weeks (i.e. 12 weeks in duration) Eligible if: Karnofsky performance status > 70
Interventions	Intervention (n = 10): Aerobic training consisted of 3 one-on-one supervised cycle ergometry sessions per week on non-consecutive days for 12 weeks. Control (n = 10): Neoadjuvant therapy only, participants were instructed to maintain their usual exercise levels throughout the duration of the study
Outcomes	Safety outcomes: • exercise testing • treatment- and exercise training-related adverse events (AEs) Efficacy outcomes: • cardiopulmonary exercise test (CPET) • cancer-specific quality of life: FACT-G • cancer site-specific quality of life: FACT-B • Fatigue: FACIT-F Outcomes were measured at: CPET, echocardiogram, and self administered questionnaire were conducted at baseline and postintervention (12 weeks), whereas treatment-related events were serially assessed across the study (i.e. baseline, 3, 6, 9, and 12 weeks). Exercise-related events were monitored during CPET procedures and aerobic training sessions. Adverse event: unexplained leg pain in 1 participant
Notes	Funding: United States Department of Defense Breast Cancer Research Program of the Office of the Congressionally Directed Medical Research Programs – Ideas Award and funds from George and Susan Beischer (1 author). 1 author is supported by research grants from the National Cancer Institute (CA143254, CA142566, CA138634, CA133895, CA164751). Conflict of interest: The authors report no conflicts of interest

Risk of bias

Hornsby 2014 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated program (n = 10/group)
Allocation concealment (selection bias)	Unclear risk	The allocation sequence was concealed from the study co-ordinator who assigned participants to groups
Blinding of participants All outcomes	High risk	It was not possible to blind participants or exercise staff to group assignment
Blinding of personnel/care providers All outcomes	High risk	It was not possible to blind participants or exercise staff to group assignment
Blinding of outcome assessment (detection bias) Fitness outcomes	Low risk	Study exercise physiologists conducting the baseline and postintervention (12 weeks) assessments were blinded to group assignment
Blinding of outcome assessment (detection bias) All outcomes except fitness outcomes	High risk	Self reported items
Incomplete outcome data (attrition bias) All outcomes	Low risk	19/20 (95%) completed all study procedures. ITT, handling of 1 dropout not described
Selective reporting (reporting bias)	Unclear risk	No study protocol published
Group similarity at baseline	Low risk	"The groups were balanced on all study outcomes at baseline."
Adherence	High risk	Overall attendance to planned exercise sessions was 82% (296 attended/360 prescribed; range 0 to 100%). Overall adherence to the planned exercise prescription was 66% (194 adhered sessions/296 attended). Adherence was calculated as the number of exercise sessions successfully completed (i.e. participant completed the exercise session at the planned duration and intensity) divided by the number of planned sessions attended
Contamination	Unclear risk	"There were no significant differences between groups for self-reported exercise behavior." Otherwise not reported

Husebo 2014

Methods	RCT, 2 groups Study start and stop dates: 2010 to 2012 Length of intervention: 17 weeks on average Length of follow-up: 6 months

Husebo 2014 *(Continued)*

Participants	67 breast cancer patients, stage I to III, surgically treated (mastectomy or lumpectomy), and allocated to adjuvant chemotherapy according to the national treatment guidelines of the Norwegian Breast Cancer Group
Interventions	Intervention: Scheduled home-based exercise intervention (n = 33), combined strength (resistance bands exercises 3 times a week) and aerobic (30 minutes of brisk walking daily) training Control group (n = 34): were advised to remain on their regular physical activity
Outcomes	• cancer-related fatigue: Schwartz Cancer Fatigue Scale (SCFS-6) • physical fitness: 6-minute walk test • activity level: MET-minutes per week, IPAQ, exercise diary The study sample completed questionnaires and physical tests after surgery prior to chemotherapy (baseline), 18 to 24 weeks after baseline, and at the end of chemotherapy (Post1), and approximately 6 months after completing the chemotherapy regimen (Post2). Adverse events: 1 participant with knee discomfort and 1 participant with a syncope related to a secondary chronic condition
Notes	Funding: None reported. No conflict of interest declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The random assignment of subjects to the intervention group or to the control group was carried out by the use of concealed envelopes, drawn by the research assistant prior to the first data collection."
Allocation concealment (selection bias)	Unclear risk	"concealed envelopes" Comment: it was not mentioned if they were opaque
Blinding of participants All outcomes	High risk	Not reported
Blinding of personnel/care providers All outcomes	High risk	Not reported. Comment: probably not done
Blinding of outcome assessment (detection bias) Fitness outcomes	High risk	Not reported. Comment: probably not done
Blinding of outcome assessment (detection bias) All outcomes except fitness outcomes	High risk	Self reported items
Incomplete outcome data (attrition bias) All outcomes	Low risk	Post1: immediately after chemo; Post2: 6 months' follow-up 60 of 67 (89.6%) participants completed the data collection at time point 1. Comment: low risk. 52 of 67 (77.6%) participants completed the data collection at time point 2. Comment: high risk.

Husebo 2014 *(Continued)*

		ITT analysis for fatigue data. Per-protocol analysis for physical activity (IPAQ)
Selective reporting (reporting bias)	Unclear risk	No study protocol published
Group similarity at baseline	Low risk	No significant differences in baseline values
Adherence	High risk	17% adhered to the walking prescription of minimum 210 minutes/week of MVPA. 15% of the participants in the intervention group achieved the prescribed number of strength training (3/week) sessions. 58% met the general recommendations of 150 minutes/week of MVPA, and participants carried out approximately 2 sessions of resistance band exercises per week
Contamination	High risk	The control group had a mean exercise volume of 144 (SD 84) MVPA minutes per week, and 39% performed 150 minutes/week of MVPA or more. Data on exercise volume indicates that 48% of participants in both groups exercised according to the general recommended physical activity level or more. "there was a tendency of a significantly larger mean exercise volume in the intervention group compared to the control group (P = 0.051)"

Ingram 2010

Methods	RCT, 2 groups, parallel-group design Study start and stop dates: not reported Length of intervention: 24 weeks Length of follow-up: study was closed early
Participants	13 breast cancer patients due to commence adjuvant chemotherapy
Interventions	Intervention (n = 8): home-based combined aerobic and resistance exercise program, 30 to 45 min of aerobic exercise, at least 4 times per week. 8 resistance exercises, which included the arms, legs, and trunk, 3 times per week with enough resistance so that she tired after 6 to 12 repetitions. Control group (n = 5): usual care
Outcomes	Primary: • Body weight • Body composition (TANITA body composition scale; dual-energy X-ray absorptiometry scans) Secondary: • Arm and hip strength (hand-held dynamometry) • Quality of life (FACT-B) • Fatigue (FACT-F)
Notes	No outcomes reported as study was closed early. Funding: Canadian Breast Cancer Research Alliance Developmental and Explanatory Grant #16542 Conflict of interest: none declared

Risk of bias

Ingram 2010 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants All outcomes	High risk	Not done
Blinding of personnel/care providers All outcomes	High risk	Not reported Comment: probably not done
Blinding of outcome assessment (detection bias) Fitness outcomes	High risk	Not reported Comment: probably not done
Blinding of outcome assessment (detection bias) All outcomes except fitness outcomes	High risk	Not reported or self reported items Comment: probably not done
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Study closed early
Selective reporting (reporting bias)	Unclear risk	No results reported because study closed early
Group similarity at baseline	Unclear risk	"No clinically meaningful or statistically significant differences between groups."
Adherence	High risk	Only 38% met all exercise targets
Contamination	High risk	"The women in the control group were unexpectedly quite active." Were asked not to begin a new exercise program

MacVicar 1989

Methods	RCT, 3 groups, stratified by functional capacity Study start and stop dates: not reported Length of intervention: 10 to 12 weeks Length of follow-up: end of intervention
Participants	62 breast cancer patients, stage II; after surgery, receiving chemotherapy, entered the study; 45 patients were analysed for cardiorespiratory fitness; 24 patients (without placebo group and further patients excluded) were analysed for weight change and body composition
Interventions	Intervention (n = 18): aerobic training (cycling, interval training), 60% to 85% HRmax, 20 to 30 min per session, 3/week Control group 1 (n = 11): flexibility and stretching exercises ("placebo group")

MacVicar 1989 *(Continued)*

	Control group 2 (n = 16): no intervention
Outcomes	• Cardiorespiratory fitness: VO_2 max • Body composition (described in related publication) Outcomes measured at baseline and end of intervention
Notes	Funding: National Institutes of Health Grants RO1 NR 01078, National Center for Nursing Research and P 3OCA 16058 14, National Cancer Institute Conflict of interest: Not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated to be randomised, but method not described
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants All outcomes	High risk	Placebo group analysed for functional capacity did stretching exercises. Comment: participants would have been aware if they were in the exercise group or the stretching group
Blinding of personnel/care providers All outcomes	High risk	Not reported. Comment: probably not done
Blinding of outcome assessment (detection bias) Fitness outcomes	High risk	Not reported. Comment: probably not done
Blinding of outcome assessment (detection bias) All outcomes except fitness outcomes	Unclear risk	No other relevant outcomes
Incomplete outcome data (attrition bias) All outcomes	High risk	Drop-out rate for all participants: 17/62 (27.4%) 45 of 62 participants were analysed for functional capacity. Per-protocol analysis (n = 45) of n = 62, who entered the study
Selective reporting (reporting bias)	High risk	It is unclear why data for only 2 groups was analysed for weight change and body composition
Group similarity at baseline	High risk	Educational status differed. Data for 17 women not shown for baseline
Adherence	Low risk	Adherence complete (missed sessions repeated)
Contamination	Unclear risk	"No subject participated in any other exercise or rehabilitation program during the 10 week data collection period." Comment: amount of physical activity outside of programs unclear

Mock 2004

Methods	RCT, 2 groups Study start and stop dates: Potential participants were identified between 1998 and 2001 Length of intervention: 6 weeks to 6 months, depending on the duration of the adjuvant therapy Length of follow-up: end of intervention
Participants	119 breast cancer patients, stages 0 to III, after surgery, receiving chemotherapy or radiotherapy, sedentary
Interventions	Intervention (n = 60): aerobic training (walking), self directed, 50% to 70% HRmax, 15 min per session, increased to 30 min as training progressed, 5 to 6/x week. Radiotherapy: 6 weeks exercise; chemotherapy: 3 to 6 months exercise. Control (n = 59): usual care
Outcomes	• fatigue: PFS • physical performance: 12-minute walk test • physical activity: Physical Activity Questionnaire (PAQ) • symptoms: Symptom Assessment Scales Outcomes measured at: baseline and end of the adjuvant therapy/intervention
Notes	Funding: FIRE (Fatigue Initiative in Research and Education) multi-institutional award from the Oncology Nursing Society Foundation Conflict of interest: Not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Consecutively numbered, sealed, opaque envelopes, opened after baseline testing
Blinding of participants All outcomes	High risk	Not done
Blinding of personnel/care providers All outcomes	High risk	Not reported Comment: probably not done
Blinding of outcome assessment (detection bias) Fitness outcomes	High risk	Not reported Comment: probably not done
Blinding of outcome assessment (detection bias) All outcomes except fitness outcomes	High risk	Self reported items
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-out: • Intervention group: 6/60 (10%)

Mock 2004 *(Continued)*

		• Control group: 5/59 (8.5%) All participants 11/119 (9.2%) Reported both ITT and per-protocol analysis
Selective reporting (reporting bias)	Unclear risk	No study protocol published
Group similarity at baseline	Low risk	No significant differences
Adherence	High risk	Not adherent: 15/54 (28%). 72% were adherent in the sense of the studies' definition (85% of minimum prescription)
Contamination	High risk	Contamination: 21/54 (39%) of the control group were exercising

Moros 2010

Methods	RCT, 2 groups Study start and stop dates: not reported Length of intervention: 18 to 22 weeks Length of follow-up: 10 to 15 days after end of intervention
Participants	22 breast cancer patients, chemotherapy, not exercising regularly
Interventions	Intervention group (n = 11): "dynamic aerobic exercise" adapted individually, 60-minute sessions at 60% to 70% of maximum heart rate, 3/week Control group (n = 11): usual care
Outcomes	• psychological status, assessed using the General Health Questionnaire • cancer-specific quality of life: EORTC QLQ-C30 Outcomes measured at time point: 10 to 15 days after end of intervention
Notes	Funding: not reported Conflict of interest: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated as randomised, but method not described
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants All outcomes	High risk	Not reported. Comment: probably not done
Blinding of personnel/care providers	High risk	Not reported. Comment: probably not done

Moros 2010 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes except fitness outcomes	High risk	Self reported items
Incomplete outcome data (attrition bias) All outcomes	High risk	Drop-out: • Intervention group: 1/11 (9%) • Control group: 4/11 (36%)
Selective reporting (reporting bias)	Unclear risk	No study protocol published
Group similarity at baseline	High risk	There were more obese women in the control group
Adherence	Unclear risk	Not described
Contamination	Unclear risk	Not described

Mutrie 2007

Methods	RCT; 2 groups, stratification for hospital and treatment Study start and stop dates: recruitment from January 2004 to January 2005 Length of intervention: 12 weeks Length of follow-up: 6 months
Participants	203 breast cancer patients during treatment, chemo- or radiotherapy or both
Interventions	Intervention (n = 101): supervised 12-week group exercise 2 times/week, 45 minutes/session at moderate intensity (aerobic and strength). Participants encouraged to exercise 1x/week at home Control (n = 102): usual care
Outcomes	Primary outcomes: • Cancer-specific quality of life: FACT-G • Cancer site-specific quality of life: FACT-B • Fatigue: FACT-F • Endocrine symptoms: FACT-ES Secondary outcomes: • Depression: BDI • Mood: PANAS • Physical functioning: 12-minute walk test • Shoulder mobility: shoulder mobility test • Physical activity: seven-day recall of physical activity (SPAQ) • Body composition: BMI Outcomes measured at time point: baseline, 12 weeks (intervention: 82, control: 92), and 6-month follow-up (intervention: 82, control: 95), 18 months and 5 years after the intervention
Notes	Funding: Cancer Research UK. One author was funded by the UK Medical Research Council.

Mutrie 2007 *(Continued)*

Conflict of interest: None declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised permuted blocks of length 4 and 6
Allocation concealment (selection bias)	Low risk	"Randomisation was done by telephone to an interactive voice response system"
Blinding of participants All outcomes	High risk	Not done
Blinding of personnel/care providers All outcomes	High risk	Not reported. Comment: probably not done
Blinding of outcome assessment (detection bias) Fitness outcomes	Low risk	"We took steps to blind the evaluation of outcomes by having questionnaire responses in sealed envelopes and ensuring that outcome measures were taken by researchers who were not involved in exercise classes"
Blinding of outcome assessment (detection bias) All outcomes except fitness outcomes	High risk	Self reported items
Incomplete outcome data (attrition bias) All outcomes	High risk	Drop-out: Intervention group: • Week 12: 19/101 (18.8%) • 6 months' postintervention: 17/99 (17.2%) Control group: • Week 12: 10/102 (9.8%) • 6 months' postintervention: 7/102 (6.9%) Comment: Differing rate between groups. Long term (18 months and 5 years >): 30% attrition ITT, no imputation of data
Selective reporting (reporting bias)	Low risk	Study protocol available
Group similarity at baseline	Low risk	"No obvious imbalances existed between study groups." Long term: Differences in baseline demographics between participants that did and did not return for follow-up
Adherence	High risk	Participation in classes: • > 70% classes: 39/99 (38.8%) • 30% to 69% classes: 30/99 (30.6%) • < 30% classes: 30/99 (30.6%)

Mutrie 2007 *(Continued)*

Contamination	Unclear risk	Not reported

Perna 2010

Methods	RCT, 2 groups Study start and stop dates: recruitment between April 2001 and July 2005 Length of intervention: 3 months Length of follow-up: end of the intervention
Participants	51 breast cancer patients, sedentary lifestyle (i.e. exercise less than 3/week for greater than 30 min/session in last 6 months); numbers in each group not reported. Many (44.1%) women received both radiation and chemotherapy, 26.5% received radiation only, 8.8% received chemotherapy only, and 20.6% received no adjuvant therapy
Interventions	Intervention: individualised walking and resistance training program, 2 phases with a hospital-based portion followed by a transition to home-based exercise. Two 30-min exercise adherence counselling sessions during the hospital-based phase. Hospital based: 3 times per week for 4 weeks, aerobic: treadmill walking at 50% to 70% of GXT-derived maximal heart rate (MHR). In subsequent weeks, duration was gradually increased by 5 min for a maximum of 40 min and a minimum of 30 min; intensity was increased to be within 70% to 85% of MHR according to participant comfort. Home based: instructed to walk 3 times per week, encouraged to walk every day for 30 minutes or more. Control: information control, 45 min session and informational brochure
Outcomes	• Depression: CES-D • Physical activity: GLTEQ Outcomes measured at baseline and 3 months
Notes	Funding: National Cancer Institute (CAR0178801) and National Institutes of Health, General Clinical Research Grant (M01RR00533) Conflict of interest: Not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number sequence table
Allocation concealment (selection bias)	Low risk	Participant assignment to groups at enrolment was concealed from the project director
Blinding of participants All outcomes	High risk	Not done
Blinding of personnel/care providers All outcomes	High risk	Not reported. Comment: probably not done

