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Preoperative exercise training for patients with non-small cell lung cancer (Review)

Cavalheri V, Granger C

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Preoperative exercise training for patients with non-small cell lung cancer.
Cochrane Database of Systematic Reviews 2017, Issue 6. Art. No.: CD012020.
DOI: 10.1002/14651858.CD012020.pub2.

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[Intervention Review]

Preoperative exercise training for patients with non-small cell lung cancer

Vinicius Cavalheri[1,2], Catherine Granger[3,4]

[1]School of Physiotherapy and Exercise Science, Curtin University, Perth, Australia. [2]Institute for Respiratory Health, Perth, Australia. [3]Department of Physiotherapy, The University of Melbourne, Parkville, Australia. [4]Physiotherapy, Royal Melbourne Hospital, Parkville, Australia

Contact address: Vinicius Cavalheri, School of Physiotherapy and Exercise Science, Curtin University, Kent Street, Perth, Western Australia, 6102, Australia. v_cavalheri@hotmail.com, vinicius.cavalher@curtin.edu.au.

Editorial group: Cochrane Lung Cancer Group.
Publication status and date: Edited (no change to conclusions), published in Issue 6, 2017.

Citation: Cavalheri V, Granger C. Preoperative exercise training for patients with non-small cell lung cancer. *Cochrane Database of Systematic Reviews* 2017, Issue 6. Art. No.: CD012020. DOI: 10.1002/14651858.CD012020.pub2.

ABSTRACT

Background

Surgical resection for early stage non-small cell lung cancer (NSCLC) offers the best chance of cure, but is associated with a risk of postoperative pulmonary complications (i.e. pneumonia (new infiltrate coupled with either fever (> 38° C) and purulent secretions, or fever and white cell count > 11,000), bronchopleural fistula, severe atelectasis that requires chest physiotherapy or bronchoscopy, and prolonged mechanical ventilation (> 48 hours)). It is currently unclear if preoperative exercise training, and the potential resultant improvement in exercise capacity, may also improve postoperative outcomes, such as the risk of developing postoperative pulmonary complications, the length of postoperative intercostal drainage, or the length of hospital stay.

Objectives

The primary aims of this study were to determine the effect of preoperative exercise training on postoperative outcomes, such as risk of developing a postoperative pulmonary complication, and postoperative duration of intercostal catheter use in adults scheduled to undergo lung resection for NSCLC. The secondary aims of this study were to determine the effect of preoperative exercise training on length of hospital stay, fatigue, dyspnoea, exercise capacity, lung function, and postoperative mortality.

Search methods

We searched CENTRAL, MEDLINE (PubMed), Embase Ovid, PEDro, and SciELO on the 28th of November 2016.

Selection criteria

We included randomised controlled trials (RCTs) in which study participants who were scheduled to undergo lung resection for NSCLC were allocated to receive either preoperative exercise training or no exercise training.

Data collection and analysis

Two review authors independently screened the studies and selected those for inclusion. We performed meta-analyses for the outcomes: risk of developing a postoperative pulmonary complication; postoperative duration of intercostal catheter; length of hospital stay; post-intervention exercise capacity (6-minute walk distance), and post-intervention forced vital capacity (FVC). Although three studies reported post-intervention forced expiratory volume in 1 second (FEV_1), we did not perform meta-analysis on this outcome due to significant statistical heterogeneity (I^2 = 93%) across the studies. Data were not available for fatigue or dyspnoea. One study reported no in-hospital postoperative mortality in either the exercise or the non-exercise groups.

Main results

We identified five RCTs involving 167 participants (mean age ranged from 54 to 72.5 years; sample size ranged from 19 to 60 participants). Overall, we found that the risk of bias in the included studies was high, and the quality of evidence for all outcomes was low. Pooled data from four studies demonstrated that preoperative exercise training reduced the risk of developing a postoperative pulmonary complication by 67% (risk ratio (RR) 0.33, 95% CI 0.17 to 0.61). The number of days patients in the exercise group needed an intercostal catheter was lower than in the non-exercise group (mean difference (MD) -3.33 days, 95% CI -5.35 to -1.30 days; two studies); postoperative length of hospital stay was also lower in the exercise group (MD -4.24 days, 95% CI -5.43 to -3.06 days; four studies). Pooled data from two studies demonstrated that compared to the non-exercise group, post-intervention 6-minute walk distance (MD 18.23 m, 95% CI 8.50 to 27.96 m), and post-intervention FVC (MD 2.97% predicted, 95% CI 1.78 to 4.16% predicted) were higher in the exercise group.

Authors' conclusions

Preoperative exercise training may reduce the risk of developing a postoperative pulmonary complication, the duration of intercostal catheter use, postoperative length of hospital stay, and improve both exercise capacity and FVC in people undergoing lung resection for NSCLC. The findings of this review should be interpreted with caution due to disparities between the studies, risk of bias, and small sample sizes. This review emphasises the need for larger RCTs.

PLAIN LANGUAGE SUMMARY

Exercise training before lung surgery in people with non-small cell lung cancer

Review question

We reviewed the evidence about the effect of exercise training undertaken before lung surgery on the risk of developing a postoperative lung complication, the number of days needing a chest drain after surgery, length of hospital stay, fitness level, and lung function in patients with non-small cell lung cancer (NSCLC).

Background

Lung surgery for NSCLC offers patients a chance of cure, however, lung surgery is associated with increased risk of postoperative lung complications. Preoperative exercise training, through its improvement in fitness levels, may have the potential to decrease the risk of postoperative lung complications and improve other postoperative outcomes, like number of days patients need a chest drain, and length of hospital stay. However, the effects of preoperative exercise training on postoperative outcomes of people with NSCLC is unclear.

Study characteristics

The evidence is current to November 2016. This review included data from 167 participants (mean age ranged from 54 to 72.5 years) in five studies (sample size of the included studies ranged from 19 to 60 participants).

Key results

Results from our review showed that compared to a control group that did not exercise before lung surgery, people with NSCLC who exercised before lung surgery had 67% less risk of developing a postoperative lung complication. Based on this result, we would expect that out of 100 people with NSCLC who exercise before lung surgery, seven will experience a postoperative lung complication, compared with 22 people with NSCLC who will experience a postoperative lung complication if they do not exercise before lung surgery. Also, compared to the control group, people with NSCLC who exercised before lung surgery had a chest drain for fewer days (three days less), had a shorter length of hospital stay (four days less), and better 6-minute walk distance (18 metres more), and lung function before surgery (3% better).

Quality of the evidence

The overall quality of evidence was low for all of the outcomes, mainly because of the small number of studies found, the small number of participants in the included studies, and limitations in the studies' methods.

Summary of findings for the main comparison. Preoperative exercise training compared to no exercise training for patients scheduled to undergo lung resection for non-small cell lung cancer

Preoperative exercise training compared to no exercise training for patients scheduled to undergo lung resection for non-small cell lung cancer

Patient or population: patients scheduled to undergo lung resection for non-small cell lung cancer
Setting: the studies were based in the USA, China, Brazil, Turkey, and Italy.
Intervention: preoperative exercise training
Comparison: no exercise training

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with no exercise training	Risk with preoperative exercise training				
Number of patients who developed postoperative pulmonary complications	Study population 22 per 100	7 per 100 (4 to 13)	RR 0.33 (0.17 to 0.61)	158 (4 RCTs)	⊕⊕⊖⊖ LOW [1, 2]	
Number of days patients needed an intercostal catheter	The mean number of days patients needed an intercostal catheter in the control groups ranged from 7.4 to 8.8 days	The number of days patients needed an intercostal catheter in the intervention groups was, on average, 3.33 fewer days (95% CI 5.35 to 1.3 fewer days)	-	38 (2 RCTs)	⊕⊕⊖⊖ LOW [1, 2]	
Postoperative length of hospital stay	The mean postoperative length of hospital stay in the control groups ranged from 9.7 to 12.2 days	The postoperative length of hospital stay in the intervention groups was, on average, 4.34 fewer days (95% CI 5.65 to 3.03 fewer days)	-	158 (4 RCTs)	⊕⊕⊖⊖ LOW [1, 2]	
Post-intervention exercise capacity assessed with: 6-minute walk distance (6MWD)	The mean post-intervention exercise capacity in the control groups ranged from 340 to 434 metres in 6 minutes.	The post-intervention exercise capacity in the intervention groups was, on average, 18.23 metres more (95% CI 8.5 to 27.96 metres more)	-	81 (2 RCTs)	⊕⊕⊖⊖ LOW [1, 2]	

*__The risk in the intervention group__ (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).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

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[1] Significant risk of bias across the studies
[2] Small sample sizes across the studies, some with wide confidence intervals

BACKGROUND

Description of the condition

Lung cancer is the leading cause of cancer death worldwide (Ferlay 2013). Despite improvements in the medical treatment of lung cancer over recent decades, the five-year survival rate remains poor, at approximately 13% (AIHW 2011; Ferlay 2013). Lung cancer is the third most commonly diagnosed cancer worldwide (Ferlay 2013), and non-small cell lung cancer (NSCLC) accounts for the majority of cases (85%) AIHW 2011).

Surgical resection of the tumour provides the best chance of cure for NSCLC (NCCN 2015). Lung resection is suitable for patients with early stage disease, and those with sufficient cardiopulmonary reserve to withstand the surgery (NCCN 2015). International clinical practice guidelines recommend that patients undergo routine preoperative evaluation, consisting of lung function tests plus the addition of exercise tests, if forced expiratory volume in one second (FEV_1) or impaired diffusing capacity of the lung for carbon monoxide, is reduced (Brunelli 2009a). For patients assessed to be unfit for surgery, or those with advanced disease, alternative treatments include chemotherapy, radiotherapy, targeted agents, or a combination (NCCN 2015). Although lung resection offers a chance of cure, it also results in an immediate insult to the cardiorespiratory system. There is a known, immediate reduction in peak oxygen consumption (VO_{2peak}) of approximately 12% post-lobectomy, and 18% post-pneumonectomy (Brunelli 2009). Postoperative pulmonary complications are common. These include: respiratory failure (such as prolonged mechanical ventilation, re-intubation, or acute respiratory distress syndrome), pneumonia, atelectasis requiring bronchoscopy, myocardial infarction, and arrhythmias (Benzo 2007). The incidence of postoperative pulmonary complications is higher in patients treated with an open thoracotomy approach (4% to 15%) than minimally invasive video-assisted thoracic surgery (VATS (2%) Agostini 2010; Lugg 2016; McKenna 2006; Reeve 2010). Independent risk factors for the development of postoperative pulmonary complications after lung resection include: age over 75 years, body mass index over 30 kg/m^2, a diagnosis of chronic obstructive pulmonary disease (COPD), and being a current smoker (Agostini 2010; Lugg 2016). Postoperative pulmonary complications following lung resection are associated with longer length of hospital stay, higher rate of intensive care unit (ICU) admissions, higher 30-day readmissions, and reduced overall survival (Lugg 2016); hence, prevention is of significant importance.