Perna 2010 *(Continued)*

Blinding of outcome assessment (detection bias) Fitness outcomes	Low risk	Physicians monitoring graded exercise tests were blinded to participant group assignment. Similarly, a physical therapist or an exercise physiologist, blinded to participant assignment, performed strength assessments. Comment: No fitness outcomes reported in this paper
Blinding of outcome assessment (detection bias) All outcomes except fitness outcomes	High risk	Self reported items
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Numbers randomised to each arm are as well as completion rates are unclear. "we used regression modeling to impute missing values to conduct our analyses." Amount of missing data was not reported
Selective reporting (reporting bias)	Unclear risk	Further outcomes to be reported in another paper
Group similarity at baseline	Low risk	"found no significant differences with respect to demographic, cancer stage, treatment, and exercise characteristics."
Adherence	Low risk	Completed an average of 83% of their scheduled hospital-based exercise sessions (M = 9.9, SD = 3.3 sessions); 76.9% completed all 12 sessions
Contamination	Unclear risk	Contamination not reported/GLTEQ scores increased from baseline by 32.7% in the control group

Rao 2012

Methods	RCT, 2 groups Study start and stop dates: all participants were diagnosed and treated between March 2009 and April 2011 Length of intervention: 4 to 6 months (duration of chemotherapy) Length of follow-up: a median follow-up of 21.6 months
Participants	Women undergoing neoadjuvant chemotherapy for locally advanced, non-metastatic breast cancer. Women had to have oestrogen receptor-positive breast cancer, a BMI greater than 25, and a Karnofsky score > 80%
Interventions	Intervention (n = 5): home-based exercise program, supervised, one on one, 3 times per week. Aerobic exercises and light weight lifting. Control (n = 5): usual care
Outcomes	• "Improving fitness levels" (stated as an outcome in the trial registration) • Body composition: BMI, per cent body fat • Ki-67 • C-peptide • Tumour size Outcomes measured before and after neoadjuvant chemotherapy

Rao 2012 *(Continued)*

Notes	ClinicalTrials.gov (NCT01411787) Funding: Grant given by the Commercial Real Estate Women of Dallas Conflict of interest: None declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomization will occur by drawing cards entitled 'exercise' or 'control' from an envelope and then assigning the patient to this group." (ClinicalTrials.gov)
Allocation concealment (selection bias)	Unclear risk	An unlabeled envelope was opened by the research co-ordinator to place the participant in either the control or boot camp arm of the study
Blinding of participants All outcomes	High risk	Not done
Blinding of personnel/care providers All outcomes	High risk	Not reported Comment: probably not done
Blinding of outcome assessment (detection bias) Fitness outcomes	High risk	Not reported Comment: probably not done
Incomplete outcome data (attrition bias) All outcomes	Low risk	10 women were randomised and completed all study parameters and were included in the analysis. All women were analysed in their respective group
Selective reporting (reporting bias)	High risk	"Improving fitness levels" not reported in results paper
Group similarity at baseline	Low risk	There were no statistically significant differences between groups with regard to tumour size, age, BMI, tumour grade, C-peptide levels, or initial Ki-67
Adherence	Low risk	All 5 women in the exercise group completed > = 80% of the advised exercise sessions
Contamination	Unclear risk	Women were allowed to engage in their own exercise regimens and diet modifications. (ClinicalTrials.gov) BMI > 25, therefore "unlikely to have previously exercised" Comment: amount of physical activity not reported

Reis 2013

Methods	RCT, 2 groups Study start and stop dates: November 2008 to January 2010 Length of intervention: 12 weeks Length of follow-up: end of intervention

Reis 2013 *(Continued)*

Participants	41 breast cancer patients randomised, stage I to III, starting adjuvant radiotherapy. 26 participants (13 in each group) additionally received chemotherapy, 19 (10 in the exercise group and 9 in the control group) received hormone therapy, the latter "typically after chemotherapy and radiation therapy"
Interventions	Intervention group (n = 22 randomised): Nia exercise ("cardiovascular and whole-body conditioning program") 20 to 60 minutes 3 x per week for 12 weeks, and 3 meetings with principal investigator Control group (n = 19 randomised): usual care and 3 meetings with principal investigator, instructed to continue normal activities
Outcomes	• Fatigue: FACIT-F • Quality of life: FACT-G • Cardiorespiratory fitness: 6-MWT • Shoulder flexibility: goniometer Outcomes were measured at start of radiation therapy, the completion of radiation therapy, and 6 weeks after completion of radiation therapy. Some participants received more than 6 weeks of radiotherapy
Notes	Funding: Not reported. Conflict of interest: "No financial relationships to disclose."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study described as "randomized", method not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants All outcomes	High risk	Not done
Blinding of personnel/care providers All outcomes	High risk	Not reported. Comment: probably not done
Blinding of outcome assessment (detection bias) Fitness outcomes	High risk	Not reported. Comment: probably not done
Blinding of outcome assessment (detection bias) All outcomes except fitness outcomes	High risk	Self reported items
Incomplete outcome data (attrition bias) All outcomes	High risk	Drop-out (did not complete the 12-week assessment): • Exercise group: 1/22 • Control group: 2/19 Outcome data not reported for non-adherent women in the exercise group. Per-protocol analysis: The statistical analyses for fatigue, QoL, aerobic capacity, and shoulder flexibility compared the 12 women who practiced Nia to the

Reis 2013 *(Continued)*

		17 women randomised to the control group for whom data were collected at baseline, 6 weeks, and 12 weeks
Selective reporting (reporting bias)	Unclear risk	No study protocol published, study not registered prospectively
Group similarity at baseline	High risk	"The two groups did not differ statistically in their demographics, although clinical differences appear to exist in age and employment, with the Nia group aged, on average, five years younger and more likely to be working full time than the control group."
Adherence	High risk	Assessed by reviewing participant logs. Logs were not uniformly maintained. Only 12 of 22 participants in the Nia group were adherent
Contamination	High risk	"66% of participants (n = 27) reported engaging in aerobic activity for at least three 20-minute sessions per week prior to the cancer diagnosis. About 74% of those women (n = 20) continued to exercise during radiation therapy. No significant difference existed in the exercise history of the Nia group compared to the control group." Women in the control group reported engaging in aerobic exercise 0 to 41 times, or an average of almost 3 days per week (34 days in 6 weeks average)

Schmidt 2014

Methods	RCT, 2 groups Study start and stop dates: April 2010 and August 2013 Length of intervention: 12 weeks Length of follow-up: "Follow-up data were also collected but not considered in the primary analyses"
Participants	101 randomised patients with breast cancer under adjuvant chemotherapy
Interventions	Intervention (n = 52): 12-week supervised machine-based progressive resistance training program, 60 minutes 2x/week, 3 sets, 8 to 12 repetitions at 60% to 80% of 1 repetition maximum (1-RM) Control group (n = 49): supervised group-based progressive muscle relaxation training according to Jacobson, 60 minutes 2x/week
Outcomes	Primary endpoint: • Cancer-related fatigue: Fatigue Assessment Questionnaire (FAQ) Secondary endpoints: • Cancer site-specific quality of life: EORTC QLQ-BR23 questionnaire • Depression: CES-D • Cognitive function: Trail Making Test • Safety of the resistance training during chemotherapy is monitored • Body composition: bioimpedance analysis, weight, height, waist and hip circumference • Muscle strength: isometric and isokinetic strength of representative muscle groups for upper and lower extremity measured at the IsoMed2000W • Cardiorespiratory fitness: spiroergometry (VO_2 peak) • Shoulder flexibility: range of motion measured at the IsoMed2000W • Biomarkers: inflammatory parameters, cortisol, and oxidative stress in blood, saliva, and urine

Schmidt 2014 *(Continued)*

	Outcomes measured during the first or second chemotherapy cycle pre-intervention (baseline) and postintervention (week 13)
Notes	BEATE study, ClinicalTrials.gov registration: NCT01106820 Funding: German Cancer Research Center (DKFZ), Division of Preventive Oncology. Foundations: "Stiftung Leben mit Krebs" and "Manfred-Lautenschlaeger-Stiftung". Conflict of interest: Not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomly allocated 1:1": predetermined lists with random block size, stratified by age and baseline physical fatigue level
Allocation concealment (selection bias)	Low risk	Allocation was performed by a biostatistician uninvolved in recruitment, based on predetermined lists with random block size, stratified by age and baseline physical fatigue level. Other study personnel did not have access to the randomisation lists
Blinding of participants All outcomes	High risk	Not done
Blinding of personnel/care providers All outcomes	High risk	Not reported. Comment: probably not done
Blinding of outcome assessment (detection bias) Fitness outcomes	High risk	Not reported. Comment: probably not done
Blinding of outcome assessment (detection bias) All outcomes except fitness outcomes	High risk	Self reported items
Incomplete outcome data (attrition bias) All outcomes	Low risk	Pre- and postintervention assessment of the primary endpoint was available in a total of 95 of 101 (94%) participants, 49 in exercise group and 46 in relaxation control group. "intent-to-treat-basis". "As very few fatigue values were missing (3%), we performed complete-case analyses"
Selective reporting (reporting bias)	High risk	Registered at ClinicalTrials.gov (NCT01106820), study protocol published, not all outcomes reported in this publication
Group similarity at baseline	High risk	Baseline characteristics, fatigue, and QoL were similarly distributed between both intervention groups, except for depression, which was significantly more common in the relaxation control group than in the exercise group. 2 in control group with metastasised cancer
Adherence	High risk	Median attendance was similar in both groups, with 17 out of 24 scheduled sessions attended (71%; interquartile range 11 to 22 in the exercise group and 11 to 23 in the relaxation control group)

Schmidt 2014 *(Continued)*

Contamination	Unclear risk	Patients already participating in systematic intensive resistance or aerobic training (at least 1 hr twice/week) were excluded. Otherwise not reported

Schwartz 2007 AET

Methods	RCT, parallel 3-group design, stratified according to menopausal status (premenopausal or post-menopausal). Study start and stop dates: not reported Length of intervention: 6 months Length of follow-up: end of intervention
Participants	72 breast cancer patients, stages I to III (histologically confirmed); planning to begin chemotherapy with doxorubicin or methotrexate and receiving a glucocorticoid as part of the antiemetic regimen. Strenuous regular exercisers, that is women who exercised more than 250 minutes per week, were excluded
Interventions	**Intervention group 1 (n = 22): 'Schwartz AET' Aerobic exercise training (participant preferences); 77% weight-bearing activities (walking/running), 15 to 30 minutes, 4 days per week** Intervention group 2 (n = 21): 'Schwartz RET' Resistance exercise (Thera-Band), 2 sets of 8 exercises (4 upper and 4 lower body) Control group (n = 23): usual care, women were instructed to continue usual activities, were not instructed to avoid exercise
Outcomes	• Cardiorespiratory fitness: 12-minute walk test • Strength: 1 repetition maximum • Bone mass density: Dual-energy X-ray absorptiometry Outcomes measured at baseline and 6 months
Notes	Funding: Not reported Conflict of interest: Not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants All outcomes	High risk	Not done
Blinding of personnel/care providers All outcomes	High risk	Not reported Comment: probably not done
Blinding of outcome assessment (detection bias) Fitness outcomes	High risk	Not reported Comment: probably not done

Schwartz 2007 AET *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes except fitness outcomes	Unclear risk	No other relevant outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-out: • Intervention group 1 (aerobic): 8.3% (2/24) • Intervention group 2 (resistance): 8.7% (2/23) • Control group: 8% (2/25) All participants: 8.3% (6/72) No data imputation
Selective reporting (reporting bias)	Unclear risk	No study protocol published
Group similarity at baseline	Low risk	No significant differences
Adherence	Unclear risk	No adherence data available
Contamination	Unclear risk	Not reported. Control group not sedentary before cancer diagnosis

Schwartz 2007 RET

Methods	RCT, parallel 3-group design, stratified according to menopausal status (premenopausal or postmenopausal). Study start and stop dates: not reported Length of intervention: 6 months Length of follow-up: end of intervention
Participants	72 breast cancer patients, stages I to III (histologically confirmed); planning to begin chemotherapy with doxorubicin or methotrexate and receiving a glucocorticoid as part of the antiemetic regimen. Strenuous regular exercisers, that is women who exercised more than 250 minutes per week, were excluded
Interventions	Intervention group 1 (n = 22): 'Schwartz AET' Aerobic exercise training (participant preferences); 77% weight-bearing activities (walking/running), 15 to 30 minutes, 4 days per week **Intervention group 2 (n = 21): 'Schwartz RET' Resistance exercise (Thera-Band), 2 sets of 8 exercises (4 upper and 4 lower body)** Control group (n = 23): usual care, women were instructed to continue usual activities, were not instructed to avoid exercise
Outcomes	• Cardiorespiratory fitness: 12-minute walk test • Strength: 1 repetition maximum • Bone mass density: Dual-energy X-ray absorptiometry Outcomes measured at baseline and 6 months
Notes	Funding: Not reported

Schwartz 2007 RET *(Continued)*

Conflict of interest: Not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants All outcomes	High risk	Not done
Blinding of personnel/care providers All outcomes	High risk	Not reported Comment: probably not done
Blinding of outcome assessment (detection bias) Fitness outcomes	High risk	Not reported Comment: probably not done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-out: • Intervention group 1 (aerobic): 8.3% (2/24) • Intervention group 2 (resistance): 8.7% (2/23) • Control group: 8% (2/25) All participants: 8.3% (6/72) No data imputation
Selective reporting (reporting bias)	Unclear risk	No study protocol published
Group similarity at baseline	Low risk	No significant differences
Adherence	Unclear risk	No adherence data available
Contamination	Unclear risk	Not reported. Control group not sedentary before cancer diagnosis

Segal 2001 SD

Methods	RCT, 3 groups Study start and stop dates: not reported Length of intervention: 26 weeks Length of follow-up: end of intervention
Participants	123 patients within 2 weeks of the initiation of their prescribed adjuvant therapy (radiotherapy, hormonal therapy, or chemotherapy). Patients receiving only alternative or dose-intensive chemotherapy regimens were excluded

Segal 2001 SD *(Continued)*

Interventions	**Intervention group 1: 'Segal 2001 SD' self directed aerobic training (n = 40): progressive walking program at an exercise intensity of 50% to 60% of the predicted maximal oxygen uptake** Intervention group 2: 'Segal 2001 SU' supervised training (n = 42): progressive walking program at an exercise intensity of 50% to 60% of the predicted maximal oxygen uptake Control group (n = 41): usual care
Outcomes	Primary outcome: • physical functioning scale of the SF-36 Secondary outcomes: • generic QoL: MOS SF-36 • cancer-specific QoL: FACT-G • cancer site-specific QoL: FACT-B • cardiorespiratory fitness: mL of O_2/kg/min • body composition: body weight Outcomes measured at baseline and 26 weeks
Notes	Funding: National Cancer Institute of Canada with funds from the Canadian Cancer Society (Grant in Aid of Research No. 7191) Conflict of interest: Not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers table
Allocation concealment (selection bias)	Unclear risk	Study co-ordinator revealed group assignment after baseline testing. Method not described
Blinding of participants All outcomes	High risk	Not done
Blinding of personnel/care providers All outcomes	High risk	Not reported. Comment: probably not done
Blinding of outcome assessment (detection bias) Fitness outcomes	High risk	Not reported. Comment: probably not done
Blinding of outcome assessment (detection bias) All outcomes except fitness outcomes	High risk	Self reported items
Incomplete outcome data (attrition bias) All outcomes	Low risk	• Self directed intervention group: 7/40 (17.5%) • Supervised intervention group: 10/42 (23.1%) • Control group: 7/41 (17.5%) End-of-intervention (26-week) data were obtained for 99 participants (80.4%)

Segal 2001 SD *(Continued)*

		ITT with imputation (most recent observed)
Selective reporting (reporting bias)	Unclear risk	No study protocol published prospectively. FACT-G and FACT-B: no detailed results, but stated that no significant differences
Group similarity at baseline	Low risk	"Baseline demographic, body weight, aerobic capacity, prior level of physical activity, and disease treatment characteristics of the subjects did not differ among the three groups. There were no baseline differences among groups for the eight SF-36 scales"
Adherence	High risk	Adherence in intervention groups: • Home based: 93/130 sessions (71.5%) • Centre based: 93/130 sessions (71.5%)
Contamination	Unclear risk	Not reported

Segal 2001 SU

Methods	RCT, 3 groups Study start and stop dates: not reported Length of intervention: 26 weeks Length of follow-up: end of intervention
Participants	123 patients within 2 weeks of the initiation of their prescribed adjuvant therapy (radiotherapy, hormonal therapy, or chemotherapy). Patients receiving only alternative or dose-intensive chemotherapy regimens were excluded
Interventions	Intervention group 1: 'Segal 2001 SD' self directed aerobic training (n = 40): progressive walking program at an exercise intensity of 50% to 60% of the predicted maximal oxygen uptake **Intervention group 2: 'Segal 2001 SU' supervised training (n = 42): progressive walking program at an exercise intensity of 50% to 60% of the predicted maximal oxygen uptake** Control group (n = 41): usual care
Outcomes	Primary outcome: • physical functioning scale of the SF-36 Secondary outcomes: • generic QoL: MOS SF-36 • cancer-specific QoL: FACT-G • cancer site-specific QoL: FACT-B • cardiorespiratory fitness: mL of O_2/kg/min • body composition: body weight Outcomes measured at baseline and 26 weeks
Notes	Funding: National Cancer Institute of Canada with funds from the Canadian Cancer Society (Grant in Aid of Research No. 7191) Conflict of interest: Not reported
Risk of bias	