People with lung cancer experience a high disease burden, physical hardship, and morbidity over the disease trajectory. The adverse physical and psychological impairments in lung cancer occur as a result of multiple processes, including the disease, the cancer treatment, and individual patient factors such as multiple co-morbidities, and a history of poor lifestyle behaviours (Jones 2009; Schmitz 2010). Common symptoms in lung cancer include dyspnoea, cough, fatigue, and pain; these commonly occur as complex symptom clusters, and are particularly debilitating to the patient (Cooley 2000; Hung 2011; Pan 2012). The majority (85% to 90%) of cases of lung cancer are caused by voluntary or involuntary exposure to cigarette smoke (NCCN 2015), and not surprisingly, 40% to 70% of patients also have COPD (Dela Cruz 2011). Many patients have a history of sedentary behaviour. At time of diagnosis, prior to treatment, patients with lung cancer are generally worse than their healthy, age-matched peers in physical activity levels, exercise capacity, muscle strength, and health-related quality of life (HRQoL; Coups 2009; Granger 2014; Novoa 2009). Following diagnosis and treatment, the subsequent vicious cycle of inactivity and functional decline is common (Granger 2014; Novoa 2009). Activity limitations, participation restrictions, and reduced HRQoL commonly ensue (Cavalheri 2015; Hung 2011; Pan 2012; Schmitz 2010; Tanaka 2002).

Description of the intervention

Exercise training is the intervention in this review. Exercise training is "a subset of physical activity that is planned, structured, and repetitive, and has as a final or an intermediate objective, the improvement or maintenance of physical fitness" (Caspersen 1985). This includes aerobic training, resistance training, or respiratory muscle training. Exercise training is not currently standard clinical practice in the preoperative or postoperative management of patients with NSCLC (Cavalheri 2013).

How the intervention might work

Numerous Cochrane and non-Cochrane systematic reviews have demonstrated that exercise training is associated with improvements in exercise capacity, muscle strength, physical function, HRQoL, depression, and symptoms for the general cancer population (Cramp 2012; Rock 2012; Schmitz 2010; Speck 2010). There is also growing evidence of the effectiveness of exercise training specifically for the postoperative NSCLC population (Cavalheri 2013a; Cavalheri 2014; Crandall 2014; Granger 2011). Consistent evidence links higher physical activity levels after cancer diagnosis (breast, colon, and prostate) with reduced cancer-specific and all-cause mortality (Ballard-Barbash 2012; Lee 2014). In NSCLC, patients who are more physically active have better exercise capacity and HRQoL, and fewer symptoms (Coups 2009; Granger 2014). Preliminary evidence suggests that higher exercise capacity at the time of a diagnosis of NSCLC is related to prolonged survival (Denehy 2013; Jones 2012). Postulated mechanisms linking exercise with improved survival in lung cancer include: the modulation of circulating metabolic and sex-steroid hormone concentrations, immune surveillance, and reduced systemic inflammation and oxidative damage (McTiernan 2008). It is currently unclear if preoperative exercise training, and the potential resultant improvement in exercise capacity, may also improve postoperative outcomes, such as reduced postoperative pulmonary complications, duration of intercostal catheter, length of hospital stay, and mortality.

Exercise training is standard clinical practice for people with many other chronic respiratory diseases, as part of their pulmonary rehabilitation (McCarthy 2015; Spruit 2013). Exercise training, the cornerstone of pulmonary rehabilitation programmes, includes aerobic and resistance training, delivered in a supervised environment. For patients with COPD, it has been demonstrated to improve exercise capacity, HRQoL, dyspnoea, and fatigue (McCarthy 2015). Given the commonalities between COPD and lung cancer, and the common co-occurrence of these two conditions, it is possible that exercise training may result in similar outcomes for those undergoing lung resection for NSCLC.

Why it is important to do this review

The primary objective of this review was to determine the effect of preoperative exercise training in adults scheduled to undergo

lung resection for NSCLC, on preoperative and postoperative clinical and patient-related outcomes. If the results of this review were positive, it would provide evidence to support preoperative exercise training, and justify the need to change clinical practice. Results of this review would also be able to direct future research, by mapping the evidence gaps, and highlighting areas of critical limitations that exist in the studies completed to date.

OBJECTIVES

The primary aims of this study were to determine the effect of preoperative exercise training on postoperative outcomes, such as risk of developing a postoperative pulmonary complication, and postoperative duration of intercostal catheter, in adults scheduled to undergo lung resection for NSCLC. The secondary aims of this study were to determine the effect of preoperative exercise training on length of hospital stay, fatigue, dyspnoea, exercise capacity, lung function, and postoperative mortality, in adults scheduled to undergo lung resection for NSCLC.

METHODS

Criteria for considering studies for this review

Types of studies

We only included randomised controlled trials (RCTs) of preoperative exercise training compared with no exercise training for patients with NSCLC. We considered studies published in any language.

Types of participants

We included studies with patients who were scheduled to undergo lung resection for NSCLC. We included lung resection of any extent, that is, wedge resection, segmentectomy, lobectomy, bi-lobectomy, or pneumonectomy. We also included studies with patients who underwent both VATS and open thoracotomy.

Types of interventions

Preoperative exercise training was the intervention, and was compared to no exercise (usual care). We included studies if the intervention group received a minimum of seven exercise sessions completed over a minimum of one week in the preoperative setting. We set up this short arbitrary cut-off point because long exercise programmes are unlikely to be conducted, due to concerns from both patients and multidisciplinary medical teams related to delaying lung resection for long periods of time following the diagnosis of cancer (Benzo 2011; Morano 2013). The exercise sessions could be supervised, unsupervised, or both, and include aerobic, resistance or respiratory muscle training, or a combination. We recorded specific details of the exercise programme, including type of exercise, setting of exercise, supervision, frequency, duration, monitoring, and safety.

Types of outcome measures

Primary outcomes

The primary outcome measures of our review were:

1. Risk of developing a postoperative pulmonary complication (i.e. pneumonia (new infiltrate coupled with either fever (> 38° C) and purulent secretions, or fever and white cell count > 11,000), bronchopleural fistula, severe atelectasis that requires chest physiotherapy, or bronchoscopy and prolonged mechanical ventilation (> 48 hours)); and
2. Number of days patients needed an intercostal catheter following surgery.

Secondary outcomes

1. Postoperative length of hospital stay;
2. Post-intervention fatigue (e.g. the Functional Assessment of Chronic Illness Therapy - Fatigue Subscale);
3. Post-intervention dyspnoea (e.g. the Borg scale or Medical Research Council scale);
4. Post-intervention and postoperative exercise capacity (e.g. six-minute walk distance (6MWD), performance during the stair climbing test, maximum work rate (Wmax), or peak rate of oxygen uptake (VO_{2peak});
5. Post-intervention lung function (e.g. volumes - FEV_1 and forced vital capacity (FVC), flows and diffusing capacity);
6. Postoperative mortality.

Search methods for identification of studies

Electronic searches

We searched the following databases to identify RCTs:

- The Cochrane Central Register of Controlled Trials (CENTRAL; Issue 11, 2016) in the Cochrane Library (searched 28 November 2016);
- MEDLINE (PubMed; 1966 to 28 November 2016);
- Embase Ovid (1974 to 28 November 2016);
- PEDro (Physiotherapy Evidence database; 1980 to 28 November 2016); and
- SciELO (the Scientific Electronic Library Online; 1978 to 28 November 2016).

We listed the search terms and strategies used to search for studies using CENTRAL, MEDLINE and Embase in Appendix 1, Appendix 2 and Appendix 3. The MEDLINE search string was developed according to the Cochrane Highly Sensitive Search Strategy, sensitivity-maximising version as referenced in Chapter 6.4.11.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We adapted the strategy for EMBASE. We also adapted both the terms and the strategies for use in PEDro and SciELO. We placed no restrictions on language or date of publication.

Searching other resources

Other searching sources included: (i) screening reference lists of all RCTs included in the review; (ii) contacting experts in the field for additional references; and (iii) hand searching abstracts from the Thoracic Society of Australia and New Zealand, European Respiratory Society, and American Thoracic Society scientific meetings (2010 to March 2016).

Data collection and analysis

Selection of studies

The two review authors independently examined the studies identified in the literature search using Covidence (Covidence 2017). First, we excluded studies based on their title and abstract

and recorded the reason for exclusion. Subsequently, the two investigators independently examined the full text of the remaining studies and coded them as (i) 'include'; (ii) 'unclear' or (iii) 'exclude', based on the review criteria. We resolved disagreements by consensus and kept a full record of the decisions.

Data extraction and management

The two review authors independently extracted data from the included studies using a standardised form. We resolved any discrepancies by consensus. We attempted to contact authors of the included studies to provide any missing data detected during the process. One of the review authors (VC) then entered data into Review Manager 5.3 (RevMan 2014). In order to interpret the findings, we created a GRADE 'Summary of findings' table (Atkins 2004; Guyatt 2008). The outcomes that were included in the 'Summary of findings' table were: (i) risk of developing a postoperative pulmonary complication; (ii) number of days patients needed an intercostal catheter; (iii) length of hospital stay; and (iv) post-intervention exercise capacity. We used both the 'Summary of findings' screen for numerical data and the 'quality assessment' screen to grade the evidence. We assessed the quality of evidence for each outcome by downgrading or upgrading the evidence according to the GRADE criteria. We used the methods and recommendations described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Chapter 11; Higgins 2011).

Assessment of risk of bias in included studies

The two review authors independently appraised the risk of bias of the included studies using the Cochrane 'seven evidence-based domains' tables. We resolved disagreements by consensus. We judged risk of bias as either high, low, or unclear for selection bias (i.e. random sequence generation and allocation concealment), performance bias (i.e. blinding of participants and personnel), detection bias (i.e. blinding of outcome assessor), attrition bias (i.e. incomplete outcome data), reporting bias (i.e. selective outcome reporting), and other potential sources of bias. The judgement was accompanied by a direct quote, specific details of the study, or both, in the 'Risk of bias' table. We contacted study authors, where applicable, to seek clarification on issues regarding bias. We also contacted authors of unpublished studies to provide us with information pertaining to bias, and we added notes in the 'Risk of bias' table. We generated both the 'Risk of bias' graph (i.e. bar chart) and the 'Risk of bias' summary (i.e. traffic lights). We also used the GRADE approach to rate the overall quality of evidence for each outcome (Atkins 2004; Guyatt 2008a).

Measures of treatment effect

For the primary outcome (i.e. risk of developing a postoperative pulmonary complication), we used the risk ratio (RR). We also used the risk difference (RD), in order to calculate the number needed to treat to benefit (NNTB). For continuous outcomes, we used either the mean difference (MD) or standardised mean difference (SMD). We also calculated 95% confidence intervals (CIs).

Unit of analysis issues

For studies that presented two or more follow-up data for a given outcome (e.g. exercise capacity post-intervention, at three months postoperatively, six months postoperatively, or some combination), we did not combine the results from the different time points in a single meta-analysis.

Dealing with missing data

We attempted to contact authors of the included studies for missing data. When our attempts to contact a study author were unsuccessful, we limited presentation of the outcome(s) of that specific study to a narrative discussion.

Assessment of heterogeneity

We assessed statistical heterogeneity across the studies using the I^2 statistic. We considered values of I^2 that were greater than 50% as substantial heterogeneity (Higgins 2011). If substantial statistical heterogeneity was detected, we investigated whether clinical or methodological heterogeneity were the potential causes. If substantial statistical heterogeneity was detected in meta-analysis, we undertook a sensitivity analysis.

Assessment of reporting biases

We searched online trial registries in order to investigate potential publication bias and to assess potential outcome reporting bias in the included studies.

Data synthesis

We used Review Manager 5.3 for statistical analyses and to generate forest plots (RevMan 2014). For studies published by the same research group which used the same sample of participants, we only included data from one of the published studies in meta-analyses. We analysed pooled data using a random-effects model. We meta-analysed the results of homogeneous studies using the inverse variance DerSimonian and Laird method (DerSimonian 1986). For I^2 values ranging between 50% and 60%, data aggregation was kept if the magnitude and direction of the studies' effects were not conflicting. Where data aggregation was not possible, due to clinical, methodological, or statistical heterogeneity, we used narrative discussion.

Subgroup analysis and investigation of heterogeneity

Where possible, we had planned to conduct subgroup analysis to evaluate the effect of the intervention in the following groups: (i) different exercise training regimens (e.g. aerobic versus resistance training); (ii) extent of lung resection (e.g. lobectomy versus pneumonectomy); (iii) type of surgical approach (e.g. open thoracotomy versus VATS); (iv) stage of NSCLC (e.g. stage I NSCLC versus stage II NSCLC) and (v) comorbidities (e.g. patients diagnosed with COPD versus patients not diagnosed with COPD, or patients with coronary artery disease versus patients without coronary artery disease). We assessed heterogeneity and the extent of inconsistency between studies by visual inspection of the forest plots, and by using the Chi^2 test, and the I^2 statistic.

Sensitivity analysis

We performed sensitivity analyses where we found significant heterogeneity among the studies. We investigated the effects of methodological differences on the results.

RESULTS

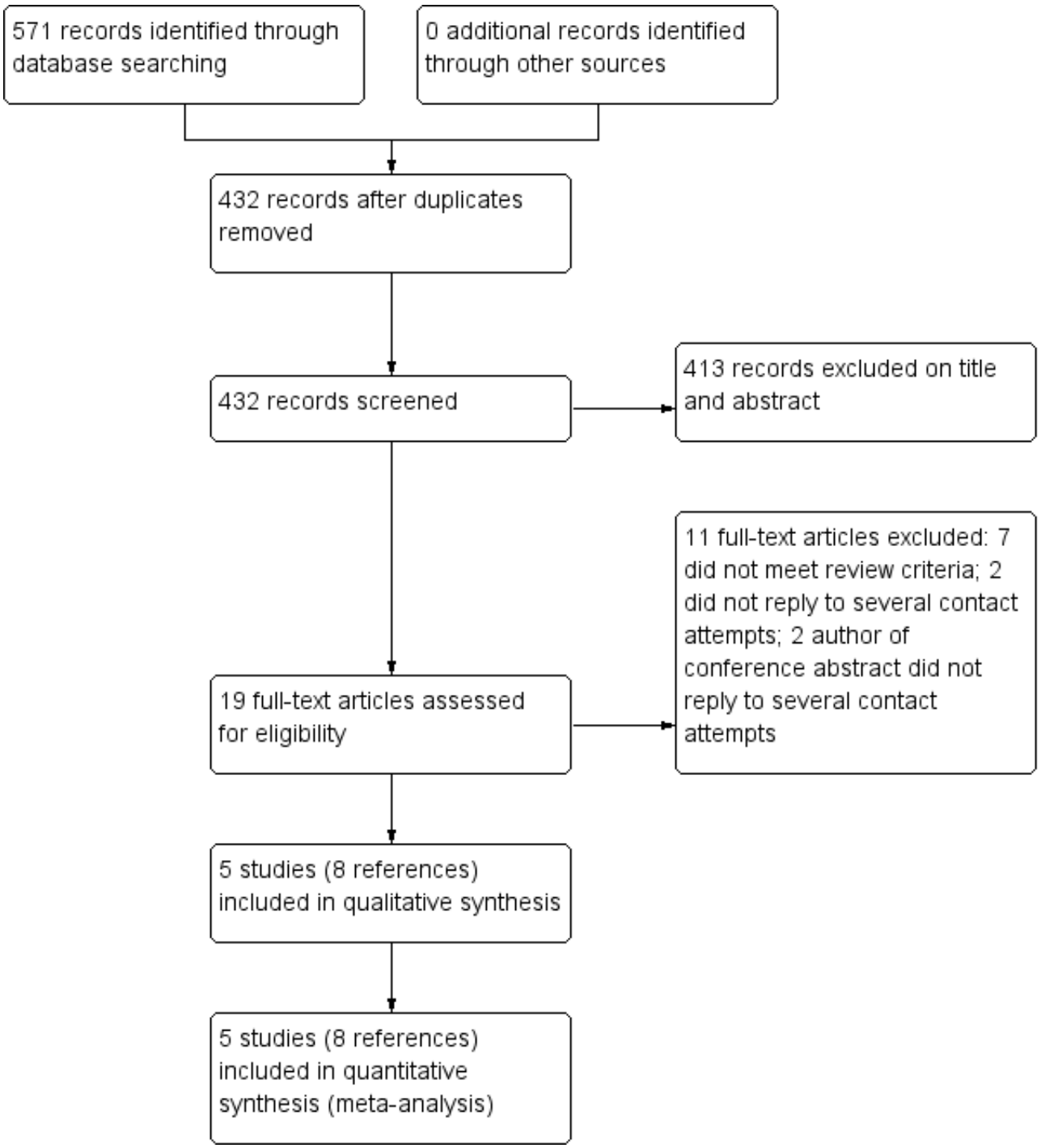
Description of studies

Results of the search

We searched all the databases until 28 November 2016. The search yielded a total of 571 records: 81 from CENTRAL; 95 from MEDLINE;

323 from Embase; 29 from PEDro, and 43 from ScIELO. After removing duplicates, we had a total of 432 records. We excluded 413 based on the title and abstract, and assessed 19 full-text articles and conference abstracts for eligibility. We excluded 11 studies: seven did not meet the review criteria, the authors of two reports did not reply to several contact attempts to confirm eligibility, and the authors of two conference abstracts did not reply to several contact attempts to confirm eligibility (Figure 1). We were able to contact the authors of two studies eligible for this review to obtain missing data.

Figure 1. Flow diagram of references identified, excluded, and included in review



Included studies

Refer to Characteristics of included studies for further details.

Study

This review included five RCTs (eight references) involving 167 participants (Benzo 2011; Lai 2017; Morano 2013; Pehlivan 2011; Stefanelli 2013).

Population

Four of the five studies only included participants with non-small cell lung cancer (NSCLC) undergoing lung resection (Lai 2017; Morano 2013; Pehlivan 2011; Stefanelli 2013). One study did not specify the type of lung cancer of the participants (Benzo 2011). Two studies specifically included participants with NSCLC and a diagnosis of chronic obstructive pulmonary disease (COPD; Benzo 2011; Stefanelli 2013). Three studies included participants undergoing lung resection via either open thoracotomy or video-assisted thoracic surgery (VATS; Benzo 2011; Lai 2017; Morano 2013). Stefanelli 2013 only included participants undergoing lung resection via open thoracotomy. One study did not specify the type of surgical technique used for the lung resection (Pehlivan 2011). The sample sizes ranged from 19 to 60, with the mean age of the participants ranging from 54 to 72.5 years.

Setting

The studies were based in the USA, China, Brazil, Turkey, and Italy.

Intervention

The type, frequency, and intensity of the exercise programs varied considerably across the included studies. The frequency and duration of exercise training programs varied from three times per day for one week (Pehlivan 2011), to five times per week for four weeks (Morano 2013). Aerobic exercise training was prescribed in all five studies. Only one study included resistance training (Benzo 2011); two studies included inspiratory muscle training and education (Benzo 2011; Morano 2013); four studies included breathing exercises (Benzo 2011; Lai 2017; Pehlivan 2011; Stefanelli 2013); and one study included stretches as well (Morano 2013).

The control groups received usual care with no formal exercise training. In one study, participants in the control group received instructions about lung expansion breathing techniques (Morano 2013).

Outcomes

The number of participants who developed a postoperative pulmonary complication was reported in four studies (Benzo 2011; Lai 2017; Morano 2013; Pehlivan 2011). The number of days participants needed an intercostal catheter following surgery was reported in two studies (Benzo 2011; Morano 2013). Four studies reported on postoperative length of hospital stay (Benzo 2011; Lai 2017; Morano 2013; Pehlivan 2011). Post-intervention fatigue was not measured in any of the five included studies and post-intervention dyspnoea was only reported by Stefanelli 2013. Post-intervention exercise capacity was reported in three studies (Lai 2017; Morano 2013; Stefanelli 2013), and post-intervention lung function was reported in three studies (Morano 2013; Pehlivan 2011; Stefanelli 2013). Mortality was only reported by Pehlivan 2011, and this was only in-hospital mortality.

Excluded studies

Of the 19 studies for which the full texts were reviewed, 11 were excluded. The reasons for the exclusion of the 11 studies are summarised in Characteristics of excluded studies.

Risk of bias in included studies

Two out of the seven domains included in the Cochrane 'seven evidence-based domains' table were identical across the five studies (allocation concealment and blinding of participants and personnel). None of the studies reported blinding participants or personnel. Intention-to-treat analysis was reported by Lai 2017 and Morano 2013. Further details can be found in the 'Risk of bias' tables (Characteristics of included studies), with summaries in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