Segal 2001 SU *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers table
Allocation concealment (selection bias)	Unclear risk	Study co-ordinator revealed group assignment after baseline testing. Method not described
Blinding of participants All outcomes	High risk	Not done
Blinding of personnel/care providers All outcomes	High risk	Not reported. Comment: probably not done
Blinding of outcome assessment (detection bias) Fitness outcomes	High risk	Not reported. Comment: probably not done
Blinding of outcome assessment (detection bias) All outcomes except fitness outcomes	High risk	Self reported items
Incomplete outcome data (attrition bias) All outcomes	Low risk	• Self directed intervention group: 7/40 (17.5%) • Supervised intervention group: 10/42 (23.1%) • Control group: 7/41 (17.5%) End-of-intervention (26-week) data were obtained for 99 participants (80.4%) ITT with imputation (most recent observed)
Selective reporting (reporting bias)	Unclear risk	No study protocol published prospectively. FACT-G and FACT-B: no detailed results, but stated that no significant differences
Group similarity at baseline	Low risk	"Baseline demographic, body weight, aerobic capacity, prior level of physical activity, and disease treatment characteristics of the subjects did not differ among the three groups. There were no baseline differences among groups for the eight SF-36 scales"
Adherence	High risk	Adherence in intervention groups: • Home based: 93/130 sessions (71.5%) • Centre based: 93/130 sessions (71.5%)
Contamination	Unclear risk	Not reported

Steindorf 2014

Methods	RCT, 2 groups Study start and stop dates: February 2011 and March 2013 Length of intervention: 12 weeks Length of follow-up: end of intervention

Steindorf 2014 *(Continued)*

Participants	160 randomised participants with breast cancer (stage I to III after lumpectomy or mastectomy) undergoing adjuvant radiotherapy
Interventions	Intervention (n = 80): supervised machine-based progressive resistance training, 60 minutes, 2x/week, 3 sets, 8 to 12 repetitions at 60% to 80% of 1 repetition maximum Control (n = 80): supervised muscle relaxation training according to Jacobson, 60 minutes 2x/week
Outcomes	Primary endpoint: • Cancer-related fatigue: Fatigue Assessment Questionnaire (FAQ) Secondary endpoints: • Quality of life: EORTC QLQ-BR23 questionnaire • Depression: CES-D • Cognitive function: Trail Making Test • Body composition: bioimpedance analysis, weight, height, waist and hip circumference • Muscle strength: isometric and isokinetic strength of representative muscle groups for upper and lower extremity measured at the IsoMed2000W • Cardiorespiratory fitness: spiroergometry (VO_2 peak) • Flexibility: range of motion measured at the IsoMed2000W • Biomarkers Outcomes measured before start of radiotherapy (baseline, T0), postradiotherapy (week 7, T1), and postintervention (week 13, T2)
Notes	BEST study, registered at ClinicalTrials.gov (NCT01468766) Funding: Interdisciplinary Research Funding Program (intramural) of the National Center for Tumor Diseases (NCT), Heidelberg, Germany (grant number IFP project VI.1); foundations “Stiftung Leben mit Krebs” and the "Manfred-Lautenschlaeger-Stiftung” Conflict of interest: None declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Predetermined list generated with a blocked randomisation SAS procedure with a fixed block size, stratified by age and baseline physical fatigue level
Allocation concealment (selection bias)	Low risk	Allocation is done by the biometrician based on a predetermined list generated with a blocked randomisation SAS procedure with a fixed block size, stratified by age and baseline physical fatigue level. To prevent possible bias, study personnel involved in the recruitment and the baseline assessment do not have access to the randomisation lists and are not aware of the block size. Conversely, the biometrician does not have influence on the recruitment procedure
Blinding of participants All outcomes	High risk	Not done
Blinding of personnel/care providers All outcomes	High risk	Not reported Comment: probably not done

Steindorf 2014 *(Continued)*

Blinding of outcome assessment (detection bias) Fitness outcomes	High risk	Not reported Comment: probably not done
Blinding of outcome assessment (detection bias) All outcomes except fitness outcomes	High risk	Self reported items
Incomplete outcome data (attrition bias) All outcomes	Low risk	Pre- and postintervention assessment of the primary endpoint was available for a total of 155 (97%) participants, 77 in the exercise group and 78 in the relaxation control group. Data were analysed on an ITT basis. As the number of missing fatigue values was very low (3%), we performed complete-case analyses
Selective reporting (reporting bias)	High risk	Registered at ClinicalTrials.gov (NCT01468766), study protocol published. Not all outcomes reported in this publication
Group similarity at baseline	Low risk	Demographics and treatment characteristics did not differ significantly between both intervention groups. All primary and secondary outcome variables were equally distributed in exercise and relaxation control groups at baseline (all $P > 0.05$), except for the EORTC symptom dry mouth ($P = 0.033$)
Adherence	High risk	The median attended number out of 24 scheduled sessions was 19 in both groups (79%). (QR: 13 to 23, range 1 to 24) in exercise group and (QR: 12 to 22, range 0 to 24) in relaxation control group
Contamination	Unclear risk	Patients already participating in systematic intensive resistance or aerobic training (at least 1 hr twice/week) were excluded. Otherwise not reported

Travier 2015

Methods	RCT, 2 groups Study start and stop dates: conducted between 2010 and 2013 Length of intervention: 18 weeks Length of follow-up: 18 weeks
Participants	Patients with breast or colon cancer undergoing cancer treatment (204 breast cancer patients of 237 patients in total), intervention started 6 weeks postdiagnosis. Unpublished data (final values) for breast cancer patients used in the analyses of this review
Interventions	Intervention (n = 102): supervised group exercise (aerobic and resistance) program based on Bandura's social cognitive theory Control (n = 102): asked to maintain their habitual physical activity pattern
Outcomes	Primary outcome: • fatigue: MFI and FQL Secondary outcomes:

Travier 2015 *(Continued)*

- HRQoL: SF-36
- cancer-specific quality of life: EORTC QLQ-C30 (Version 3)
- anxiety and depression: HADS (Dutch version)
- physical fitness: VO_2 peak; peak power output
- strength: thigh muscle strength, handgrip strength
- body composition: BMI, body fat distribution
- physical activity level: Short QUestionnaire to ASsess Health enhancing physical activity (SQUASH)
- self efficacy about the performance of physical activity (design paper)
- perceived impact of the disease on participation and autonomy assessed: Impact on Participation and Autonomy (IPA) questionnaire (design paper)

Notes	Trial registration: Current Controlled Trials (ISRCTN43801571), Dutch Trial Register (NTR2138)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Concealed computer-generated randomisation, 1:1 ratio, stratified per age, adjuvant treatment, use of tissue expander, and hospital by sequential balancing
Allocation concealment (selection bias)	Low risk	"After the patient signed informed consent, the researcher (who was with the patient) called the data management department and provided the participants study number and the information necessary for stratification. The data manager then performed the randomization using a computer program and informed the researcher about the allocation (and also noted the allocation in the randomization log)."
Blinding of participants All outcomes	High risk	"not possible"
Blinding of personnel/care providers All outcomes	High risk	Not reported Comment: probably not done
Blinding of outcome assessment (detection bias) Fitness outcomes	Low risk	Outcome measures were assessed by researchers not involved with the participants
Blinding of outcome assessment (detection bias) All outcomes except fitness outcomes	High risk	Self reported items
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-out after 18 weeks: • intervention group: 13/102 (12.7%) • control group: 9/102 (8.8%) Follow-up: high risk Drop-out after 36 weeks: • intervention group: 15/102 (14.7%) • control group: 25/102 (24.5%)
Selective reporting (reporting bias)	High risk	Design paper published.

Travier 2015 *(Continued)*

		EQ-5D, IPA (Impact on Participation and Autonomy), self efficacy (items based on social cognitive theory) mentioned in the design paper, but not in the publication
Group similarity at baseline	High risk	"were comparable on most characteristics" Comment: More women in the intervention group were highly educated, had triple-negative breast cancer, and were postmenopausal. Total physical activity levels tended to be higher in the control group
Adherence	Low risk	Participation in 83% (IQR 69% to 91%) of the classes. Reported to be physically active in 11 (IQR 6 to 14) of 18 weeks
Contamination	High risk	High level of physical activity reported by 56% of the controls at 18 weeks

van Waart 2014 high

Methods	RCT, 3 groups Study start and stop dates: recruitment between March 2010 and December 2012 Length of intervention: approximately 20 weeks Length of follow-up: 6 months
Participants	Patients with breast or colon cancer receiving adjuvant chemotherapy, 230 patients with breast cancer of 253 patients in total. Both intervention groups started exercising in the week of the first cycle of chemotherapy and continued until 3 weeks after the last cycle of chemotherapy. Mean length of chemotherapy 119.6 days (17 weeks)
Interventions	1. Intervention group (n = 77): Onco-Move, a relatively low-intensity, home-based, individualised, self managed physical activity program **2. Intervention group (n = 76): OnTrack, a relatively high-intensity exercise program supervised by a physical therapist in an outpatient or general physical therapy practice setting** 3. Control group (n = 77): usual care
Outcomes	Primary outcomes: • Cardiorespiratory fitness: Steep Ramp Test; endurance test at 70% of the estimated maximal workload • Muscle strength: microFET handheld dynamometer for elbow flexion and knee extension; grip strength dynamometer; lower limb muscle endurance with the 30-second chair stand test • Fatigue: MFI; FQL Secondary outcomes: • Cancer-specific quality of life: EORTC QLQ-C30 • Chemotherapy completion rates • Psychological distress: HADS • Self reported physical activity level: Physical Activity Scale for the Elderly • Functioning in daily life: Impact on Participation and Autonomy • Quality of sleep: Pittsburgh Sleep Quality Index • Return to work: Return to work questionnaire (study specific) • Anthropometric measures: skinfold measurements (Harpenden); waist and hip circumferences

van Waart 2014 high *(Continued)*

	Outcomes assessed: before random assignment and start of chemotherapy (T0), at completion of chemotherapy (T1), and 6 months after completion of chemotherapy (T2)
Notes	Published protocol. Trial registration: The Netherlands Trial Register (NTR 2159) Funding: Supported by Alpe d'Huzes/Dutch Cancer Society Grant No. ALPE-2009-4299, the CZ Fund, Zilveren Kruis Achmea, and the Comprehensive Cancer Centre of the Netherlands. Conflicts of interest: 2 authors disclosed research funding by pharmaceutical companies

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomly assigned to Onco-Move, OnTrack, or UC using the minimization method, which balanced groups with respect to age, primary diagnosis, treating hospital, and use of trastuzumab."
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants All outcomes	High risk	Not done
Blinding of personnel/care providers All outcomes	High risk	Not reported. Comment: probably not done
Blinding of outcome assessment (detection bias) Fitness outcomes	High risk	Not reported. Comment: probably not done
Blinding of outcome assessment (detection bias) All outcomes except fitness outcomes	High risk	Self reported items
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data were available for 204 participants (89%) directly after chemotherapy, and for 196 (85%) at the 6-month follow-up. ITT without imputation
Selective reporting (reporting bias)	High risk	Differences between design paper and final publication (EQ-5D, anthropometric measures and actigraph not mentioned in the final publication). Chemotherapy completion rate mentioned as outcome in the final publication, but not in the design paper
Group similarity at baseline	Low risk	Baseline characteristics were balanced across groups
Adherence	High risk	On average, participants in OnTrack attended 71% of the planned sessions. On the basis of the exercise diary, 48% of the OnTrack group and 55% of the Onco-Move group followed the recommendations regarding daily activity levels at least 75% of the time
Contamination	Unclear risk	Not reported

van Waart 2014 low

Methods	RCT, 3 groups Study start and stop dates: recruitment between March 2010 and December 2012 Length of intervention: approximately 20 weeks Length of follow-up: 6 months
Participants	Patients with breast or colon cancer receiving adjuvant chemotherapy, 230 patients with breast cancer of 253 patients in total. Both intervention groups started exercising in the week of the first cycle of chemotherapy and continued until 3 weeks after the last cycle of chemotherapy. Mean length of chemotherapy 119.6 days (17 weeks)
Interventions	**1. Intervention group (n = 77): Onco-Move, a relatively low-intensity, home-based, individualised, self managed physical activity program** 2. Intervention group (n = 76): OnTrack, a relatively high-intensity exercise program supervised by a physical therapist in an outpatient or general physical therapy practice setting 3. Control group (n = 77): usual care
Outcomes	Primary outcomes: • Cardiorespiratory fitness: Steep Ramp Test; endurance test at 70% of the estimated maximal workload • Muscle strength: microFET handheld dynamometer for elbow flexion and knee extension; grip strength dynamometer; lower limb muscle endurance with the 30-second chair stand test • Fatigue: MFI; FQL Secondary outcomes: • Cancer-specific quality of life: EORTC QLQ-C30 • Chemotherapy completion rates • Psychological distress: HADS • Self reported physical activity level: Physical Activity Scale for the Elderly • Functioning in daily life: Impact on Participation and Autonomy • Quality of sleep: Sleep Quality Inventory • Return to work: Return to work questionnaire (study specific) • Anthropometric measures: skinfold measurements (Harpenden); waist and hip circumferences Outcomes assessed: before random assignment and start of chemotherapy (T0), at completion of chemotherapy (T1), and 6 months after completion of chemotherapy (T2)
Notes	Published protocol. Trial registration: The Netherlands Trial Register (NTR 2159) Funding: Supported by Alpe d'Huzes/Dutch Cancer Society Grant No. ALPE-2009-4299, the CZ Fund, Zilveren Kruis Achmea, and the Comprehensive Cancer Centre of the Netherlands. Conflicts of interest: 2 authors disclosed research funding by pharmaceutical companies

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomly assigned to Onco-Move, OnTrack, or UC using the minimization method, which balanced groups with respect to age, primary diagnosis, treating hospital, and use of trastuzumab."

van Waart 2014 low *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants All outcomes	High risk	Not done
Blinding of personnel/care providers All outcomes	High risk	Not reported. Comment: probably not done
Blinding of outcome assessment (detection bias) Fitness outcomes	High risk	Not reported. Comment: probably not done
Blinding of outcome assessment (detection bias) All outcomes except fitness outcomes	High risk	Self reported items
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data were available for 204 participants (89%) directly after chemotherapy, and for 196 (85%) at the 6-month follow-up. ITT without imputation
Selective reporting (reporting bias)	High risk	Differences between design paper and final publication (EQ-5D, anthropometric measures and actigraph not mentioned in the final publication). Chemotherapy completion rate mentioned as outcome in the final publication, but not in the design paper
Group similarity at baseline	Low risk	Baseline characteristics were balanced across groups
Adherence	High risk	On average, participants in OnTrack attended 71% of the planned sessions. On the basis of the exercise diary, 48% of the OnTrack group and 55% of the Onco-Move group followed the recommendations regarding daily activity levels at least 75% of the time
Contamination	Unclear risk	Not reported

Visovsky 2014

Methods	RCT, 2 groups Study start and stop dates: final enrolment completed August 2010, otherwise not reported Length of intervention: 12 weeks Length of follow-up: 12 weeks' postintervention
Participants	Breast cancer patients receiving weekly paclitaxel for 2 months, randomisation after 4 cycles of doxorubicin and cyclophosphamide were completed, and prior to the first paclitaxel infusion
Interventions	Intervention group (n = 9): home-based aerobic (walking and progressive interval training) and resistance exercises for upper and lower extremities using resistance power bands. Brisk walking 5 to 7 days per week for the first 4 weeks, weeks 4 to 12 interval-based workout consisting of light- to moderate-intensity exercises performed for 30 minutes. Strength training sessions: 3 times/week, initially: 1 to 2 sets of each exercise for 8 repetitions 1 to 2 times per week. From week 4, the number of sets was increased to 2 to 3 sets and 8 to 12 repetitions of each exercise per session.

Visovsky 2014 *(Continued)*

	Control group (n = 10): breast cancer educational information, avoiding those topics related to exercise/physical activity in order to prevent contamination between groups. Educational sessions at the same intervals as intervention group
Outcomes	• Neuropathic symptoms: FACT-Taxane • Cancer-specific quality of life: FACT-G • Gait and balance: Timed Get-up and Go Test • Symptom experience: Symptom Experience Scale Outcomes were assessed at baseline, 4 weeks, 12 weeks, 24 weeks. Adverse events: No injuries or falls were reported
Notes	Funding: This study was supported by a grant from the University of Nebraska Medical Center, Eppley Cancer Center, Dean's Grant. Conflict of interest: None reported. Registered prospectively on ClinicalTrials.gov: NCT00869804

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation was generated using sealed envelopes that were numbered and selected sequentially
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes. Comment: not mentioned if they were opaque
Blinding of participants All outcomes	High risk	Not done
Blinding of personnel/care providers All outcomes	High risk	The research nurses conducted all recruitment, data collection, and study interventions. The principal investigator provided ongoing supervision of the intervention
Blinding of outcome assessment (detection bias) Fitness outcomes	High risk	The research nurses conducted all recruitment, data collection, and study interventions. The principal investigator provided ongoing supervision of the intervention
Blinding of outcome assessment (detection bias) All outcomes except fitness outcomes	High risk	Self reported items
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No dropouts or missing data reported. All study participants were evaluated according to the randomisation schema regardless of completion of exercise sessions
Selective reporting (reporting bias)	High risk	Outcomes muscle strength, cold thermal sensation, and vibratory sensation, which were mentioned on ClinicalTrials.gov, were not reported. Results for symptom experience were not reported
Group similarity at baseline	Unclear risk	"No significant differences"

Visovsky 2014 *(Continued)*

Adherence	High risk	Participants were given a diary to record both aerobic and resistance exercises. In order to objectively capture the aerobic exercise component, each exercise group participant was given a pedometer to be worn for each walking session throughout the entire 24-week study. Mean walking time per week in minutes: 44.6
Contamination	Unclear risk	Participants completed the Leisure Time Exercise (LTE) questionnaire at the baseline interview; "No significant differences" Participants assigned to the attention control group agreed not to begin a new exercise program or change their level of exercise during the course of the study. Level of exercise during study not reported

Winningham 1988

Methods	RCT, 3 groups Study start and stop dates: not reported Length of intervention: 10 weeks Length of follow-up: end of intervention
Participants	42 breast cancer patients, after surgery, receiving chemotherapy, within the first 6 months of chemotherapy, but having had at least 3 treatments prior to entering the study program, not on doxorubicin, Karnofsky 60% to 100%. None of the participants received antiemetic medication
Interventions	Intervention (n = 16): aerobic training (cycling, interval training), 60% to 85% HRmax, 20 to 30 min per session, 3/week, 10 weeks, supervised Control group 1 (n = 12): no intervention Control group 2 (n = 14): "placebo" mild stretching, conversation, 1/week, supervised
Outcomes	• Nausea: Symptom Checklist 90 Revised (SCL-90-R) • Somatisation: SCL-90-R Outcomes measured at baseline and end of intervention
Notes	Funding: Not reported Conflict of interest: Not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated as randomised. The generation of the random sequence was not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants All outcomes	High risk	Placebo group Comment: Patients in the placebo group would have been aware that they were not in the exercise group, but in the stretching group

Winningham 1988 *(Continued)*

Blinding of personnel/care providers All outcomes	High risk	Not reported. Comment: probably not done
Blinding of outcome assessment (detection bias) All outcomes except fitness outcomes	High risk	Self reported items
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were accounted for
Selective reporting (reporting bias)	High risk	Participants answered all 90 items of the SCL-90-R. Hereby, "the investigators hoped to avoid sensitizing patients to awareness of any one symptom". Results for other items apart from nausea and somatisation part were not reported
Group similarity at baseline	High risk	"similar in age, height and body weight". Participants in control group were higher educated than those in exercise and placebo groups. Placebo group had more married women than exercise and placebo groups.
Adherence	Unclear risk	Not reported
Contamination	Unclear risk	Contamination not reported. Inclusion criterion: "not in an exercise program". Control participants were advised to notify project personnel if they began exercising on a regular basis either as part of a group or on their own

Yang 2011

Methods	RCT, 2 groups Study start and stop dates: 2008 to 2009 Length of intervention: 12 weeks Length of follow-up: end of intervention
Participants	44 sedentary breast cancer patients randomised, 40 completed the study
Interventions	Intervention group (n = 19): home-based walking program, developed using the American College of Sports Medicine guidelines. Walking starting 2 to 3 days after each chemotherapy session, included 5 minutes warm-up, 30 minutes brisk walking (60% to 80% of age-adjusted HRmax), 5 minutes cool-down Control group (n = 21): maintenance of their previous lifestyle for 12 weeks
Outcomes	• symptom severity: MDASI-T • symptom interference with daily life: MDASI-T • emotional distress: Profile of Mood States-Short Form • self reported physical activity level: Seven-Day Physical Activity Recall Outcomes measured at baseline, 6 and 12 weeks
Notes	Funding: Taipei Medical University Hospital (95TMU-TMUH-19), Taipei, Taiwan, Republic of China. Conflict of interest: None declared

Yang 2011 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants All outcomes	High risk	Not done
Blinding of personnel/care providers All outcomes	High risk	Not reported. Comment: probably not done
Blinding of outcome assessment (detection bias) All outcomes except fitness outcomes	High risk	Self reported items
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-out: • Exercise group: 3/22 (13.6%) • Control group: 1/22 (4.5%) Total: 4/44 (9%)
Selective reporting (reporting bias)	Unclear risk	No study protocol published, study not registered prospectively
Group similarity at baseline	Low risk	The groups were generally balanced at baseline regarding demographic and disease-related characteristics
Adherence	High risk	"About 20% did not completely adhere." Adherence was about 77% of the prescribed exercise sessions and 100% of the prescribed exercise intensity
Contamination	Unclear risk	Not reported

6-MWT: 6-minute walk test
ACSM: American College of Sports Medicine
BDI: Beck Depression Inventory
BMI: body mass index
CES-D: Center for Epidemiological Studies-Depression Scale
DASH: Disabilities of the Arm, Shoulder and Hand Questionnaire
DEXA: dual-energy X-ray absorptiometry
EORTC QLQ-BR23: European Organisation for Research and Treatment of Cancer Breast Cancer-Specific Quality of Life Questionnaire
EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 36
FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue Scale
FACT-An: Functional Assessment of Cancer Therapy-Anaemia
FACT-B: Functional Assessment of Cancer Therapy-Breast
FACT-ES: Functional Assessment of Cancer Therapy-Endocrine Symptoms
FACT-G: Functional Assessment of Cancer Therapy-General
FACT-Taxane: Functional Assessment of Cancer Therapy-Taxane
FQL: Fatigue Quality List
GLTEQ: Godin Leisure-Time Exercise Questionnaire
GXT: Graded Exercise Test

HADS: Hospital Anxiety and Depression Scale
HRmax: maximum heart rate
HRQoL: health-related quality of life
IPAQ: International Physical Activity Questionnaire
IQR: interquartile range
ITT: intention-to-treat
L-Dex: lymphoedema index
MDASI-T: Taiwanese version of the MD Anderson Symptom Inventory
MET: metabolic equivalent of task
MFI: Multidimensional Fatigue Inventory
MOS SF-36: Medical Outcomes Study 36-Item Short Form Health Survey
MQOLS-CA: Multidimensional Quality of Life Scale-Cancer
MVPA: moderate to vigorous physical activity
QoL: quality of life
QR: Quartile Range
PAL: physical activity level
PANAS: Positive and Negative Affect Schedule
PFS: Piper Fatigue Scale
POMS: Profile of Mood States
RCT: randomised controlled trial
SD: standard deviation
SF-36: 36-Item Short Form Health Survey
SPAQ: Scottish Physical Activity Questionnaire
SWLS: Satisfaction With Life Scale
VO_2 max: maximal oxygen uptake

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

Study	Reason for exclusion
Aaronson 2011	Post-treatment
Adamsen 2009	Participants not predominantly breast cancer patients
Aghili 2007	Duration of exercise intervention less than 6 weeks
Backman 2013	Participants not predominantly breast cancer patients
Banasik 2011	Post-treatment
Banerjee 2007	Yoga
Basen 2006	Post-treatment
Baumann 2009	Not an RCT
Baumann 2011	Not an RCT
Bower 2012	Yoga
Burnham 2002	Exercise intervention not concurrent with adjuvant cancer treatment
Cantarero-Villanueva 2012	Post-treatment
Cantarero-Villanueva 2013	Post-treatment
Carson 2009	Post-treatment

Study	Reason for exclusion
Charbonnier 2012	Not an exercise intervention
Chetiyawardana 2004	Radiotherapy ongoing for maximum 3 weeks
Courneya 2003a	Participants not predominantly breast cancer patients (40%), exercise as part of a complex intervention (group psychotherapy plus exercise)
Courneya 2003b	Exercise intervention not concurrent with adjuvant cancer treatment (< 50% under current hormone therapy)
Courneya 2006	Participants were post-treatment. Exercise intervention not concurrent with adjuvant cancer treatment
Culos-Reed 2006	Post-treatment
Danhauer 2009	Yoga
Demark-Wahnefried 2002	No clinical trial, protocol status, exercise as part of a complex intervention (diet and exercise-based counselling program)
Demark-Wahnefried 2003	No clinical trial, design paper
Demark-Wahnefried 2005	Complex intervention
Demark-Wahnefried 2006	Complex intervention
Demark-Wahnefried 2008	Complex intervention
Dimeo 1999	Participants not predominantly breast cancer patients
Duijts 2009	Post-treatment
Duijts 2012	Post-treatment
Emami 2012	Post-treatment
Ergun 2013	Post-treatment
Fairey 2003	Exercise intervention not concurrent with adjuvant cancer treatment
Fairey 2005	Post-treatment
Fairey 2005a	Post-treatment
Fernandez 2013	Post-treatment
Galantino 2010	No exercise intervention
Given 2002	Participants not predominantly breast cancer patients
Gomes 2011	Not an exercise intervention
Gomez 2011	Post-treatment
Griffith 2009	Participants not predominantly breast cancer patients

Study	Reason for exclusion
Hartmann 2013	Not an RCT
Hatchett 2013	Post-treatment
Herrero 2006	Post-treatment
Ho 1986	No exercise intervention
Huang 2014	No health-related outcome measure (adherence study)
Irwin 2008	Post-treatment
Irwin 2009	Post-treatment
Irwin 2009a	Post-treatment
Janelsins 2011	Post-treatment
Kim 2006	Complex intervention: exercise and stress management training
Kleine-Tebbe 2006	Data were not analysed to be used for a full publication (personal communication September 2013)
Kohler 2008	Not an RCT
Kovacic 2011	Yoga
Latikka 1997	No clinical trial, review
Latka 2009	Post-treatment
Lauridsen 2005	Exercise restricted to shoulder
Lee 2006	Qigong
Ligibel 2006	Post-treatment
Ligibel 2008	Post-treatment
Ligibel 2009	Post-treatment
MacVicar 1986	Not an RCT
Mamom 2012	Duration of exercise intervention less than 6 weeks
Martin 2013	Post-treatment
Maryam 2010	Not an RCT
McGuire 2011	Post-treatment
McKenzie 2003	Intervention and adjuvant treatment not concurrent
Milecki 2013	Radiotherapy ongoing for maximum 5 weeks

Study	Reason for exclusion
Moadel 2007	Yoga
Mock 1994	Exercise as part of a complex intervention (walking plus support group)
Mock 1997	Not an RCT
Mock 2001	Trial does not compare 2 groups as assigned by investigator
Mock 2002	No exercise intervention
Moller 2013	Participants not predominantly breast cancer patients
Mulero 2008	Post-treatment
Murtezani 2014	Post-treatment
Musanti 2012	Post-treatment
Mustian 2002	No clinical trial, review
Mustian 2006	Less than 6 weeks
Pickett 2002	No health-related outcome measure (adherence study)
Pinto 2003	Exercise intervention not concurrent with adjuvant cancer treatment
Pinto 2008	Post-treatment
Pinto 2009	Post-treatment
Rabin 2006	Post-treatment
Raghavendra 2007	Yoga
Rahnama 2010	Post-treatment
Rao 2008	Yoga
Rao 2009	Yoga
Rogers 2011	Post-treatment
Sandel 2005	Not an exercise intervention
Schmitz 2005	Post-treatment
Schwartz 1999	Trial does not compare 2 groups as assigned by investigator
Schwartz 2001	Trial does not compare 2 groups as assigned by investigator
Scott 2013	Post-treatment
Segar 1998	Exercise intervention not concurrent with adjuvant cancer treatment

Study	Reason for exclusion
Shaw 2003	No clinical trial, protocol status, exercise as part of a complex intervention (calcium-rich diet and exercise)
So 2006	Not an RCT
Sprod 2012	Post-treatment
Stevinson 2009	Commentary
Swenson 2009	Complex intervention
Swenson 2010	Complex intervention
Twiss 2009	Post-treatment
Vadiraja 2009	Yoga
Vadiraja 2010	Commentary
Vallance 2007	Post-treatment
Vallance 2008	Post-treatment
Vallance 2008a	Post-treatment
Vincent 2013	Not an RCT
Waltman 2010	Post-treatment
Wang 2010	Exercise intervention does not coincide with adjuvant therapy at least 6 weeks
Wilkie 2003	Participants not predominantly breast cancer patients (63% female), duration of intervention programme 4 weeks
Yeh 2006	Qigong
Yuen 2007	Post-treatment

RCT: randomised controlled trial

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

Lotzke 2016

Methods	RCT, 2 groups
Participants	Women with stage I to III breast cancer during (neo-)adjuvant therapy
Interventions	Weekly 60-minute physical exercise session together with individual home-based, self contained 20-minute sessions twice a week. Control group: weekly 60-minute Iyengar yoga session together with individual home-based, self contained 20-minute sessions twice a week
Outcomes	• Health-related quality of life: EORTC QLQ-C30

Lotzke 2016 *(Continued)*

	• Fatigue: Cancer Fatigue Scale German • Life satisfaction: Brief Multidimensional Life Satisfaction Scale (BMLSS) • Mindfulness: Freiburg Mindfulness Inventory (FMI) • Spiritual/religious attitudes and disease coping (SpREUK-SF 10) • "Inner Correspondence and Peaceful Harmony with Practices“ (ICPH)
Notes	

Petrella 2012

Methods	RCT, 2 groups Study start and stop dates: not reported Length of intervention: 6 months Length of follow-up: 6 months after the end of the intervention
Participants	Women who were within 4 to 12 weeks of surgery for stage I to III breast cancer and undergoing adjuvant chemotherapy
Interventions	Structured exercise program (6 months), aerobic and resistance training Control group: usual oncology care
Outcomes	• cancer-specific quality of life: FACT-B • quality of life: SF-36 • body composition: weight, waist circumference, waist-hip ratio, per cent body fat • cardiorespiratory fitness: peak oxygen • strength • arm volume Outcomes assessed at: baseline and 3-month intervals through 12 months
Notes	Abstract

EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 36
FACT-B: Functional Assessment of Cancer Therapy-Breast
RCT: randomised controlled trial
SF-36: 36-Item Short Form Health Survey

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

ACTRN12614000051640

Trial name or title	Preventing ‘chemo-brain’: Can exercise mitigate chemotherapy-induced cognitive impairment in breast cancer patients?
Methods	RCT
Participants	Breast cancer patients scheduled to receive adjuvant chemotherapy with fluorouracil-epirubicin-cyclophosphamide-docetaxel (FEC-T) or docetaxel-cyclophosphamide (TC) regimens, target sample size: 66
Interventions	Combination of resistance (i.e. lifting weights) and aerobic exercise (e.g. walking, jogging, cycling), 2 times/week in an exercise clinic. moderate to high intensity (i.e. a perceived exertion of some-

ACTRN12614000051640 *(Continued)*

	what hard to hard) and will be relative to each participant's capabilities. Progressive exercise prescription, modified according to individual response. Approximately 60 min/session, small groups under the supervision of an accredited exercise physiologist. Length of program: will vary from 2.5 to 4 months according to the duration of the chemotherapy regimen Control group: usual care
Outcomes	Primary outcome: • Cognitive function: Hopkins Verbal Learning Test-Revised, Trail Making Test, Controlled Oral Word Association of the Multilingual Aphasia Examination. Secondary outcomes: • Quality of life: Medical Outcomes Study 36-Item Short Form Health Survey, Functional Assessment of Cancer Therapy for patients with breast cancer questionnaire • Psychological distress: Brief Symptom Inventory-18 (BSI-18), Hospital Anxiety and Depression Scale (HADS) • Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue • Neuropathies: Functional Assessment of Cancer Therapy-Neurotoxicity • Musculoskeletal symptoms including myalgias and arthralgias: Muscle and Joint Measure questionnaire • Sleep quality: Insomnia Severity Index • Physical function: 400-m walk (aerobic capacity), 1 repetition maximum in the leg press (muscular strength), repeated chair rise (muscular power), usual and fast pace 6-m walk (ambulation), backwards tandem 6-m walk (dynamic balance), and Sensory Organization Test (static balance) • Physical activity level: Godin Leisure-Time Exercise Questionnaire
Starting date	June 2014 first participant enrolment
Contact information	Dr Prue Cormie ECU Health and Wellness Institute Edith Cowan University 270 Joondalup Drive Joondalup, WA 6027, Australia
Notes	

NCT01943695

Trial name or title	Aerobic training during or after adjuvant therapy
Methods	RCT, 4 arms
Participants	Sedentary breast cancer patients, estimated enrolment: 160 participants
Interventions	1. Aerobic training during therapy: target of 3 treadmill walking sessions/week at 60% to 85% of baseline VO_2 peak for 150 minutes/week. 2. Aerobic training after therapy: target of 3 treadmill walking sessions/week at 60% to 85% of baseline VO_2 peak for 150 minutes/week. 3. Continuous aerobic training: This group will follow the identical aerobic training during and after therapy prescription as described for Groups 1 and 2 for the first 24 weeks (i.e. during therapy). After primary therapy (i.e. at ˜24 weeks, T1), the aerobic training prescription will be re-prescribed based on the end-of-therapy VO_2 peak assessment (at T1) with the goal of 3 exercise sessions per week, for 30 to 45 minutes/session at 60% to 85% of VO_2 peak.