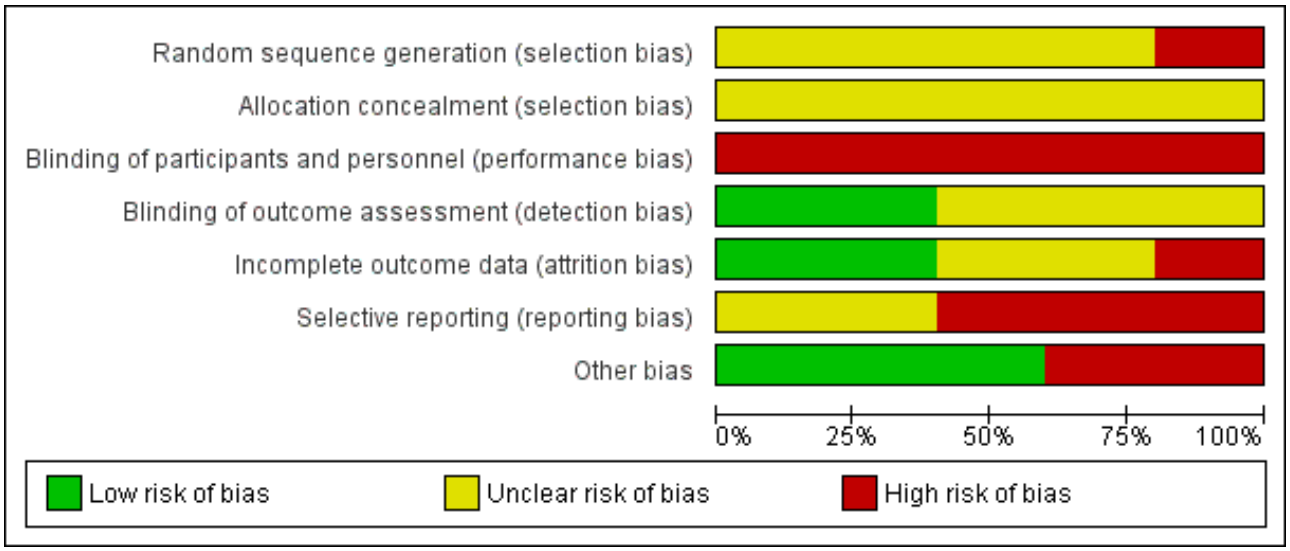
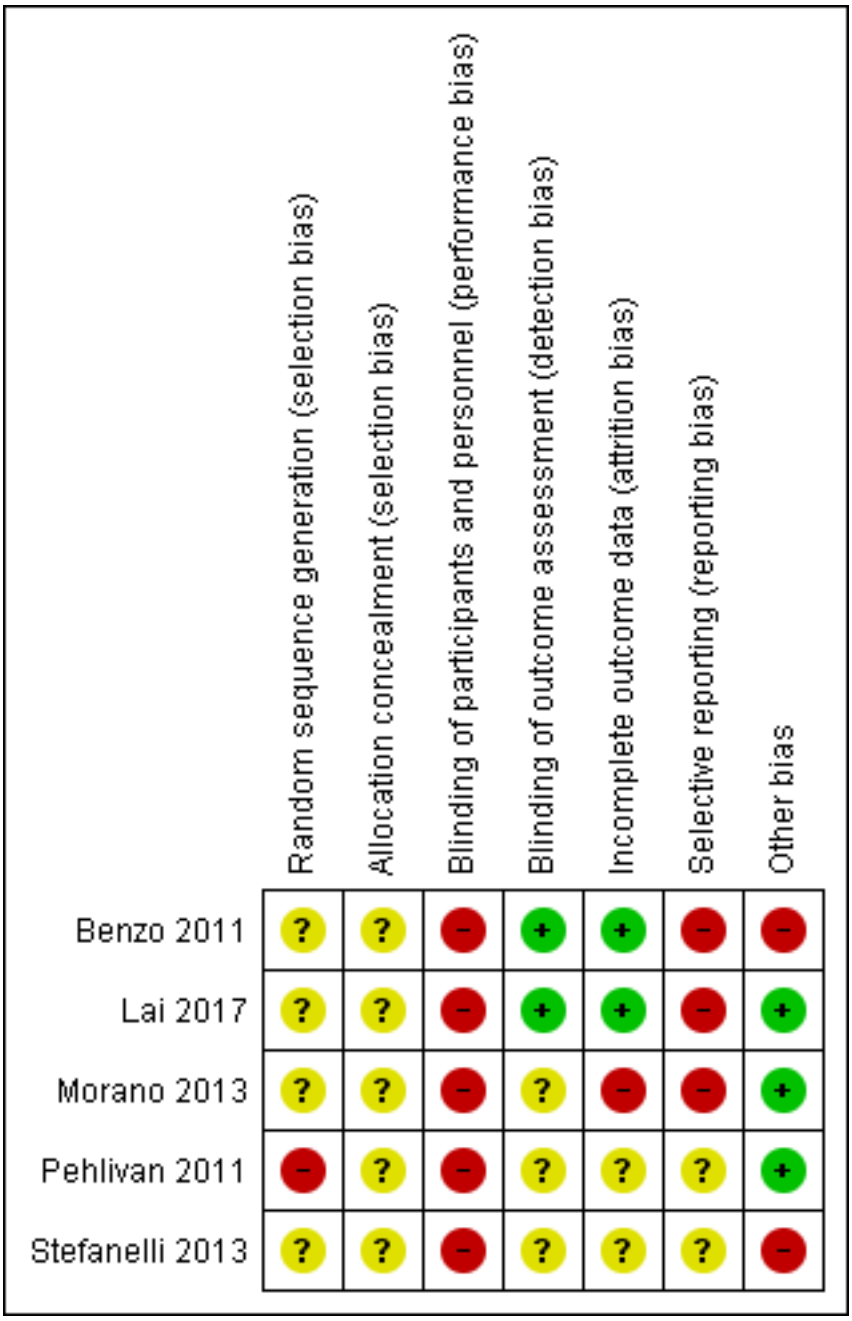


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

We judged one study to be at high risk of selection bias (random sequence generation) because their allocation was based on hospital record number (Pehlivan 2011). We judged the other four studies at unclear risk, since they failed to report sufficient information about the random sequence generation process to permit judgement. We judged all studies to be at unclear risk of selection bias (allocation concealment), since they failed to report sufficient information about allocation concealment to permit judgement.

Blinding

We rated all studies at a high risk of performance bias, since neither the participants nor the personnel responsible for delivering the intervention were blinded to group allocation in any of the studies. Therefore, some of our results may be influenced by a placebo effect. Blinding of the outcome assessor was fully ensured in two studies, which were rated at low risk of detection bias (Benzo 2011; Lai 2017). Two studies did not describe blinding of outcome assessors, and were rated as unclear (Pehlivan 2011; Stefanelli 2013). Postoperative outcomes were obtained by a physical therapist blinded to the treatment assignment in Morano 2013. However, it was not clear whether post-intervention outcome

measures were taken by a blinded assessor, therefore, we judged the risk to be unclear.

Incomplete outcome data

We rated two studies at low risk of attrition bias because missing outcome data were balanced in numbers between the intervention and control groups, with similar reasons for missing data across groups (Benzo 2011), and because all participants successfully completed the training program and assessments (Lai 2017). One study was rated at high risk of bias, due mainly to a large loss to follow-up (25%) in the control group (reasons were given; (Morano 2013)). We rated Pehlivan 2011 and Stefanelli 2013) as unclear risk of attrition bias due to insufficient reporting of attrition and exclusions.

Selective reporting

We rated three studies as high risk of reporting bias as (i) reported outcomes were not pre-specified in the trial registration, (ii) not all of the pre-specified outcomes were reported, and (iii) inclusion criteria were differently reported between trial register and published report (Benzo 2011; Lai 2017; Morano 2013). Two studies were judged to be at unclear risk of reporting bias because of insufficient information (Pehlivan 2011; Stefanelli 2013).

Other potential sources of bias

Two of the five included studies were rated at high risk of bias due to other sources of bias. Benzo 2011 reported findings of two studies they had undertaken; one study was stopped early due to poor recruitment; (ii) Stefanelli 2013 did not report numbers of patients allocated to each group.

Effects of interventions

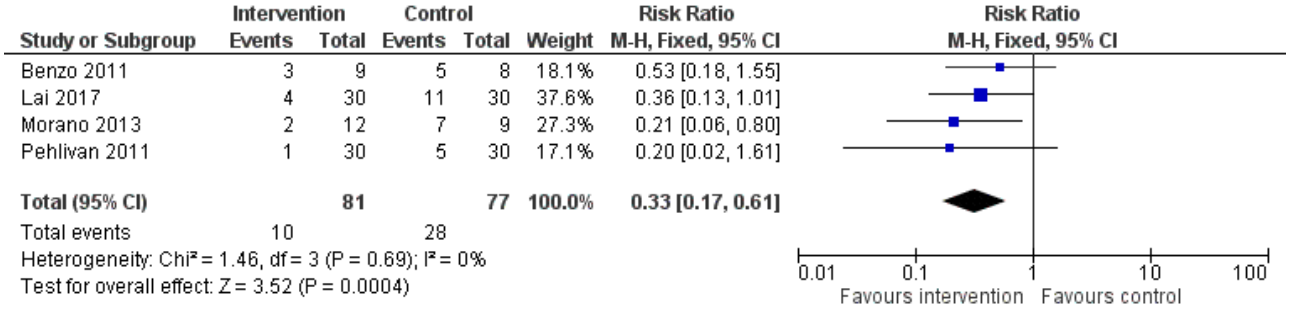
See: **Summary of findings for the main comparison** Preoperative exercise training compared to no exercise training for patients scheduled to undergo lung resection for non-small cell lung cancer

See: Summary of findings for the main comparison.

I. Primary outcome: risk of developing a postoperative pulmonary complication

Four studies reported the number of patients who developed a postoperative pulmonary complication (Benzo 2011; Lai 2017; Morano 2013; Pehlivan 2011; Table 1). Low-quality evidence suggested that exercise training reduced the risk of developing a postoperative pulmonary complication by 67% (RR 0.33, 95% CI 0.17 to 0.61; Analysis 1.1; Figure 4). It is expected that one less person will develop a postoperative pulmonary complication for every four participants receiving preoperative exercise training rather than usual care (RD -0.25, 95% CI -0.37, -0.13; NNTB = 4).

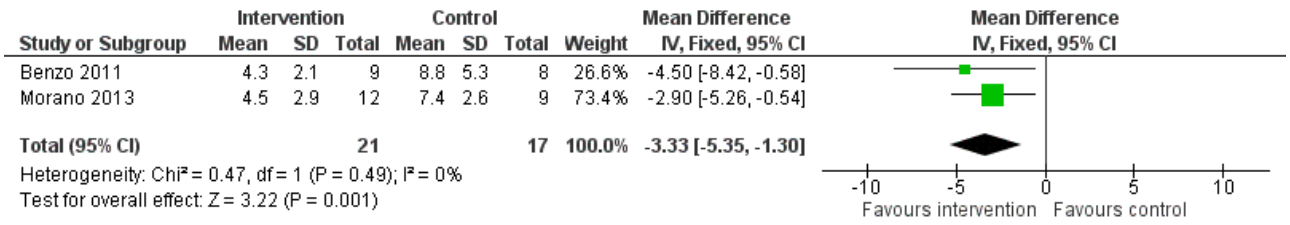
Figure 4. Forest plot of comparison: 1 Intervention group versus control group, outcome: 1.1 Risk of developing a postoperative pulmonary complication.



II. Primary outcome: number of days patients needed an intercostal catheter following surgery

Low-quality evidence from two studies reported the number of days patients needed an intercostal catheter following surgery (Benzo 2011; Morano 2013; Table 1). Compared to the non-exercise group, the number of days patients in the exercise group needed an intercostal catheter following surgery was lower (MD -3.33 days, 95% CI -5.35 to -1.30 days; Analysis 1.2; Figure 5).

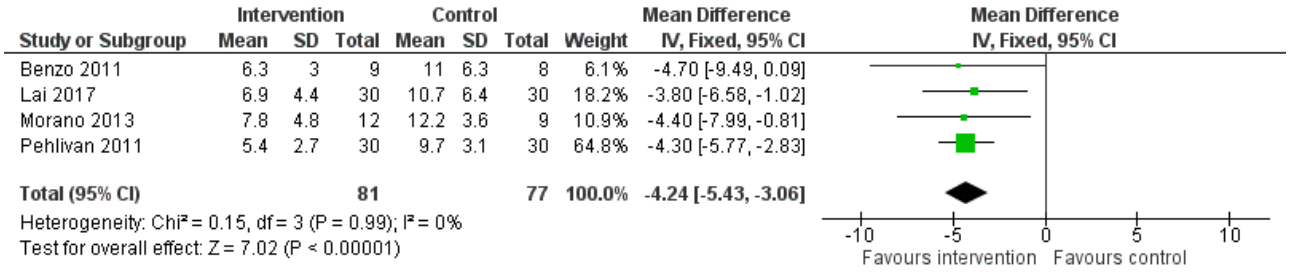
Figure 5. Forest plot of comparison: 1 Intervention group versus control group, outcome: 1.2 Number of days patients needed an intercostal catheter.