NCT01943695 *(Continued)*

	4. Control group: educational information.
Outcomes	Primary: • Change in VO_2 peak (functional capacity) Secondary: • Quality of life • Sleeping patterns • Depression • Physical activity • Skeletal muscle function
Starting date	January 2013
Contact information	Lee W Jones Duke University Medical Center Durham, NC, USA, 27710
Notes	Estimated study completion date: August 2017

NCT02117011

Trial name or title	Effects of a structured exercise program on cancer-related fatigue in women receiving radiation therapy for breast cancer
Methods	RCT, estimated enrolment: 30
Participants	African-Americans undergoing radiation therapy for localised breast cancer. Sedentary, as defined as < 60 minutes of recreation or work requiring modest physical activity/week based on the 7-day physical activity recall questionnaire. Having completed neo-adjuvant or adjuvant chemotherapy
Interventions	8-week, moderate-intensity aerobic exercise program Participants will be required to meet and maintain a goal of 75 min/week of aerobic exercise by using portable cycle ergometers, that is 15 min/day, 5 days/week
Outcomes	Fatigue: FACIT-F Cancer-specific quality of life: FACT-G
Starting date	June 2013
Contact information	
Notes	Estimated study completion date: December 2016

NCT02159157

Trial name or title	A randomized, controlled trial to determine the effects of an exercise intervention on physical activity during chemotherapy for patients with early stage breast cancer

NCT02159157 *(Continued)*

Methods	RCT
Participants	Women or men with histologically confirmed breast cancer and no evidence of metastatic disease with a recommendation to begin chemotherapy within 4 weeks. Sedentary: participants must have a baseline activity level of < 150 minutes/wk of moderate to vigorous activity as calculated using the moderate to vigorous components of the Leisure-Time Exercise Questionnaire for physical activity (completed during screening). Karnofsky performance status > or = to 80%. Estimated enrolment: 120 participants
Interventions	A physical therapist will design an exercise plan for each participant on the intervention arm. The participants randomised to the intervention arm will also receive phone calls to assist with tracking the study participant's exercise and motivating the study participant to adhere to the exercise prescription. Exercise prescription aimed at increasing physical activity by a minimum of 10 MET hours/week
Outcomes	Primary: • Change in activity: Activity Log Secondary: • Received dose intensity of chemotherapy • Fatigue: FACIT-F • Body composition: % of total body fat, bone density (g/cm^2), and T score, change in waist-hip ratio from baseline • Change in resting heart rate from baseline • Change in steps recorded from baseline: pedometer data
Starting date	June 2014
Contact information	Contact: Mary Chamberlin, MD Cancer.Research.Nurse@Dartmouth.edu
Notes	Estimated primary completion rate: June 2017 (Final data collection date for primary outcome measure)

NCT02240836

Trial name or title	Energy Balance and Breast Cancer Aspects-II (EBBA-II)
Methods	RCT, 2 groups
Participants	Newly diagnosed breast cancer patients undergoing adjuvant therapy, DCIS grade 3, stage I + II breast cancer Estimated enrolment: 600 participants
Interventions	12-month exercise program comprised of strength and endurance training. Exercise groups supervised by experienced physiotherapists, the participants will attend the exercise groups for training 60 min, 2/week. Additionally, home-based exercise for > = 120 minutes a week, aiming to perform a total of 240 minutes of exercise per week.

NCT02240836 *(Continued)*

	The control group told to follow standard-care regimen
Outcomes	Primary: • metabolic profile Secondary: • Relapse of breast cancer disease, breast cancer-specific mortality, overall mortality, disease-free survival, recurrence-free interval • QoL parameters: QoL, fatigue, anxiety, depression • Cardiopulmonary function: cardiopulmonary exercise testing (CPET), VO_2 max, forced expiratory volume in 1 second (FEV1), peak expiratory flow (PEF), diffusing capacity of the lung for carbon monoxide (DLCO)
Starting date	September 2014
Contact information	Inger Thune inger.thune@uit.no
Notes	Estimated primary completion date: May 2016 Planned follow-up: 10 years

NCT02252991

Trial name or title	Adapted Physical Activity in Cancerology (APACAN)
Methods	RCT
Participants	Breast cancer patients receiving radio- or chemotherapy or both, estimated enrolment: 200 participants
Interventions	Physical activity, from 2 to 6 months Control group: physical activity after treatment
Outcomes	Fatigue: MFI QoL: EORTC QLQ-C30
Starting date	September 2014
Contact information	Yves-Jean.BIGNON@jp.fr
Notes	Estimated primary completion date: December 2016 (final data collection date for primary outcome measure)

NCT02350582

Trial name or title	e-CUIDACHEMO: Telerehabilitation During Chemotherapy in Breast Cancer
Methods	RCT

NCT02350582 *(Continued)*

Participants	Breast cancer patients with internet access, estimated enrolment: 40 participants
Interventions	Resistance and endurance exercise via telerehabilitation
Outcomes	Primary: • cardiorespiratory fitness: 6-MWT Secondary: • strength • fatigue: PFS • pain: Brief Pain Inventory • cancer-related QoL: EORTC QLQ-C30 and BR23
Starting date	April 2012
Contact information	Manuel Arroyo-Morales marroyo@ugr.es
Notes	Estimated study completion date: June 2015

6-MWT: 6-minute walk test
DCIS: ductal carcinoma in situ
EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 36
FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue Scale
FACT-G: Functional Assessment of Cancer Therapy-General
MET: metabolic equivalent of task
MFI: Multidimensional Fatigue Inventory
PFS: Piper Fatigue Scale
QoL: quality of life
RCT: randomised controlled trial

DATA AND ANALYSES

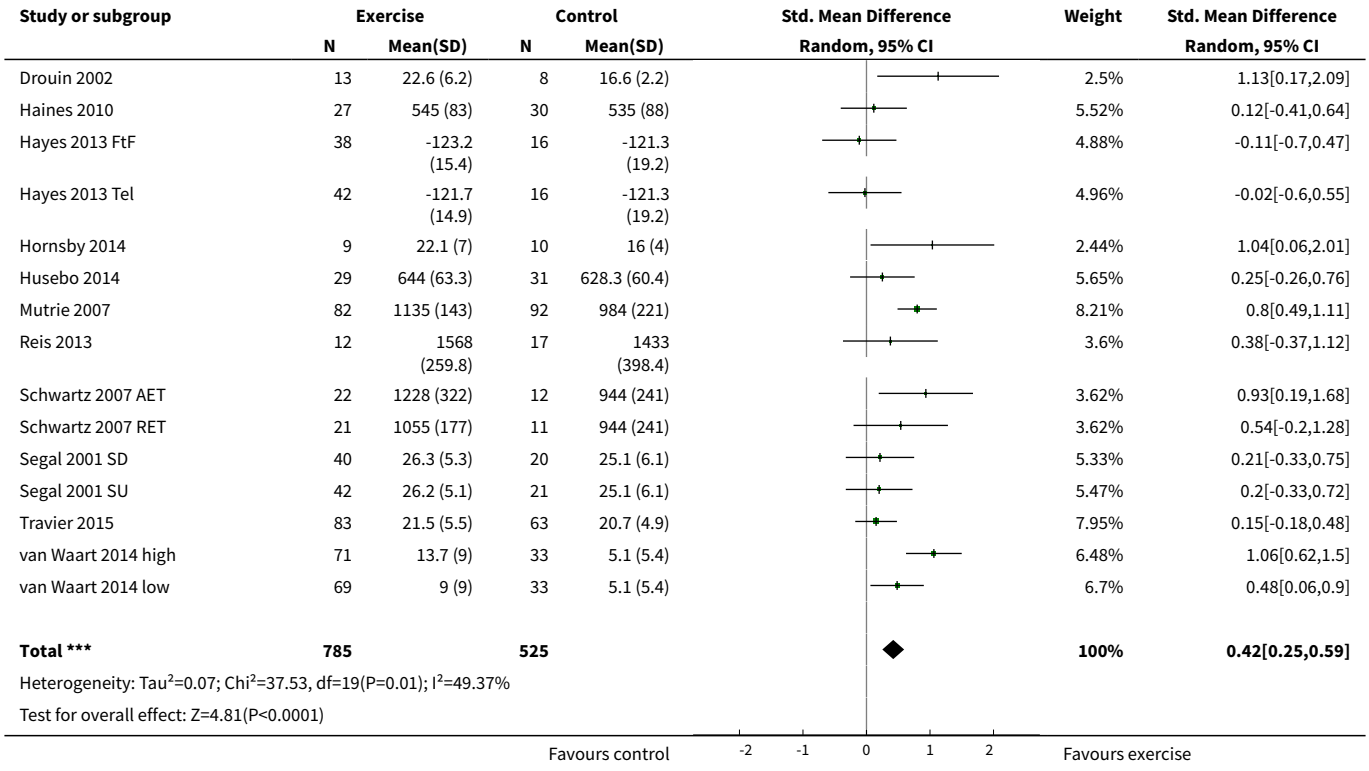
Comparison 1. Exercise versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Physical fitness	20	1310	Std. Mean Difference (IV, Random, 95% CI)	0.42 [0.25, 0.59]
2 Fatigue	22	1698	Std. Mean Difference (IV, Random, 95% CI)	-0.28 [-0.41, -0.16]
3 Cancer-specific quality of life	13	1012	Std. Mean Difference (IV, Random, 95% CI)	0.12 [-0.00, 0.25]
4 Health-related quality of life	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5 Cancer site-specific quality of life	4	262	Mean Difference (IV, Random, 95% CI)	4.24 [-1.81, 10.29]

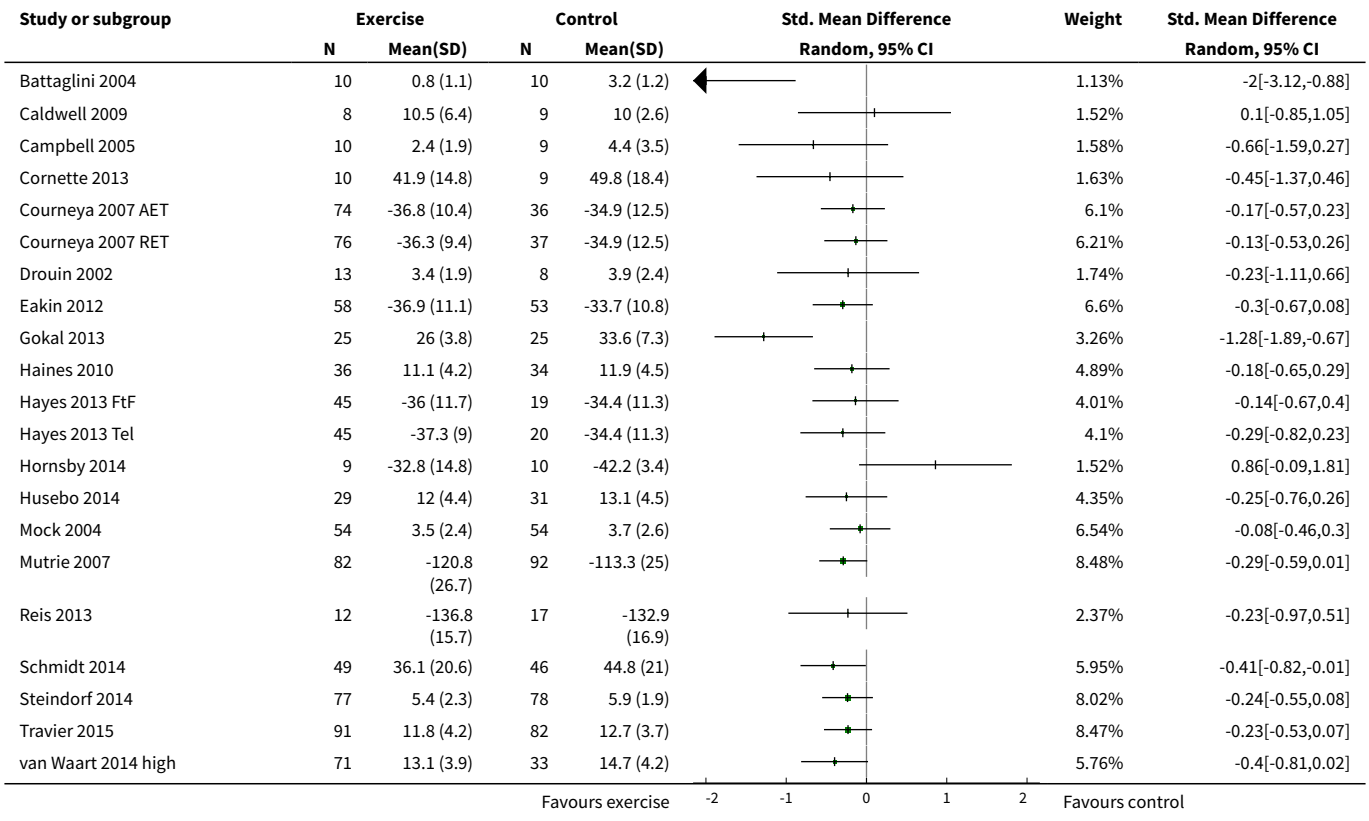
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Depression	6	674	Std. Mean Difference (IV, Random, 95% CI)	-0.15 [-0.30, 0.01]
7 Cognitive function	2	213	Mean Difference (IV, Random, 95% CI)	-11.55 [-22.06, -1.05]
8 Strength	13	912	Std. Mean Difference (IV, Random, 95% CI)	0.27 [0.04, 0.50]
9 Subjective upper body function	3	231	Mean Difference (IV, Random, 95% CI)	-0.52 [-4.45, 3.41]
10 Shoulder mobility	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
11 Arm morbidity	3	240	Mean Difference (IV, Random, 95% CI)	1.11 [-4.07, 6.29]
12 Anxiety	3	331	Mean Difference (IV, Random, 95% CI)	-1.45 [-4.36, 1.46]
13 Mood disturbances	3	111	Std. Mean Difference (IV, Random, 95% CI)	-1.00 [-1.40, -0.60]
14 Hospital Anxiety and Depression Scale	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
15 Self esteem	4	323	Mean Difference (IV, Random, 95% CI)	1.69 [-0.01, 3.39]
16 Physical activity	8	549	Std. Mean Difference (IV, Random, 95% CI)	0.29 [0.12, 0.47]
17 Neuropathic pain	2	130	Mean Difference (IV, Random, 95% CI)	3.64 [-1.32, 8.60]
18 Neuropathy symptoms	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
19 Endocrine symptoms	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
20 Gait and balance	3	122	Std. Mean Difference (IV, Random, 95% CI)	0.10 [-0.25, 0.46]
21 Lymphoedema incidence	4	436	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.35, 1.45]

Analysis 1.1. Comparison 1 Exercise versus control, Outcome 1 Physical fitness.

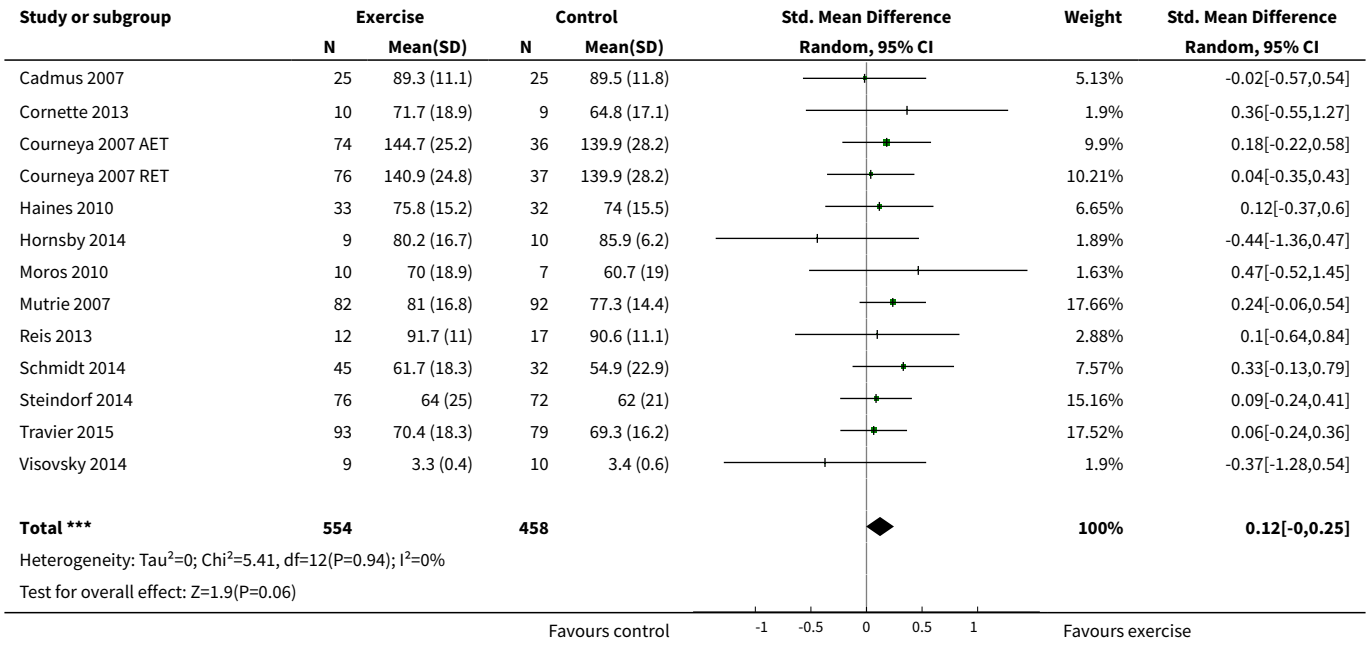
Study or subgroup	Exercise N	Exercise Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Caldwell 2009	7	1761.9 (343.7)	8	1749 (245.5)		2.28%	0.04[-0.97,1.06]
Campbell 2005	10	1423 (261)	9	1083 (176)		2.2%	1.44[0.41,2.48]
Cornette 2013	20	549 (53)	22	517.5 (69.3)		4.59%	0.5[-0.12,1.11]
Courneya 2007 AET	71	25.7 (7.4)	36	23.5 (5.4)		6.92%	0.32[-0.08,0.72]
Courneya 2007 RET	77	24.2 (6.1)	37	23.5 (5.4)		7.07%	0.12[-0.27,0.51]
				Favours control	-2 -1 0 1 2		Favours exercise



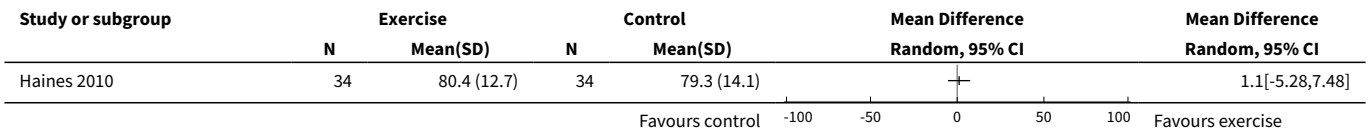
Analysis 1.2. Comparison 1 Exercise versus control, Outcome 2 Fatigue.