III. Secondary outcome: postoperative length of hospital stay

Low-quality evidence from four studies reported postoperative length of hospital stay (Benzo 2011; Lai 2017; Morano 2013; Pehlivan 2011; Table 1). Compared to the non-exercise group, postoperative length of hospital stay was lower in the exercise group (MD -4.24 days, 95% CI -5.43 to -3.06 days; Analysis 1.3; Figure 6).

Figure 6. Forest plot of comparison: 1 Intervention group versus control group, outcome: 1.3 Postoperative length of hospital stay.



IV. Secondary outcomes: post-intervention fatigue and dyspnoea

Data were not available for these outcomes.

V. Secondary outcome: post-intervention and postoperative exercise capacity

Three studies reported post-intervention exercise capacity (Table 1). Two used the 6MWD (Lai 2017; Morano 2013), one used VO_{2peak} (Stefanelli 2013). Data from the three studies were not pooled due to significant methodological and statistical heterogeneity (I^2 = 69%) across the studies. However, we conducted a meta-analysis with data from the two studies that measured the 6MWD (Lai 2017; Morano 2013). There was low-quality evidence that post-intervention 6MWD was higher in the exercise group than in the non-exercise group (MD 18.23 m, 95% CI 8.50 to 27.96 m; Analysis 1.4).

Stefanelli 2013 reported an improvement in VO_{2peak} from baseline to post-intervention in the exercise group (14.9 ± 2.3 ml/kg/min to 17.8 ± 2.1 ml/kg/min; P < 0.01), but no change in VO_{2peak} in the non-exercise group (14.8 ± 1.4 ml/kg/min to 14.5 ± 1.2 ml/kg/min; P > 0.05). Between-group difference was reported as P > 0.05.

Only one study reported postoperative exercise capacity (Stefanelli 2013). This study found that exercise capacity decreased from immediately before surgery (post-intervention time point) to 60 days postoperatively in both groups (VO_{2peak} exercise group: 17.8 ± 2.1 to 15.1 ± 2.4; P < 0.01; non-exercise group: 14.5 ± 1.2 to 11.4 ± 1.2; P < 0.01), however, there was no significant between-group difference.

VI. Secondary outcome: post-intervention lung function

Three studies reported post-intervention FEV_1 (Morano 2013; Pehlivan 2011; Stefanelli 2013; Table 1). We did not conduct a meta-analysis due to significant statistical heterogeneity (I^2 = 93%) across the studies. None of the three studies reported between-group difference in FEV_1.

Two studies reported post-intervention FVC (Morano 2013; Pehlivan 2011; Table 1). Compared to the non-exercise group, post-intervention FVC was greater in the exercise group (MD 2.97% predicted, 95% CI 1.78 to 4.16% predicted; Analysis 1.5).

VII. Secondary outcome: postoperative mortality

Only one study reported postoperative mortality (Pehlivan 2011). This study reported no in-hospital postoperative mortality in either the intervention or the control group.

DISCUSSION

Our meta-analyses found that compared to no exercise training (i.e. usual care), preoperative exercise training conferred a 67% reduction in the risk of developing a postoperative pulmonary complication (RR 0.33, 95% CI 0.17 to 0.61), a three-day reduction in intercostal catheter duration (MD -3.33 days, 95% CI -5.35 to -1.30 days), a four-day reduction in postoperative length of hospital stay (MD -4.24 days, 95% CI -5.43 to -3.06 days), and improved preoperative 6MWD (MD 18.23 m, 95% CI 8.50, 27.96 m). None of the three studies that assessed FEV_1 reported a change in FEV_1 following preoperative exercise trainwhereas the meta-analysis demonstrated that FVC improved 2.97% more in the exercise group compared to the non-exercise group (MD 2.97% predicted, 95% CI 1.78 to 4.16% predicted). There were no data available for fatigue or dyspnoea, and only limited data available on postoperative mortality (one study only and no in-hospital postoperative mortality in either group). Our findings should be viewed with caution as overall, we ratedi the quality of evidence as low. This was due to the significant risk of bias of the included studies and small sample sizes. Further higher quality trials are required to confirm the efficacy of preoperative exercise training.

Measurement of maximal exercise capacity (i.e. VO_{2peak}) is recommended before lung resection in high risk patients (i.e. those with FEV_1 and/or diffusing capacity for carbon monoxide < 80% of predicted values) to determine their eligibility for surgery (Brunelli 2009a). Patients with a VO_2peak > 20ml/kg/min are considered operable and those with a VO_{2peak} < 10ml/kg/min are considered inoperable. Patients with a VO_{2peak} < 16ml/kg/min are at higher risk for peri or postoperative complications (Loewen 2007). Only one of our included studies (Stefanelli 2013) reported data on VO_{2peak}. The mean VO_{2peak} of participants in the intervention and control group in that study was 14.9 ± 2.3 ml/kg/min and 14.8 ± 1.4 ml/kg/min, respectively. That is, according to the cut-off proposed by Loewen et al (Loewen 2007), they were at higher risk for peri or postoperative complications. Importantly, Stefanelli

et al demonstrated that participants in the intervention group significantly improved their VO_{2peak} to 17.8 ± 2.1 ml/kg/min, a value that is higher than the cut-off for increased risk of peri or postoperative complications. Additionally, our meta-analysis demonstrated an improvement in 6MWD in the intervention group that was over and above changes seen in the control group (MD 18.23 m; 95% CI 8.50, 27.96 m). Further studies are needed in order to investigate relationships between a significant improvements in exercise capacity following preoperative exercise training and better postoperative outcomes. However, we suggest that patients within the lower range of VO_2peak (10-15ml/kg/min) should be referred to preoperative exercise training as an attempt to decrease their risk of postoperative pulmonary complications.

The interventions provided in the studies included in our review varied in nature of exercise training. All studies included aerobic exercise training and supplemented this with either resistance training (Benzo 2011), respiratory muscle training (Benzo 2011; Morano 2013) and or breathing exercises (Benzo 2011; Pehlivan 2011; Stefanelli 2013). We cannot attribute one component of the exercise training to the benefits observed, and therefore until further studies are completed comparing respective types of exercise training, or study numbers increase significantly to allow us to undertake subgroup analyses, the optimal preoperative exercise prescription remains unknown. The studies included in the review did not report harm associated with preoperative exercise training. There is the potential that patients may experience short term temporary general muscle soreness after exercising, especially if they are unaccustomed to the specific types of exercises undertaken (Armstrong 1984). However, this is a usual response to exercise and not associated with permanent impairment.

Summary of main results

This review aimed to determine the effect of preoperative exercise training on outcomes such as risk of developing a postoperative pulmonary complication, number of days patients needed an intercostal catheter following surgery, postoperative length of hospital stay, post-intervention fatigue and dyspnoea, post-intervention and postoperative exercise capacity, lung function, and postoperative mortality in adults scheduled to undergo lung resection for non-small cell lung cancer (NSCLC). We included data from five RCTs with 167 participants. This review showed that in patients who were scheduled to undergo lung resection for NSCLC, preoperative exercise training decreased the risk of postoperative pulmonary complications by 63%, reduced both intercostal catheter duration (by three days) and length of hospital stay (by four days), and improved preoperative exercise capacity and FVC. The evidence we found did not find that preoperative exercise training improved other outcomes including FEV_1or postoperative mortality; there were no data for fatigue or dyspnoea .

The ability to reduce postoperative pulmonary complications is of significant value to patients and to the healthcare system. We found a number needed to treat for an additional beneficial outcome (NNTB) of four, meaning that for every four participants receiving preoperative exercise training, one less patient will develop a postoperative pulmonary complication.

Overall completeness and applicability of evidence

Data from a survey that described the management of people undergoing lung resection for lung cancer in 47 hospitals across Australia and New Zealand indicated that preoperative exercise training was provided in only four hospitals, to a 'few' patients (Cavalheri 2013). Our review suggests that patients scheduled for lung resection for NSCLC might benefit from a preoperative exercise training program. We did not find any evidence that surgery should be delayed to allow patients to undertake a preoperative exercise training program and therefore, delivery of the exercise program should take place in the available time before surgery. Preoperative exercise training has the potential to improve important patient-focused postoperative outcomes.

Previous work demonstrated that, compared to patients undergoing lung resection who did not develop a postoperative pulmonary complication, those who developed a postoperative pulmonary complication required increase healthcare utilisation (Lugg 2016). This included more admissions to intensive care unit, longer length of hospital stay and higher readmission rates. Therefore, it could be suggested that preventing postoperative pulmonary complications may have a significant financial impact on patients and the healthcare system, although this was not a focus of our review.

Quality of the evidence

We rated the quality of evidence as low, mainly due to significant risk of bias and small sample sizes (the largest study only included 60 participants). We rated all of the studies as unclear risk of selection bias, as they did not provide sufficient information on allocation concealment, and high risk of performance bias, since none of the studies blinded study personnel or participants. Of note, blinding of personnel and participants cannot be achieved in studies of exercise training, as the personnel are required to deliver the exercise intervention, and participants are often aware of whether they are receiving usual care or exercise training. Lastly, intention-to-treat analysis was only reported in two studies.

Our review only included five RCTs, and since not all outcomes were measured in every study, each meta-analysis included data from only two to four of the studies. Therefore, the low number of small studies impacted the overall quality of evidence. The low number of studies also prevented us from undertaking the planned subgroup analyses. Further RCTs are required to add data to improve the quality of evidence.

Potential biases in the review process

Our review was strengthened by a number of systematic processes followed to ensure rigor and completeness. This included the registration and publication of our protocol prior to starting the search; the use of broad search terms not restricted to language; the inclusion of two independent assessors to determine study inclusion, as well as assessing their agreement for study inclusion; and multiple attempts to contact authors of studies to clarify their suitability for inclusion, methodological details for assessment of risk of bias, and missing or unpublished outcome data. The limitation of this review was the exclusion of two studies where authors could not be contacted to clarify details required for inclusion, which added potential selection bias.

Agreements and disagreements with other studies or reviews

This is the first Cochrane review of preoperative exercise training in lung cancer. We found five published systematic reviews investigating exercise training in lung cancer (Crandall 2014; Granger 2011; Pouwels 2015; Rodriguez-Larrad 2014; Sebio Garcia 2016). Two of these reviews also included studies examining exercise in the postoperative period for people following lung resection (Crandall 2014; Granger 2011), and one review also included perioperative physiotherapy interventions (i.e. not limited to exercise training; Rodriguez-Larrad 2014). In contrast to our review, these previously published reviews included a wide range of study designs (i.e. RCTs, non-RCTs, single group studies, and retrospective cohort studies), and therefore, their results should be interpreted with caution. The two most recently published systematic reviews specifically investigated the effectiveness of preoperative exercise training in people scheduled to undergo lung resection for NSCLC (Pouwels 2015; Sebio Garcia 2016). Pouwels 2015 did not include one RCT included in our review, and did not undertake meta-analyses. Sebio Garcia 2016 included all the RCTs included in our review, and undertook meta-analyses for lung function, length of hospital stay, and postoperative pulmonary complications. Consistent with our findings, Sebio Garcia 2016 reported a significant reduction of postoperative pulmonary complications (MD 0.55, 95% CI 0.34 to 0.89), and hospital length of stay (MD -4.83 days, 95% CI -5.90 to -3.76 days) with preoperative exercise training. The magnitude of difference of their findings was different to our findings, and this was likely because they included prospective non-RCT studies and retrospective cohort studies, in addition to RCTs. Our review is the first to show the positive effect of preoperative exercise training on risk of developing a postoperative pulmonary complication, number of days patients needed an intercostal catheter postoperatively, length of hospital stay, and preoperative exercise capacity and FVC for people with NSCLC.

AUTHORS' CONCLUSIONS

Implications for practice

Low-quality evidence from our meta-analyses suggests that preoperative exercise training for patients scheduled for lung resection for NSCLC may decrease the risk of developing a postoperative pulmonary complication, number of days patients needed an intercostal catheter following surgery, length of hospital stay, and improve preoperative exercise capacity and FVC. Whilst the studies were small and few in number, and the quality of evidence is low, referrals to exercise programs could be considered for patients waiting lung resection.

Implications for research

This review highlights the need for further large RCTs to confirm the impact of preoperative exercise training. In particular, further RCTs are needed to investigate the effect of preoperative exercise training on mortality, and the cost/benefit ratio of this intervention. This is particularly important due to the lack of studies and small sample sizes. The methodological limitations found in many of the current studies should be addressed and minimised in future studies. This includes intention-to-treat analysis, attempts to blind participants, improved reporting of attrition, and reporting full outcome data. The addition of longer term follow-up measures is also important for future trials.

ACKNOWLEDGEMENTS

The authors would like to thank Corynne Marchal, Managing Editor of the Cochrane Lung Cancer Group, for her feedback and support; Fergus MacBeth, Frederic Fiteni, and Ramon Rami Porta, Editors of the Cochrane Lung Cancer Group, as well as Paul Van Schil, Bruno Degano and Pierre-Emmanuel Falcoz, peer referees, and André Stoop, consumer, for their feedback and assistance; François Calais and Giorgio Maria Agazzi for their work on the search strategies; and Virginie Westeel, Sign-off Editor.

This research was supported by a Cancer Council WA Postdoctoral Fellowship (VC) and a Victorian Cancer Agency Clinical Research Fellowship (CG).

REFERENCES

References to studies included in this review

Benzo 2011 *{published data only}*

Benzo R, Wetztein M, Novotny P, Wigle D, Shen RS, Nichols F, et al. Randomized study of pulmonary rehabilitation before lung cancer resection in severe COPD. *American Journal of Respiratory and Critical Care Medicine* 2011;**183**:A3973.

* Benzo R, Wigle D, Novotny P, Wetztein M, Nichols F, Shen RS, et al. Preoperative pulmonary rehabilitation before lung cancer resection: Results from two randomized studies. *Lung Cancer* 2011;**74**:441-5.

Lai 2017 *{published data only}*

Lai Y, Huang J, Yang M, Su J, Liu J, Che G. Seven-day intensive preoperative rehabilitation for elderly patients with lung cancer: a randomized controlled trial. *Journal of Surgical Research* 2017;**209**:30-6.

Morano 2013 *{published data only}*

Morano MT, Araujo AS, Nascimento FB, da Silva GF, Mesquita R, Pinto JS, et al. Preoperative pulmonary rehabilitation versus chest physical therapy in patients undergoing lung cancer resection: A pilot randomized controlled trial. *Archives of Physical Medicine and Rehabilitation* 2013;**94**:53-8. [UTN Number: U1111-1122-2906]

Morano MTAP, Mesquita R, da Silva GF, Araujo AS, Pinto JS, Neto AG, et al. Comparison of the effects of pulmonary rehabilitation with chest physical therapy on the levels of fibrinogen and albumin in patients with lung cancer awaiting lung resection: a randomized clinical trial. *BMC Pulmonary Medicine* 2014;**14**:121.

Pereira ED, Morano M, Araujo A, Nascimento F, Pinheiro G, Mesquita R, et al. Preoperative pulmonary rehabilitation versus chest physical therapy in patients undergoing lung cancer resection: a pilot randomized clinical trial. *American Journal of Respiratory and Critical Care Medicine* 2013;**187**:A5119.

Pehlivan 2011 *{published data only}*

Pehlivan E, Turna A, Gurses A, Gurses HN. The effects of preoperative short-term intense physical therapy in lung cancer patients: A randomized controlled trial. *Annals of Thoracic and Cardiovascular Surgery* 2011;**17**:461-8.

Stefanelli 2013 *{published data only}*

Stefanelli F, Meoli I, Cobuccio R, Curcio C, Amore D, Casazza D, et al. High-intensity training and cardiopulmonary exercise testing in patients with chronic obstructive pulmonary disease and non-small-cell lung cancer undergoing lobectomy. *European Journal of Cardio-thoracic Surgery* 2013;**44**:e260–5.

References to studies excluded from this review

Bradley 2013 *{published data only}*

Bradley A, Marshall A, Stonehewer L, Reaper L, Parker K, Bevan-Smith E, et al. Pulmonary rehabilitation programme for patients undergoing curative lung cancer surgery. *European Journal of Cardio-thoracic Surgery* 2013;**44**(4):e266-71.

Bridevaux 2012 *{published data only}*

Bridevaux PO, Tschopp JM, Bhatia C, Frésard I, Triponez F, Schnyder JM, et al. Effect of pre-operative short-term rehabilitation on peak VO2 in patients with NSCLC. *European Respiratory Journal* 2012;**40**(Suppl 56):3306.

Cesario 2007 *{published data only}*

Cesario A, Ferri L, Galetta D, Cardaci V, Biscione G, Pasqua F, et al. Pre-operative pulmonary rehabilitation and surgery for lung cancer. *Lung Cancer* 2007;**57**(1):118-9.

Gao 2015 *{published data only}*

Gao K, Yu PM, Su JH, He CQ, Liu LX, Zhou YB, et al. Cardiopulmonary exercise testing screening and pre-operative pulmonary rehabilitation reduce postoperative complications and improve fast-track recovery after lung cancer surgery: a study for 342 cases. *Thoracic Cancer* 2015;**6**(4):443-9.

Horch 1991 *{published data only}*

Horch R, Dannhauser J. Can lung function be improved by preoperative respiratory therapy before planned lung resection?. *Zentralblatt fur Chirurgie* 1991;**116**(1):33-8.

Jarosz 2014 *{published data only}*

Jarosz A, Szlubowski A, Grochowski Z, Janczura M, Ładyńska M, Pominkiewicz Ł, et al. The evaluation of utility of preoperative systematized pulmonological physiotherapy among non-small-cell lung cancer patients undergoing anatomical lung resection. *Interactive Cardiovascular and Thoracic Surgery* 2014;**18**:S32.

Kerti 2013 *{published data only}*

Kerti M, Varga J. Activity monitoring in perioperative pulmonary rehabilitation in patients with lung cancer and COPD. *European Respiratory Journal* 2013;**42**(Suppl 57):2234.

Kim 2014 *{published data only}*

Kim I, Lee H. Effects of a progressive walking program on physical activity, exercise tolerance, recovery, and post-operative complications in patients with a lung resection. *Journal of Korean Academy of Nursing* 2014;**44**(4):381-90.

Sommer 2016 *{published data only}*

Sommer MS, Trier K, Vibe-Petersen J, Missel M, Christensen M, Larsen KR, et al. Perioperative Rehabilitation in Operable Lung Cancer patients (PROLUCA): a feasibility study. *Integrative Cancer Therapies* 2016;**15**(4):455-66.

Weiner 1997 *{published data only}*

Weiner P, Man A, Weiner M, Rabner M, Waizman J, Magadle R, et al. The effect of incentive spirometry and inspiratory muscle training on pulmonary function after lung resection. *The Journal of Thoracic and Cardiovascular Surgery* 1997;**113**(3):552-7.

Wotton 2013 *{published data only}*

Wotton R, Bradley A, Parker K, Bishay E, Kalkat M, Rajesh P, et al. Patient quality of life improves with introduction of a

Rehabilitation for Operated lung Cancer (ROC) programme: evaluation of patient-reported outcome measures. *Lung Cancer* 2013;**79**:S72-3.

Additional references

Agostini 2010

Agostini P, Cieslik H, Rathinam S, Bishay E, Kalkat M, Rajesh P, et al. Postoperative pulmonary complications following thoracic surgery: are there any modifiable risk factors?. *Thorax* 2010;**65**:815-8.

AIHW 2011

Australian Institute of Health and Welfare. Lung cancer in Australia: an overview. Cancer series no. 64. Cat. no. CAN 58. Available from www.aihw.gov.au/WorkArea/DownloadAsset.aspx?id=10737421095&libID=10737421094 (accessed 20 July 2015).

Armstrong 1984

Armstrong RB. Mechanisms of exercise-induced delayed onset muscular soreness: a brief review. *Medicine and Science in Sports and Exercise* 1984;**16**(6):529-38.

Atkins 2004

Atkins D, Eccles M, Flottorp S, Guyatt GH, Henry D, Hill S, et al. Systems for grading the quality of evidence and the strength of recommendations I: critical appraisal of existing approaches The GRADE Working Group. *BMC Health Services Research* 2004;**4**(1):38.

Ballard-Barbash 2012

Ballard-Barbash R, Friedenreich C, Courneya K, Siddiqi S, McTiernan A, Alfano C. Physical activity, biomarkers, and disease outcomes in cancer survivors: a systematic review. *Journal of the National Cancer Institute* 2012;**104**(11):815-40.

Benzo 2007

Benzo R, Kelley G, Recchi L, Hofman A, Sciurba F. Complications of lung resection and exercise capacity: a meta-analysis. *Respiratory Medicine* 2007;**101**(8):1790-7.

Brunelli 2009

Brunelli A, Belardinelli R, Refai M, Salati M, Socci L, Pompili C, et al. Peak oxygen consumption during cardiopulmonary exercise test improves risk stratification in candidates to major lung resection. *Chest* 2009;**135**(5):1260-7.

Brunelli 2009a

Brunelli A, Charloux A, Bolliger CT, Rocco G, Sculier JP, Varela G, et al. ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy). *European Respiratory Journal* 2009;**34**(1):17-41.

Caspersen 1985

Caspersen C. Physical activity, exercise and physical fitness: definitions and distinctions for health related research. *Public Health Reports* 1985;**100**(2):126-31.

Cavalheri 2013

Cavalheri V, Jenkin S, Hill K. Physiotherapy practice patterns for patients undergoing surgery for lung cancer: a survey of hospitals in Australia and New Zealand. *Internal Medicine Journal* 2013;**43**(4):394-401.