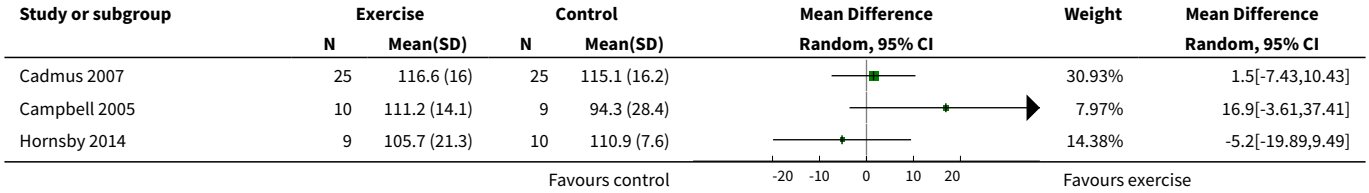
Analysis 1.3. Comparison 1 Exercise versus control, Outcome 3 Cancer-specific quality of life.

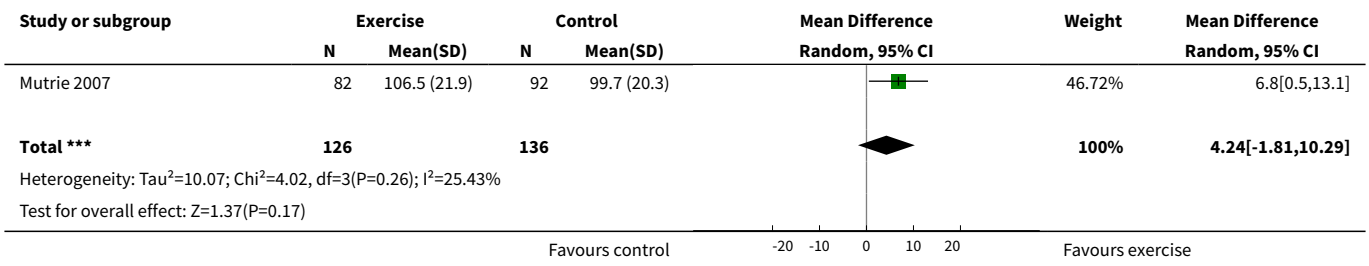


Analysis 1.4. Comparison 1 Exercise versus control, Outcome 4 Health-related quality of life.

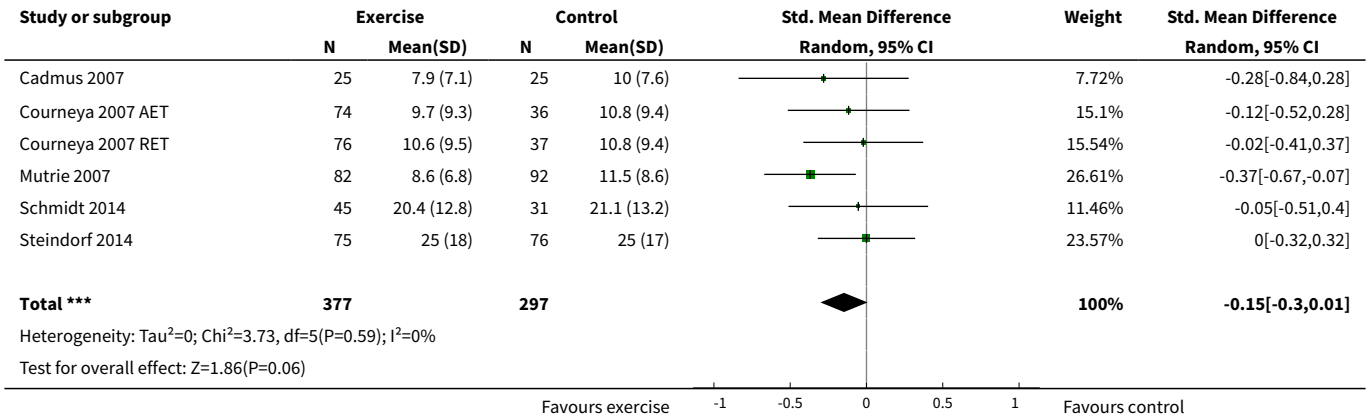


Analysis 1.5. Comparison 1 Exercise versus control, Outcome 5 Cancer site-specific quality of life.

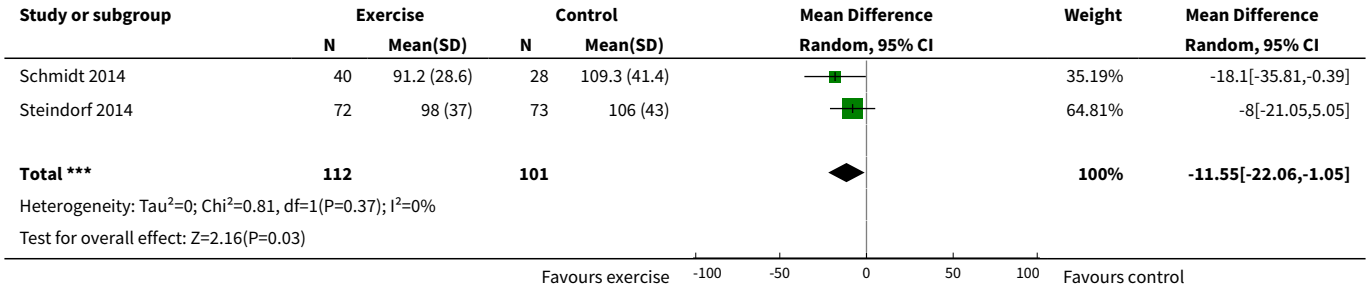




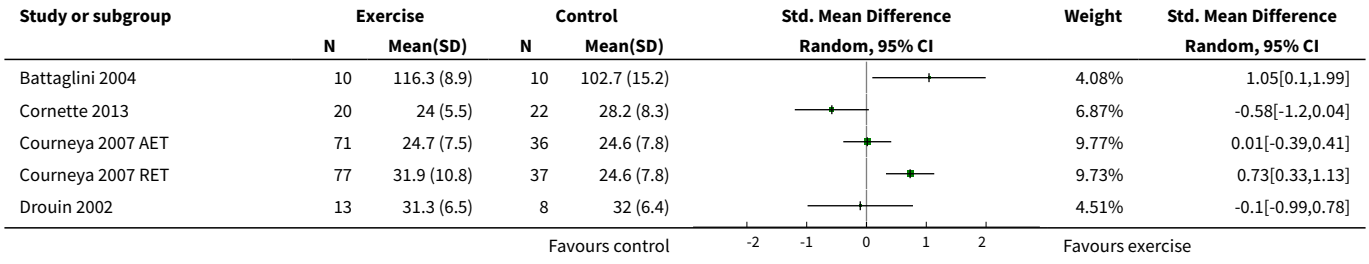
Analysis 1.6. Comparison 1 Exercise versus control, Outcome 6 Depression.

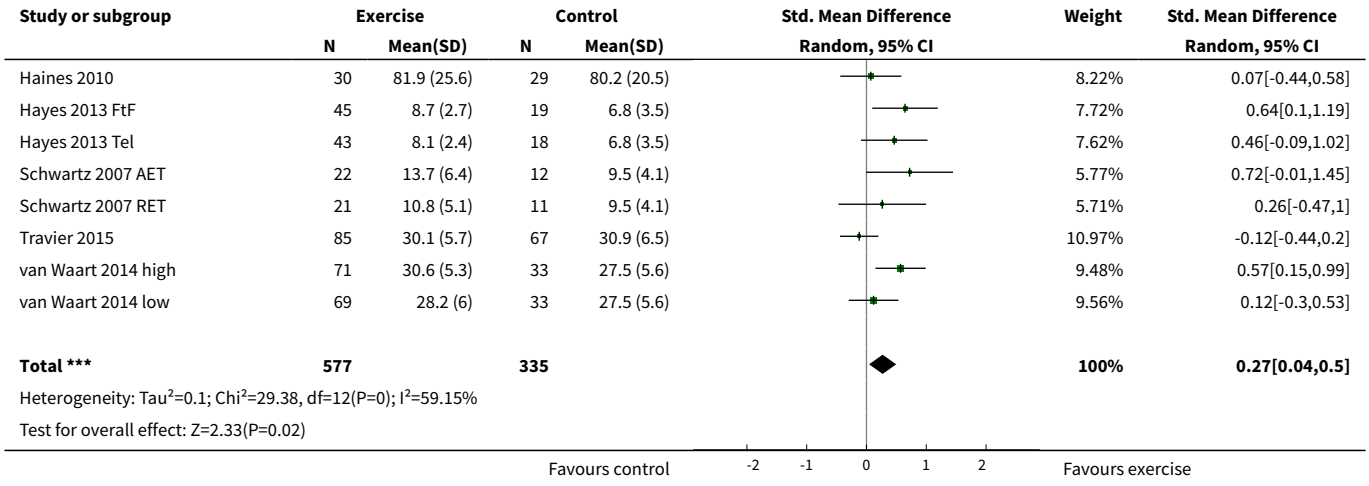


Analysis 1.7. Comparison 1 Exercise versus control, Outcome 7 Cognitive function.

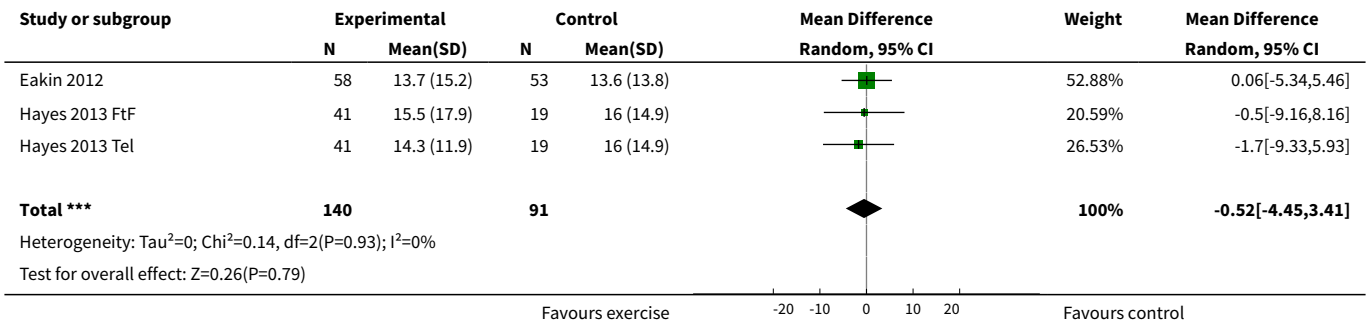


Analysis 1.8. Comparison 1 Exercise versus control, Outcome 8 Strength.

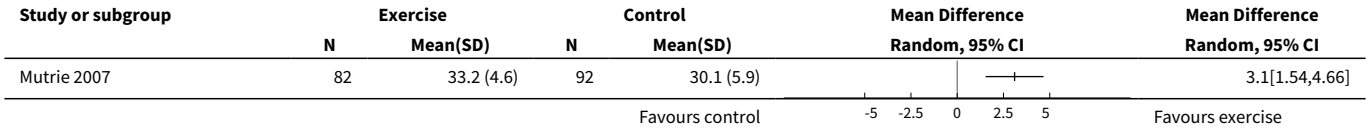




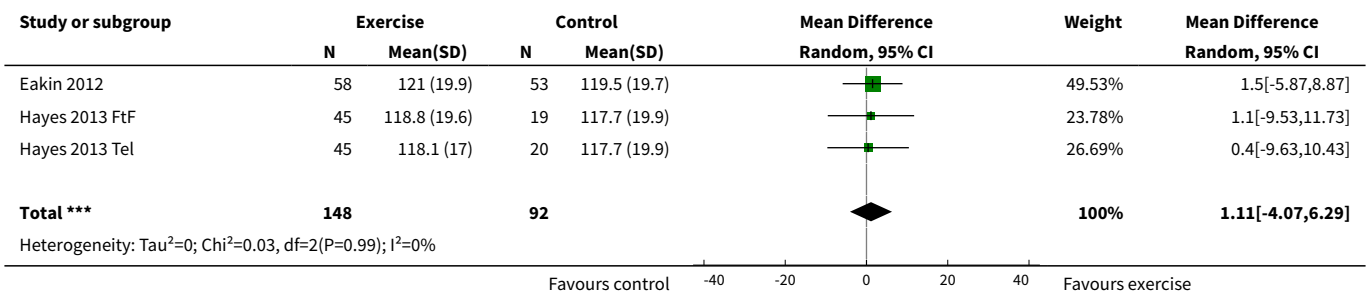
Analysis 1.9. Comparison 1 Exercise versus control, Outcome 9 Subjective upper body function.

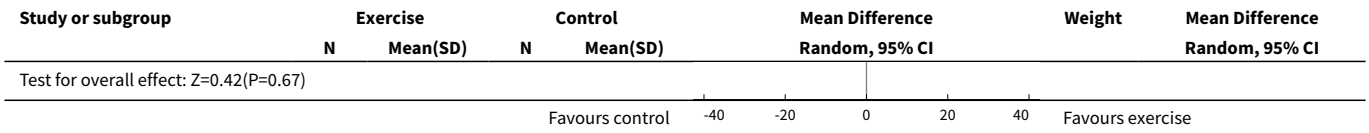


Analysis 1.10. Comparison 1 Exercise versus control, Outcome 10 Shoulder mobility.

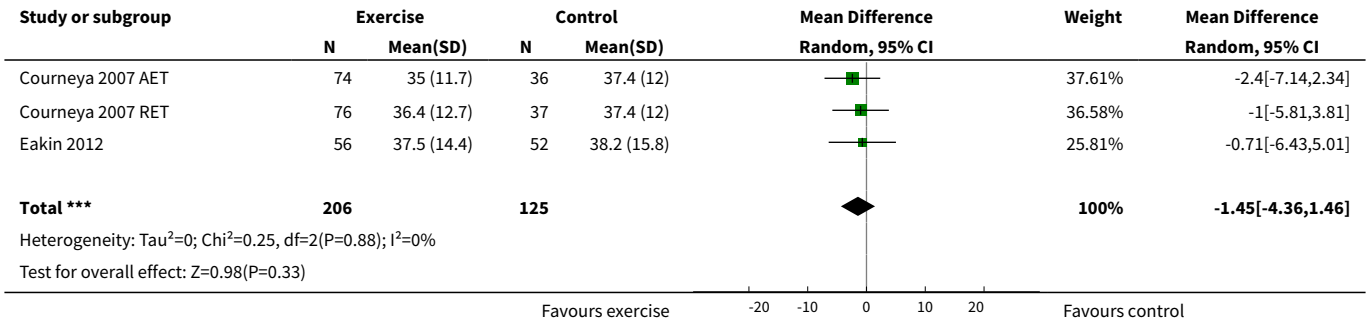


Analysis 1.11. Comparison 1 Exercise versus control, Outcome 11 Arm morbidity.