Cavalheri 2013a

Cavalheri V, Tahirah F, Nonoyama M, Jenkins S, Hill K. Exercise training undertaken by people within 12 months of lung resection for non-small cell lung cancer. *Cochrane Database of Systematic Reviews* 2013, Issue 7. [DOI: 10.1002/14651858.CD009955.pub2]

Cavalheri 2014

Cavalheri V, Tahirah F, Nonoyama M, Jenkins S, Hill K. Exercise training for people following lung resection for non-small cell lung cancer - a Cochrane systematic review. *Cancer Treatment Reviews* 2014;**40**(4):585-94.

Cavalheri 2015

Cavalheri V, Jenkins S, Cecins N, Gain K, Phillips M, Sanders LH, et al. Impairments after curative intent treatment for non-small cell lung cancer: a comparison with age and gender-matched healthy controls. *Respiratory Medicine* 2015;**109**(10):1332-9.

Cooley 2000

Cooley ME. Symptoms in adults with lung cancer. A systematic research review. *Journal of Pain and Symptom Management* 2000;**19**(2):137-53.

Coups 2009

Coups E, Park B, Feinstein M, Steingart R, Egleston B, Wilson D, et al. Physical activity among lung cancer survivors: changes across the cancer trajectory and associations with quality of life. *Cancer Epidemiology, Biomarkers & Prevention* 2009;**18**(2):664-72.

Covidence 2017 [Computer program]

Veritas Health Innovation. Available at www.covidence.org. Covidence systematic review software. Version (accessed 14/06/2016). Melbourne, Australia: Veritas Health Innovation. Available at www.covidence.org, 2016.

Cramp 2012

Cramp F, Daniel J. Exercise for the management of cancer-related fatigue in adults. *Cochrane Database of Systematic Reviews* 2012, Issue 11. [DOI: 10.1002/14651858.CD006145.pub3]

Crandall 2014

Crandall K, Maguire R, Campbell A, Kearney N. Exercise intervention for patients surgically treated for non-small cell lung cancer (NSCLC): a systematic review. *Surgical Oncology* 2014;**23**(1):17-30.

Dela Cruz 2011

Dela Cruz C, Tanoue L, Matthay R. Lung cancer: epidemiology, etiology, and prevention. *Clinics in Chest Medicine* 2011;**32**(4):605-44.

Denehy 2013

Denehy L, Hornsby W, Herndon J, Thomas S, Ready N, Granger C, et al. Prognostic validation of the body mass index, airflow obstruction, dyspnea, and exercise capacity (BODE) index in inoperable non-small-cell lung cancer. *Journal of Thoracic Oncology* 2013;**8**(12):1545-50.

DerSimonian 1986

DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986;**7**(3):177-88.

Ferlay 2013

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al (editors), International Agency for Research on Cancer. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11.Lyon, France: 2013. Available from: globocan.iarc.fr (accessed 1 July 2015).

Granger 2011

Granger C, McDonald C, Berney S, Chao C, Denehy L. Exercise intervention to improve exercise capacity and health related quality of life for patients with non-small cell lung cancer: a systematic review. *Lung Cancer* 2011;**72**(2):139-53.

Granger 2014

Granger C, McDonald C, Irving L, Clark R, Gough K, Murnane A, et al. Low physical activity levels and functional decline in individuals with lung cancer. *Lung Cancer* 2014;**83**(2):292-9.

Guyatt 2008

Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;**336**:924-6.

Guyatt 2008a

Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schunemann HJ. What is "quality of evidence" and why is it important to clinicians?. *BMJ* 2008;**336**:995-8.

Higgins 2011

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org.

Hung 2011

Hung R, Krebs P, Coups E, Feinstein M, Park B, Burkhalter J, et al. Fatigue and functional impairment in early-stage non-small cell lung cancer survivors. *Journal of Pain and Symptom Management* 2011;**41**(2):426-35.

Jones 2009

Jones L, Eves N, Haykowsky M, Freedland S, Mackey J. Exercise intolerance in cancer and the role of exercise therapy to reverse dysfunction. *Lancet Oncology* 2009;**10**(6):598-605.

Jones 2012

Jones L, Hornsby W, Goetzinger A, Forbes L, Sherrard E, Quist M, et al. Prognostic significance of functional capacity and exercise behavior in patients with metastatic non-small cell lung cancer. *Lung Cancer* 2012;**76**(2):248-52.

Lee 2014

Lee I, Wolin K, Freeman S, Sattlemair J, Sesso H. Physical activity and survival after cancer diagnosis in men. *Journal of Physical Activity & Health* 2014;**11**(1):85-90.

Loewen 2007

Loewen GM, Watson D, Kohman L, Herndon JE, Shennib H, Kernstine K, et al. Preoperative exercise VO2 measurement for lung resection candidates: results of Cancer and Leukemia Group B Protocol 9238. *Journal of Thoracic Oncology* 2007;**2**(7):619-25.

Lugg 2016

Lugg ST, Agostini PJ, Tikka T, Kerr A, Adams K, Bishay E, et al. Long-term impact of developing a postoperative pulmonary complication after lung surgery. *Thorax* 2016;**71**(2):171-6.

McCarthy 2015

McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2015, Issue 2. [DOI: 10.1002/14651858.CD003793.pub3]

McKenna 2006

McKenna R, Houck W, Fuller C. Video-assisted thoracic surgery lobectomy: experience with 1100 cases. *Annals of Thoracic Surgery* 2006;**81**(2):421-5.

McTiernan 2008

McTiernan A. Mechanisms linking physical activity with cancer. *Nature Reviews. Cancer* 2008;**8**(3):205-11.

NCCN 2015

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Non-small cell lung cancer. 2015. Available from www.nccn.org/professionals/physician_gls/f_guidelines.asp#site (accessed 1 July 2015); Vol. Version 3.

Novoa 2009

Novoa N, Varela G, Jimenez M, Aranda J. Influence of major pulmonary resection on postoperative daily ambulatory activity of the patients. *Interactive Cardiovascular and Thoracic Surgery* 2009;**9**(6):934-8.

Pan 2012

Pan HH, Lin KC, Ho ST, Liang CY, Lee SC, Wang KY. Factors related to daily life interference in lung cancer patients: a cross-sectional regression tree study. *European Journal of Oncology Nursing* 2012;**16**(4):345-52.

Pouwels 2015

Pouwels S, Fiddelaers J, Teijink JA, Woorst JF, Siebenga J, Smeenk FW. Preoperative exercise therapy in lung surgery patients: a systematic review. *Respiratory Medicine* 2015;**109**(12):1495-504.

Reeve 2010

Reeve JC, Nicol K, Stiller K, McPherson KM, Birch P, Gordon IR, et al. Does physiotherapy reduce the incidence of postoperative pulmonary complications following pulmonary resection via open thoracotomy? A preliminary randomised single-blind clinical trial. *European Journal of Cardio-thoracic Surgery* 2010;**37**(5):1158-66.

RevMan 2014 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Rock 2012

Rock CL, Doyle C, Demark-Wahnefried W, Meyerhardt J, Courneya KS, Schwartz AL, et al. Nutrition and physical activity guidelines for cancer survivors. *CA: A Cancer Journal for Clinicians* 2012;**62**(4):243-74.

Rodriguez-Larrad 2014

Rodriguez-Larrad A, Lascurain-Aguirrebena I, Abecia-Inchaurregui L, Seco J. Perioperative physiotherapy in patients undergoing lung cancer resection. *Interactive Cardiovascular and Thoracic Surgery* 2014;**19**:269-81.

Schmitz 2010

Schmitz KH, Courneya KS, Matthews C, Demark-Wahnefried W, Galvao DA, Pinto BM, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Medicine and Science in Sports and Exercise* 2010;**42**(7):1409-26.

Sebio Garcia 2016

Sebio Garcia R, Yanez Brage MI, Gimenez Moolhuyzen E, Granger CL, Denehy L. Functional and postoperative outcomes after preoperative exercise training in patients with lung cancer: a systematic review and meta-analysis. *Interactive Cardiovascular and Thoracic Surgery* 2016;**23**:486-97.

Speck 2010

Speck RM, Courneya KS, Mâsse LC, Duval S, Schmitz KH. An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. *Journal of Cancer Survivorship: Research and Practice* 2010;**4**(2):87-100.

Spruit 2013

Spruit MA, Singh SJ, Garvey C, Zu Wallack R, Nici L, Rochester C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *American Journal of Respiratory and Critical Care Medicine* 2013;**188**(8):e13-64.

Tanaka 2002

Tanaka K, Akechi T, Okuyama T, Nishiwaki Y, Uchitomi Y. Impact of dyspnea, pain, and fatigue on daily life activities in ambulatory patients with advanced lung cancer. *Journal of Pain and Symptom Management* 2002;**23**(5):417-23.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Benzo 2011

Methods	Two randomised controlled trials Setting: USA (University of Pittsburgh and Mayo Clinic) Study duration: Study 1 – 18 months. Exercise training - 4 weeks. Study 2 – 1 year. Exercise training - 1 week.
Participants	Participants were included in the studies if they were undergoing lung cancer resection by open thoracotomy (segmentectomy, lobectomy, or pneumonectomy) or by video-assisted thoracoscopy (at least lobectomy), and had moderate to severe chronic obstructive pulmonary disease. Study 1 – 9 participants were randomised in 18 months from a large surgical practice (5 hospitals: academic (three) and community (two)) Study 2 – 19 participants (mean age 72 ± 7 years – control group; 70 ± 9 years – exercise group) were randomised in one year from one site (Mayo Clinic). 2 were considered inoperable and therefore, postoperative data are missing.
Interventions	Study 1 Control (N = 4): usual care, which was not defined in the paper.