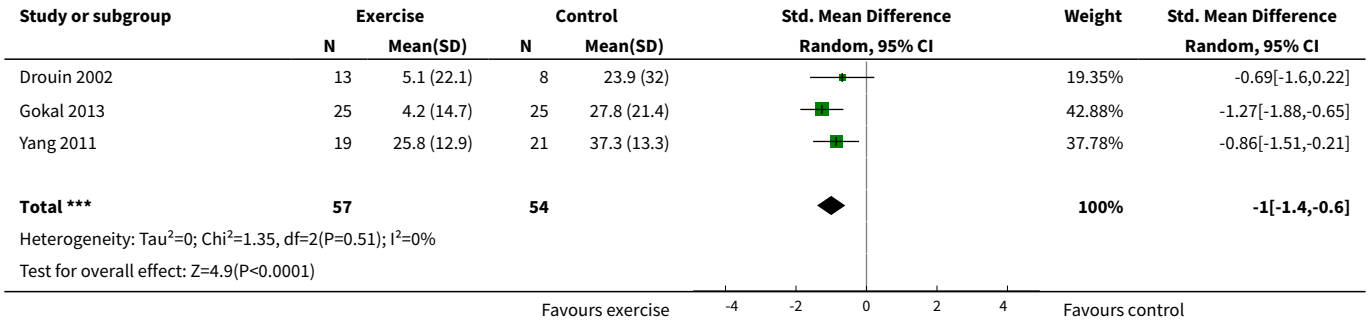




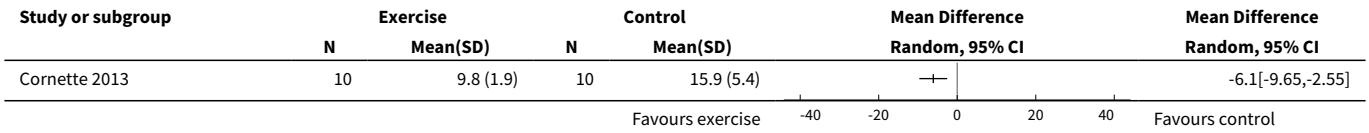
Analysis 1.12. Comparison 1 Exercise versus control, Outcome 12 Anxiety.



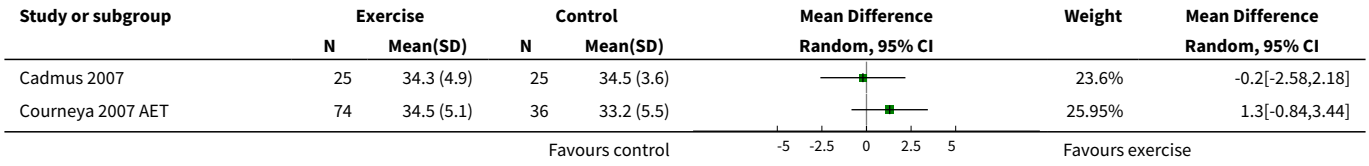
Analysis 1.13. Comparison 1 Exercise versus control, Outcome 13 Mood disturbances.

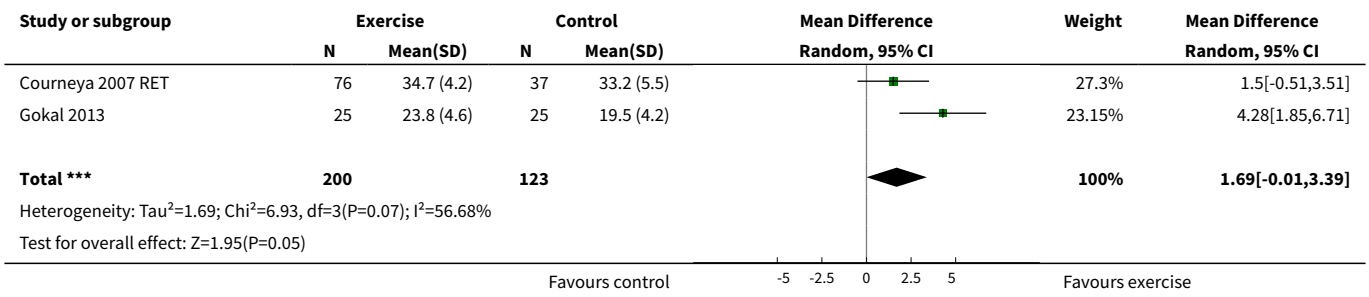


Analysis 1.14. Comparison 1 Exercise versus control, Outcome 14 Hospital Anxiety and Depression Scale.

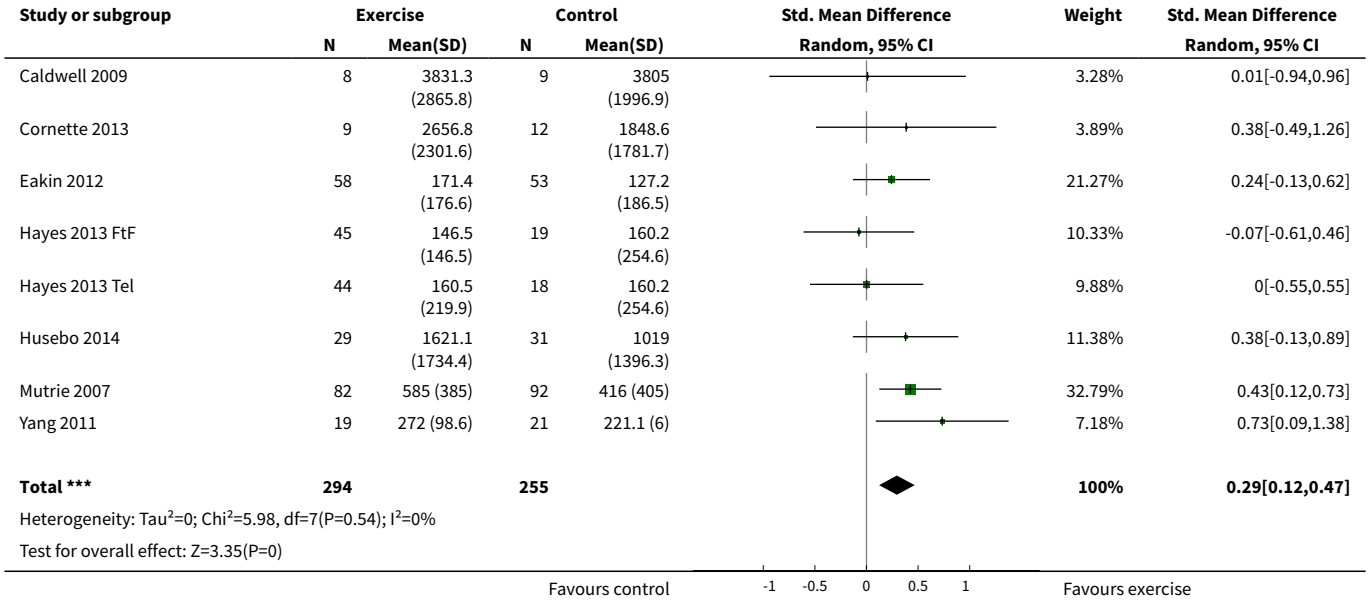


Analysis 1.15. Comparison 1 Exercise versus control, Outcome 15 Self esteem.

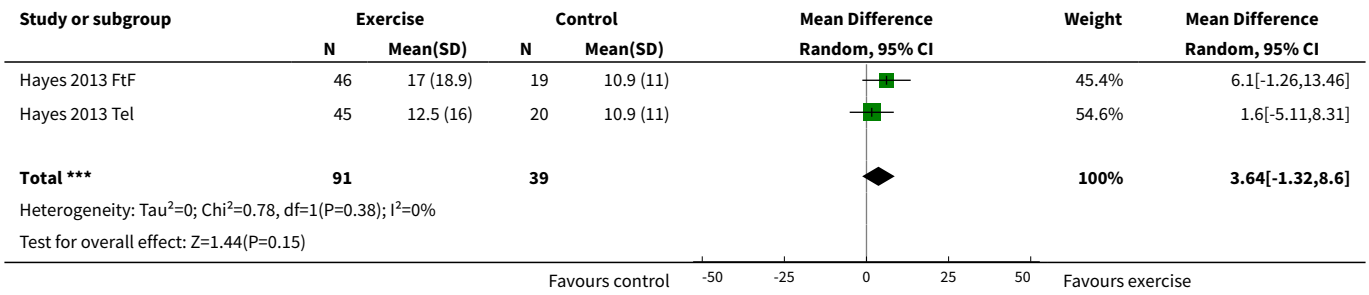




Analysis 1.16. Comparison 1 Exercise versus control, Outcome 16 Physical activity.

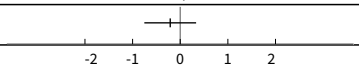


Analysis 1.17. Comparison 1 Exercise versus control, Outcome 17 Neuropathic pain.



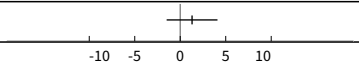
Analysis 1.18. Comparison 1 Exercise versus control, Outcome 18 Neuropathy symptoms.

Study or subgroup	Exercise N	Exercise Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Visovsky 2014	9	0.7 (0.4)	10	0.9 (0.8)		-0.21[-0.75,0.33]



Analysis 1.19. Comparison 1 Exercise versus control, Outcome 19 Endocrine symptoms.

Study or subgroup	Exercise N	Exercise Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Mutrie 2007	82	41.6 (9.1)	92	40.3 (9.7)		1.3[-1.49,4.09]

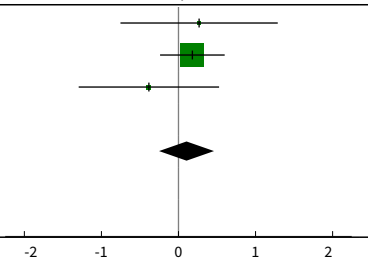


Analysis 1.20. Comparison 1 Exercise versus control, Outcome 20 Gait and balance.

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
Caldwell 2009	7	7.1 (2.7)	8	6.4 (2)		12.22%	0.27[-0.75,1.29]
Haines 2010	46	-15.1 (3.5)	42	-15.8 (4.2)		72.44%	0.18[-0.24,0.6]
Visovsky 2014	9	5.5 (0.6)	10	5.9 (1.2)		15.34%	-0.38[-1.29,0.53]
Total ***	**62**		**60**			**100%**	**0.1[-0.25,0.46]**

Heterogeneity: $Tau^2=0$; $Chi^2=1.33$, df=2(P=0.51); $I^2=0\%$

Test for overall effect: Z=0.57(P=0.57)



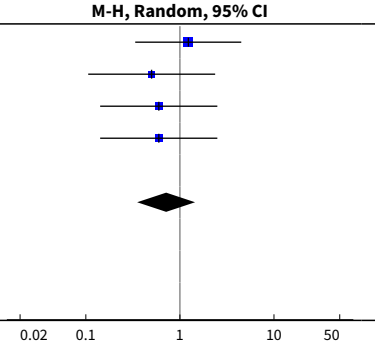
Analysis 1.21. Comparison 1 Exercise versus control, Outcome 21 Lymphoedema incidence.

Study or subgroup	Exercise n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Courneya 2007 AET	7/78	3/41		29.96%	1.23[0.33,4.49]
Courneya 2007 RET	3/82	3/41		20.87%	0.5[0.11,2.37]
Hayes 2013 FtF	4/67	3/30		24.58%	0.6[0.14,2.5]
Hayes 2013 Tel	4/67	3/30		24.58%	0.6[0.14,2.5]
Total (95% CI)	**294**	**142**		**100%**	**0.71[0.35,1.45]**

Total events: 18 (Exercise), 12 (Control)

Heterogeneity: $Tau^2=0$; $Chi^2=0.99$, df=3(P=0.8); $I^2=0\%$

Test for overall effect: Z=0.93(P=0.35)

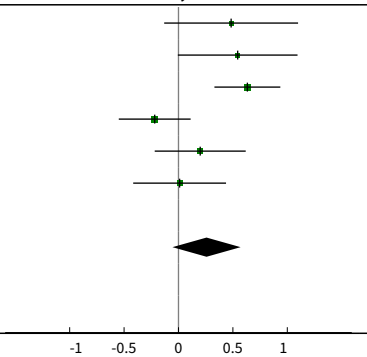


Comparison 2. Exercise versus control follow-up

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Physical fitness	6	612	Std. Mean Difference (IV, Random, 95% CI)	0.26 [-0.06, 0.57]
2 Fatigue	8	814	Std. Mean Difference (IV, Random, 95% CI)	-0.21 [-0.35, -0.07]
3 Cancer-specific quality of life	6	583	Std. Mean Difference (IV, Random, 95% CI)	0.18 [0.01, 0.35]
4 Depression	3	378	Std. Mean Difference (IV, Random, 95% CI)	-0.27 [-0.48, -0.06]
5 Strength	4	386	Std. Mean Difference (IV, Random, 95% CI)	-0.00 [-0.30, 0.30]
6 Physical activity	3	261	Std. Mean Difference (IV, Random, 95% CI)	0.28 [-0.05, 0.61]
7 Anxiety	2	201	Mean Difference (IV, Random, 95% CI)	-3.61 [-7.24, 0.03]
8 Self esteem	2	201	Mean Difference (IV, Random, 95% CI)	1.20 [-0.41, 2.81]
9 Endocrine symptoms	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
10 Neuropathy symptoms	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
11 Gait and balance	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
12 Lymphoedema incidence	2	194	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.37, 1.69]

Analysis 2.1. Comparison 2 Exercise versus control follow-up, Outcome 1 Physical fitness.

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
Cornette 2013	20	552 (54.2)	22	522.3 (65.2)		12.63%	0.48[-0.13,1.1]
Husebo 2014	25	678.6 (73.3)	28	643.4 (54)		14%	0.54[-0.01,1.09]
Mutrie 2007	82	1127 (166)	95	1013 (190)		20.02%	0.63[0.33,0.94]
Travier 2015	78	23.5 (5.8)	65	24.8 (5.8)		19.34%	-0.22[-0.55,0.11]
van Waart 2014 high	71	13.7 (10)	32	11.7 (9.8)		17.11%	0.2[-0.22,0.62]
van Waart 2014 low	62	11.8 (9.4)	32	11.7 (9.8)		16.9%	0.01[-0.42,0.44]
Total ***	**338**		**274**			**100%**	**0.26[-0.06,0.57]**
Heterogeneity: Tau^2=0.1; Chi^2=16.8, df=5(P=0); I^2=70.24%							
Test for overall effect: Z=1.61(P=0.11)							



Analysis 2.2. Comparison 2 Exercise versus control follow-up, Outcome 2 Fatigue.

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
Cornette 2013	14	38 (12.3)	12	44.2 (13.9)		3.35%	-0.46[-1.24,0.32]
Courneya 2007 AET	68	-42.1 (10.5)	30	-41.5 (9.8)		11.11%	-0.06[-0.49,0.37]
Courneya 2007 RET	73	-40.8 (10.5)	30	-41.5 (9.8)		11.35%	0.07[-0.36,0.49]
Husebo 2014	25	10.4 (3.3)	28	10.4 (3.2)		7.05%	0[-0.54,0.54]
Mutrie 2007	82	-41.3 (9.7)	95	-37.6 (11.8)		23.17%	-0.34[-0.64,-0.04]
Travier 2015	84	10.2 (4.1)	76	11 (4.3)		21.19%	-0.21[-0.52,0.1]
van Waart 2014 high	71	10 (4.6)	32	11.7 (4.1)		11.6%	-0.38[-0.8,0.04]
van Waart 2014 low	62	10.6 (4.2)	32	11.7 (4.1)		11.18%	-0.26[-0.69,0.17]
Total ***	**479**		**335**			**100%**	**-0.21[-0.35,-0.07]**

Heterogeneity: Tau^2=0; Chi^2=4.5, df=7(P=0.72); I^2=0%

Test for overall effect: Z=2.87(P=0)

Favours exercise — Favours control

Analysis 2.3. Comparison 2 Exercise versus control follow-up, Outcome 3 Cancer-specific quality of life.

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
Cornette 2013	13	75 (16.7)	13	69.9 (21.7)		4.73%	0.26[-0.52,1.03]
Courneya 2007 AET	68	156.3 (24)	30	152.4 (26.4)		15.26%	0.16[-0.27,0.59]
Courneya 2007 RET	73	152.9 (26)	30	152.4 (26.4)		15.63%	0.02[-0.41,0.44]
Mutrie 2007	82	83.2 (12.8)	95	77.1 (17)		31.71%	0.4[0.1,0.7]
Travier 2015	85	78.9 (16.4)	75	79 (14.6)		29.29%	-0.01[-0.32,0.31]
Visovsky 2014	9	3.4 (0.4)	10	3.2 (0.5)		3.37%	0.46[-0.46,1.37]
Total ***	**330**		**253**			**100%**	**0.18[0.01,0.35]**

Heterogeneity: Tau^2=0; Chi^2=4.4, df=5(P=0.49); I^2=0%

Test for overall effect: Z=2.09(P=0.04)

Favours control — Favours exercise

Analysis 2.4. Comparison 2 Exercise versus control follow-up, Outcome 4 Depression.

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
Courneya 2007 AET	68	7.2 (7.5)	30	10.2 (9.5)		24.08%	-0.36[-0.8,0.07]
Courneya 2007 RET	73	9.6 (10.4)	30	10.2 (9.5)		24.95%	-0.06[-0.48,0.37]
Mutrie 2007	82	8.4 (7.2)	95	10.8 (7.5)		50.97%	-0.32[-0.62,-0.03]
Total ***	**223**		**155**			**100%**	**-0.27[-0.48,-0.06]**

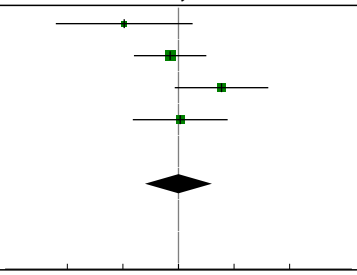
Heterogeneity: Tau^2=0; Chi^2=1.26, df=2(P=0.53); I^2=0%

Test for overall effect: Z=2.47(P=0.01)

Favours exercise — Favours control

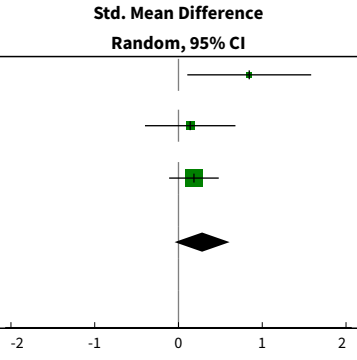
Analysis 2.5. Comparison 2 Exercise versus control follow-up, Outcome 5 Strength.

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
Cornette 2013	20	24.6 (7.1)	22	28.6 (8.8)		16.41%	-0.49[-1.1,0.13]
Travier 2015	82	30.3 (6.5)	65	30.8 (5.9)		32.34%	-0.08[-0.4,0.25]
van Waart 2014 high	71	29.7 (5.7)	32	27.5 (5.5)		25.81%	0.39[-0.03,0.81]
van Waart 2014 low	62	27.6 (6.7)	32	27.5 (5.5)		25.45%	0.02[-0.41,0.44]
Total ***	**235**		**151**			**100%**	**-0[-0.3,0.3]**
Heterogeneity: Tau^2=0.05; Chi^2=5.87, df=3(P=0.12); I^2=48.88%							
Test for overall effect: Z=0(P=1)							



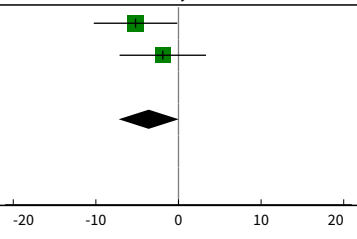
Analysis 2.6. Comparison 2 Exercise versus control follow-up, Outcome 6 Physical activity.

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
Cornette 2013	16	2810 (1209.4)	15	1581.9 (1607.9)		16.58%	0.84[0.11,1.58]
Husebo 2014	25	2105.6 (2104.8)	28	1844.9 (1555.4)		27.26%	0.14[-0.4,0.68]
Mutrie 2007	82	492 (327)	95	427 (370)		56.17%	0.18[-0.11,0.48]
Total ***	**123**		**138**			**100%**	**0.28[-0.05,0.61]**
Heterogeneity: Tau^2=0.03; Chi^2=2.83, df=2(P=0.24); I^2=29.37%							
Test for overall effect: Z=1.68(P=0.09)							



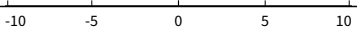
Analysis 2.7. Comparison 2 Exercise versus control follow-up, Outcome 7 Anxiety.

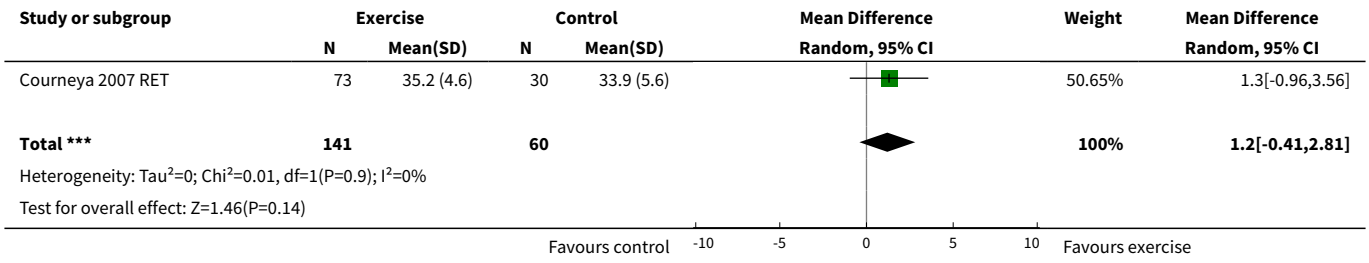
Study or subgroup	Exercise N	Exercise Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Courneya 2007 AET	68	32.2 (11.2)	30	37.4 (12)		51.71%	-5.2[-10.25,-0.15]
Courneya 2007 RET	73	35.5 (13)	30	37.4 (12)		48.29%	-1.9[-7.13,3.33]
Total ***	**141**		**60**			**100%**	**-3.61[-7.24,0.03]**
Heterogeneity: Tau^2=0; Chi^2=0.79, df=1(P=0.37); I^2=0%							
Test for overall effect: Z=1.95(P=0.05)							



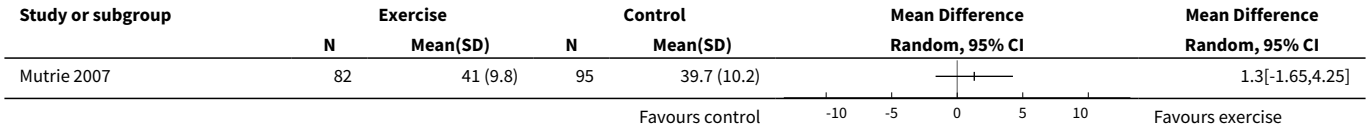
Analysis 2.8. Comparison 2 Exercise versus control follow-up, Outcome 8 Self esteem.

Study or subgroup	Exercise N	Exercise Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Courneya 2007 AET	68	35 (4.7)	30	33.9 (5.6)		49.35%	1.1[-1.19,3.39]

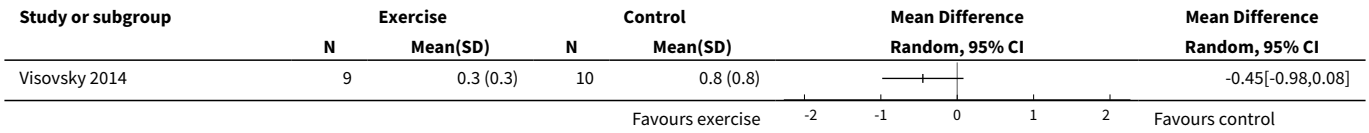




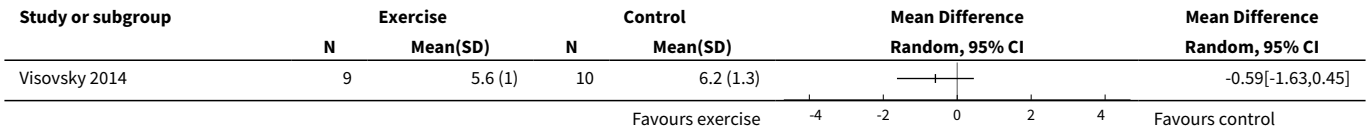
Analysis 2.9. Comparison 2 Exercise versus control follow-up, Outcome 9 Endocrine symptoms.



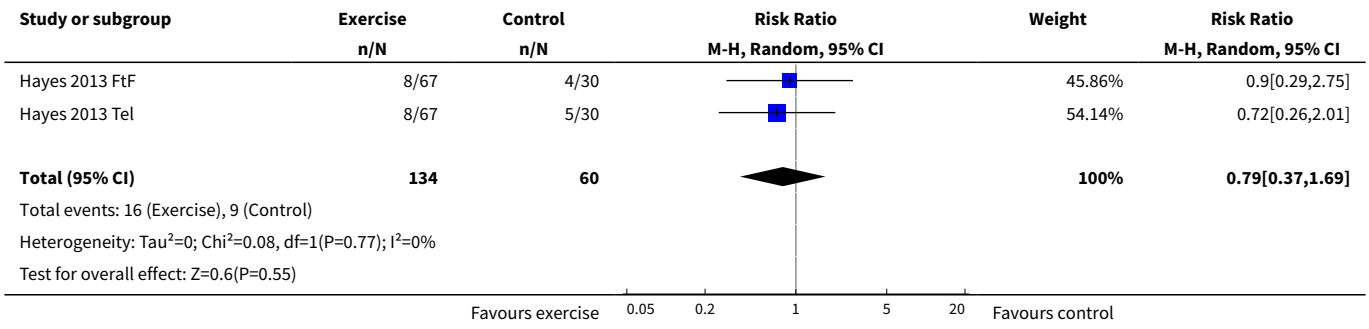
Analysis 2.10. Comparison 2 Exercise versus control follow-up, Outcome 10 Neuropathy symptoms.



Analysis 2.11. Comparison 2 Exercise versus control follow-up, Outcome 11 Gait and balance.



Analysis 2.12. Comparison 2 Exercise versus control follow-up, Outcome 12 Lymphoedema incidence.



APPENDICES

Appendix 1. CENTRAL

#1 MeSH descriptor: [Breast Neoplasms] explode all trees
#2 breast near cancer
#3 breast near neoplasm*
#4 breast near carcinoma*
#5 breast near tumour*
#6 breast near tumor*
#7 #1 or #2 or #3 or #4 or #5 or #6
#8 MeSH descriptor: [Exercise] explode all trees
#9 MeSH descriptor: [Exercise Movement Techniques] explode all trees
#10 MeSH descriptor: [Physical Education and Training] explode all trees
#11 MeSH descriptor: [Exercise Therapy] explode all trees
#12 MeSH descriptor: [Physical Fitness] explode all trees
#13 exercise or exercise movement technique or exercise therapy or physical education or physical fitness or weight or training or strengthening endurance
#14 #8 or #9 or #10 or #11 or #12 or #13
#15 #7 and #14

Appendix 2. MEDLINE search strategy (via OvidSP)

# ▲	Searches
1	randomized controlled trial.pt.
2	controlled clinical trial.pt.
3	randomized.ab.
4	placebo.ab.
5	Clinical Trials as Topic/
6	randomly.ab.
7	trial.ti.
8	(crossover or cross-over).tw.
9	Pragmatic Clinical Trials as Topic/
10	pragmatic clinical trial.pt.
11	or/1-10
12	exp Breast Neoplasms/
13	(breast adj6 cancer$).mp.
14	(breast adj6 neoplasm$).mp.
15	(breast adj6 carcinoma$).mp.
16	(breast adj6 tumour$).mp.

(Continued)

17	(breast adj6 tumor$).mp.
18	12 or 13 or 14 or 15 or 16 or 17
19	exp Exercise/
20	exp Exercise Movement Techniques/
21	exp Exercise Therapy/
22	exercise.mp.
23	exp "Physical Education and Training"/
24	physical-education-and-training.mp.
25	exp Physical Fitness/
26	physical fitness.mp.
27	Physical Exertion/
28	exertion.mp.
29	exp Sports/
30	sport$.mp.
31	physical activity.mp.
32	physical activities.mp.
33	exp Walking/
34	walking.ti,ab.
35	exp Jogging/
36	jogging.ti,ab.
37	exp Swimming/
38	swimming.ti,ab.
39	exp Bicycling/
40	bicycling.ti,ab.
41	cycling.ti,ab.
42	weight.ti,ab.
43	training.ti,ab.
44	muscle.ti,ab.

(Continued)

45	strengthening.ti,ab.
46	endurance.ti,ab.
47	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46
48	adjuvant therapy.mp.
49	chemotherapy.mp. or exp Drug Therapy/
50	radiotherapy.mp. or exp Radiotherapy/
51	hormonal therapy.mp.
52	48 or 49 or 50 or 51
53	11 and 18 and 47 and 52
54	Animals/ not Humans/
55	53 not 54

Appendix 3. EMBASE search strategy (via Embase.com)

1. 'breast cancer'/exp OR 'breast cancer'
2. 'breast carcinoma'/exp
3. 'breast neoplasm'
4. 'breast tumour'
5. 'breast tumor'/exp
6. #1 OR #2 OR #3 OR #4 OR #5
7. 'exercise'/exp
8. exercise*
9. 'exercise movement techniques'/exp OR 'exercise movement techniques'
10. 'physical education training'
11. 'physical education'/exp OR 'physical education'
12. 'physical training'/exp OR 'physical training'
13. 'physical fitness'/exp OR 'physical fitness'
14. 'exercise therapy'/exp OR 'exercise therapy'
15. 'exertion'/exp OR exertion
16. 'sports'/exp OR sports
17. 'walking'/exp OR walking
18. 'jogging'/exp OR jogging
19. 'swimming'/exp OR swimming
20. 'cycling'/exp OR cycling
21. 'bicycling'/exp OR bicycling
22. 'endurance'/exp OR endurance
23. 'weight'/exp OR weight
24. 'training'/exp OR training
25. 'muscle'/exp OR muscle
26. strengthening
27. 'endurance'/exp OR endurance

28.#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR **#23** OR **#24** OR**#25** OR **#26** OR **#27**

29.'adjuvant therapy'/exp OR 'adjuvant therapy'

30.'chemotherapy'/exp OR chemotherapy

31.'radiotherapy'/exp OR radiotherapy

32.hormonal AND ('therapy'/exp OR therapy)

33.#29 OR #30 OR #31 OR #32

34.random* OR factorial* OR crossover* OR cross NEXT/1 over* OR placebo* OR (doubl* AND blind*) OR (singl* AND blind*) OR assign*OR allocat* OR volunteer* OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'randomized controlled trial'/exp OR'single blind procedure'/exp

35.#6 AND #28 AND #33 AND #34

36.#35 NOT ([animals]/lim NOT [humans]/lim)

37.#36 AND [embase]/lim

Appendix 4. WHO ICTRP search strategies

Basic Searches:

1. Exercise for women receiving adjuvant therapy for breast cancer

2. Breast cancer AND exercise

Advanced Searches:

1. Title: Exercise for women receiving adjuvant therapy for breast cancer

Recruitment Status: ALL

2. Condition: breast cancer

Intervention: exercise

Recruitment Status: ALL

3. Condition: breast cancer

Intervention: exercise% OR exercise therap% OR physical education

Recruitment Status: ALL

Appendix 5. ClinicalTrials.gov search strategies

Basic Searches:

1. Exercise for women receiving adjuvant therapy for breast cancer

2. Breast cancer AND exercise

Advanced Searches:

1. Title: Exercise for women receiving adjuvant therapy for breast cancer

Recruitment: All studies

Study Results: All studies

Study Type: All studies

Gender: All Studies

2. Condition: breast cancer

Intervention: exercise OR exercises OR exercise therapy OR exercise therapies OR exercise movement technique OR exercise movement techniques OR physical education OR physical training OR physical fitness OR physical activity OR physical activities

Recruitment: All studies

Study Results: All studies

Study Type: All studies

Gender: All Studies

WHAT'S NEW

Date	Event	Description
22 September 2016	Amended	Amended an author's affiliation

HISTORY

Protocol first published: Issue 4, 2004
Review first published: Issue 4, 2006

Date	Event	Description
30 March 2015	New citation required and conclusions have changed	24 new studies added, with 2174 new participants. We added full 'Risk of bias' tables. Conclusions changed
30 March 2015	New search has been performed	Performed searches for new studies on 30 March 2015
9 September 2008	Amended	Converted to new review format

CONTRIBUTIONS OF AUTHORS

ACF: handsearching and screening search results, study selection, data extraction, contacted experts for unpublished trials and trial investigators for additional data, methodological assessments, quantitative and qualitative synthesis of included studies, reporting.

MM: screening search results, study selection, methodological assessments, contributed to consensus finding when disagreement in study selection, data extraction or methodological assessments persisted between the other two review authors (ACF, MHM), quantitative and qualitative synthesis of included studies, manuscript review.

MHM: handsearching and screening search results, study selection, data extraction, methodological assessments, contributed to consensus finding when disagreement in study selection or methodological assessments persisted between the other two review authors (ACF, MM), quantitative and qualitative synthesis of included studies, reporting.

DECLARATIONS OF INTEREST

ACF, MM, MHM: None known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We included only randomised controlled trials in this updated version of the review, as opposed to the original version of the review, in which we also included controlled trials without a randomisation procedure. This was due to the increasing number of randomised trials.

We excluded hormonal therapy only as adjuvant therapy in this version of the review as we did not consider the side effects of hormonal therapy comparable in their severity to chemo- or radiotherapy or both. We did not include biological outcomes like immune function measured with T-cells in this version of the review, as the focus of the review is on directly participant-relevant outcomes. The same applied to morphological outcomes (changes in body weight or body composition).

We classified outcomes into primary and secondary outcomes in this version of the review.

We did not include data for outcomes assessed with subscales of questionnaires (for example physical functioning subscale of the SF-36 or vitality subscale of the SF-36, nausea item of the SCL-90) in this version of the review.

We also assessed the quality of evidence for the main outcomes using the GRADE methodology and developed a 'Summary of findings' table. This ensures that the review complies with new Cochrane methodological standards.

INDEX TERMS

Medical Subject Headings (MeSH)

*Exercise Therapy; Breast Neoplasms [psychology] [*therapy]; Chemotherapy, Adjuvant [adverse effects]; Cognition; Depression [therapy]; Fatigue [rehabilitation]; Lymphedema [etiology]; Physical Fitness; Quality of Life; Radiotherapy, Adjuvant [adverse effects]; Randomized Controlled Trials as Topic; Weight Gain

MeSH check words

Female; Humans