Benzo 2011 *(Continued)*

	Exercise (N = 5): four weeks of preoperative pulmonary rehabilitation that followed American Thoracic Society/ European Respiratory Society guidelines on exercise prescription (details on the exercise training program were not given). Study 2 Control (N = 9): usual care, which was not defined in the paper. Exercise (N = 10): twice-daily, ten-session preoperative pulmonary rehabilitation that included 20 minutes of lower extremity endurance training on a treadmill, upper extremity endurance training on an arm ergometer, strengthening exercises for upper and lower limbs with Thera-band (every second day), 15 to 10 minutes of inspiratory muscle training, 10 minutes of pursed-lip breathing and prescription of weekend exercises based on their performance during the pulmonary rehabilitation program.
Outcomes	The outcomes of the two studies were hospital length of stay and postoperative pulmonary complications, defined as pneumonia (new infiltrate + either fever (> 38.5° C) and white cell count > 11,000, or fever and purulent secretions), severe atelectasis (requiring bronchoscopy), prolonged chest tubes (> 7 days), and prolonged mechanical ventilation (> 24 h).
Notes	Study 1 had poor recruitment (providers were not willing to delay the curative surgery for 4 weeks) and was stopped, due to the low likelihood of meaningful accrual during the funding period. Therefore, only data from study 2 have been extracted for this systematic review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Comment: Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: No blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “Outcomes were obtained using chart review by a nurse trained in the abstraction of the desired outcomes from the medical records and blinded to the treatment”
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: “Two patients (one on each arm) were missing length of stay data; because they were considered inoperable once they were in the operating room and were excluded from the outcome analysis” Comment: Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	High risk	Quote: “Patients did not improve the shuttle walk test after the short term PR (P = NS)”. Comment: One of the outcomes of interest in the review (exercise capacity) is reported incompletely, so it could not be entered in a meta-analysis.
Other bias	High risk	Comment: Study 1 ceased early due to poor recruitment

Lai 2017

Methods	Randomised controlled trial Setting: Department of Thoracic Surgery, West China Hospital, China. Study duration: One week before lung resection until hospital discharge.
Participants	60 patients who were ≥ 70 yr (mean age 71.6 ± 1.9 years – control group; 72.5 ± 3.4 years – exercise group), with NSCLC, referred for lung resection.
Interventions	Control (N = 30): conventional preoperative respiratory management, and no formal preoperative exercise training. Exercise (N = 30): abdominal breathing training, expiration exercises and aerobic training using the NuStep (NuStep, Inc. Ann Arbor, MI).
Outcomes	Post-intervention: 6-minute walk distance, health-related quality of life, and pulmonary function. Postoperatively: length of hospital stay, postoperative complications.
Notes	N/A

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "…randomly allocated into the PR or control (non-pulmonary rehabilitation, NPR) group." Comment: insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: No blinding of participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All participants were assessed, and data were recorded by a physiotherapist who was blinded to the grouping and the study purpose."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "During the study, four patients in the PR group suspended the training because they could not endure the highly intensive regimen, one perceived a lack of benefit, and one suffered from knee pain. According to the intention-to-treat principle, we included those who did not complete the regimen in the final analysis"
Selective reporting (reporting bias)	High risk	Comment: protocol was registered retrospectively (ChiCTR-IOR-16008109). Age inclusion criterion on the registration was different (> 60 yr) and two outcome measures (cardiopulmonary function and blood gas analysis) listed on the registration were not reported in the published study.
Other bias	Low risk	Comment: the study appears to be free of other sources of bias

Morano 2013

Methods	Randomised controlled trial Setting: teaching hospital in Ceara, Brazil Study duration: March 2008 to March 2011. Exercise training - 4 weeks preoperatively. Assessments were performed before and after the preoperative intervention. Postoperative outcomes were obtained from medical records.
Participants	24 participants (mean age 69 ± 7 years – control group; 65 ± 8 years – exercise group) with non-small cell lung cancer, who were undergoing lung resection via open thoracotomy or video-assisted thoracoscopy, and had impaired lung function. 31 patients recruited, 7 patients were excluded, 5 of whom refused participation, and 2 who did not meet inclusion criteria because of normal pulmonary function.
Interventions	Control (N = 12): usual care that consisted of instructions about lung expansion techniques. Exercise (N = 12): 5 sessions/week for 4 weeks of upper and lower limb endurance training (prescribed at 80% of maximum work rate achieved during a treadmill incremental test), inspiratory muscle training as well as flexibility, stretching, and balance exercises. Both groups had education: classes about the importance of preoperative and postoperative care and knowledge of the surgical process, energy conservation techniques, relaxation and stress management techniques, focus on nutrition, and the need to seek health services when necessary.
Outcomes	Post-intervention: physical capacity measured using the following tests: unsupported upper limb exercise test (UULEX), endurance testing, and the 6-min walk test (6MWT). Quality of life was assessed using the Medical Outcomes Study 36 – Item Short Form Health Survey (SF-36). Feelings of anxiety and depression were determined using the Hospital Anxiety and Depression Scale (HADS). Serum levels of fibrinogen and albumin were measured using a blood sample collected in disposable Vacutainer tubes. Lung function was assessed using spirometry. Postoperatively: length of hospital stay and postoperative pulmonary complications: pneumonia (new infiltrate plus either fever (temperature > 38° C), and white blood cell count > 11,000, or fever and purulent secretions), bronchopleural fistula, bronchospasm, severe atelectasis (confirmed by chest radiographs, requiring chest physiotherapy or bronchoscopy), prolonged need for chest tubes (> 7 d), and prolonged mechanical ventilation (> 48 h)).
Notes	This study was published in two different papers. The paper published in 2013 focused on postoperative outcomes, whereas the paper published in 2014 focused on post-intervention (preoperative) outcomes.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: “patients were randomly assigned to undergo a preoperative PR or CPT program. The randomisation was done in blocks of 4”. Comment: Insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	Quote: “The randomisation was done in blocks of 4, and individual allocations were placed in sealed envelopes. An external investigator blinded to the allocation sequence picked the envelopes” Comment: Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	High risk	Quote: “Single-blinded”. Comment: No blinding of participants and personnel

Morano 2013 *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Postoperative outcomes were obtained from the medical records by a physical therapist blinded to the treatment assignment" Comment: although postoperative outcomes were obtained by a physical therapist blinded to the treatment assignment, it is not clear whether post-intervention outcome measures were taken by a blind assessor. Therefore, there is insufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: 2013 study - "Three patients in the CPT arm were not submitted to lung resection because of inoperable cancer." Quote: 2014 study - "All 24 participants successfully completed the training assignments." Comment: 2013 study - All patients accounted for. Greater drop-outs in control group but reasons given.
Selective reporting (reporting bias)	High risk	Comment: Some reported outcomes were not pre-specified in the study protocol (UTN Number: U1111-1122-2906) and not all of the study's pre-specified outcomes were reported.
Other bias	Low risk	Comment: The study appears to be free of other sources of bias

Pehlivan 2011

Methods	Randomised controlled trial Setting: not described. The study was undertaken in Turkey. Study duration: between January 2007 and August 2008. Exercise training - One week before lung resection until hospital discharge.
Participants	60 patients (mean age 55 ± 8 years – control group; 54 ± 9 years – exercise group), with NSCLC (stage I to IIIB), referred for lung resection.
Interventions	Control (N = 30): usual care with no formal preoperative exercise training. Exercise (N = 30): intensive physical therapy (IPT; chest physiotherapy and walking exercise). Chest physiotherapy consisted of diaphragmatic, pursed lip, segmental breathing exercise, usage of incentive spirometry, coughing exercise. The walking exercise was done by the patient on a treadmill three times a day, according to the patient's tolerance to exercise speed and time. *Postoperatively - Routine physical therapy was performed until discharge in both groups.
Outcomes	Post-intervention: lung function, arterial blood gases Postoperatively: length of hospital stay, postoperative complications, mortality
Notes	Nil

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Comment: different quotes in two parts of the paper. Both methods described are at high risk of failure.

Pehlivan 2011 *(Continued)*

		Quotes: 1 "… randomly allocated (according to hospital record number) to control or study group."; 2 "Allocation was based on hospital record number."
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: no blinding of participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Comment: insufficient information to permit judgement
Other bias	Low risk	Comment: The study appears to be free of other sources of bias

Stefanelli 2013

Methods	Randomised controlled trial Setting: outpatient clinic. The study was undertaken in Naples, Italy. Study duration: February 2010 until December 2011
Participants	40 patients (23 males; age 65 ± 7 years) with chronic obstructive pulmonary disease, undergoing lobectomy (via open thoracotomy) for stage I/II NSCLC were enrolled in the study.
Interventions	Control (N = not reported): usual care with no formal exercise training. Exercise (N = not reported): 3-week (15 3-h sessions, from Monday to Friday) preoperative outpatient intensive pulmonary rehabilitation program based on high-intensity training of both upper- and lower-limb muscles (the upper limbs with the rowing ergometer, and the lower limbs by means of the treadmill and the ergometric bicycle). The exercise work load for each patient was set according to the results of the cardiopulmonary exercise test, starting with 70% of the maximum work rate and increased by 10 W when the patient was able to tolerate the set load for 30 min. The program also included respiratory exercises on the bench, mattress pad and wall bars.
Outcomes	Post-intervention and 60 days postoperatively: lung function (forced expired volume in 1 second, forced vital capacity, and diffusing capacity for carbon monoxide); dyspnoea (Borg scale), and exercise capacity (peak oxygen uptake during the cardiopulmonary exercise test).
Notes	The study did not report on length of hospital stay or postoperative pulmonary complications.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly assigned to two groups"

Stefanelli 2013 *(Continued)*

		Comment: insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: no blinding of participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: Insufficient reporting of attrition/exclusions to permit judgement
Selective reporting (reporting bias)	Unclear risk	Comment: insufficient information to permit judgement
Other bias	High risk	Comment: number of participants in each group not reported.

NSCLC - non-small cell lung cancer

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

Study	Reason for exclusion
Bradley 2013	Not an RCT
Bridevaux 2012	Conference abstract. Unpublished study
Cesario 2007	Not an RCT
Gao 2015	Did not reply to contact attempts
Horch 1991	No exercise training
Jarosz 2014	Did not reply to contact attempts
Kerti 2013	Not an RCT
Kim 2014	Not an RCT
Sommer 2016	Included early postoperative exercise training
Weiner 1997	Not an RCT
Wotton 2013	Conference abstract. Unpublished study

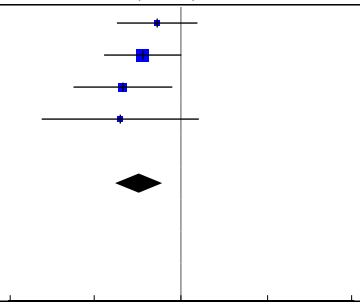
DATA AND ANALYSES

Comparison 1. Intervention group versus control group

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Risk of developing a postoperative pulmonary complication	4	158	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.17, 0.61]
2 Number of days patients needed an intercostal catheter	2	38	Mean Difference (IV, Fixed, 95% CI)	-3.33 [-5.35, -1.30]
3 Postoperative length of hospital stay	4	158	Mean Difference (IV, Fixed, 95% CI)	-4.24 [-5.43, -3.06]
4 Preoperative exercise capacity (6-minute walk distance)	2	81	Mean Difference (IV, Fixed, 95% CI)	18.23 [8.50, 27.96]
5 Forced vital capacity (% pred)	2	84	Mean Difference (IV, Fixed, 95% CI)	2.97 [1.78, 4.16]

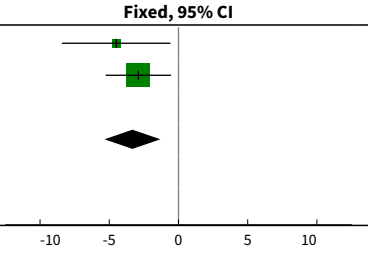
Analysis 1.1. Comparison 1 Intervention group versus control group, Outcome 1 Risk of developing a postoperative pulmonary complication.

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Benzo 2011	3/9	5/8		18.07%	0.53[0.18,1.55]
Lai 2017	4/30	11/30		37.55%	0.36[0.13,1.01]
Morano 2013	2/12	7/9		27.31%	0.21[0.06,0.8]
Pehlivan 2011	1/30	5/30		17.07%	0.2[0.02,1.61]
Total (95% CI)	**81**	**77**		**100%**	**0.33[0.17,0.61]**
Total events: 10 (Intervention), 28 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.46, df=3(P=0.69); I^2=0%					
Test for overall effect: Z=3.52(P=0)					



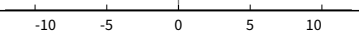
Analysis 1.2. Comparison 1 Intervention group versus control group, Outcome 2 Number of days patients needed an intercostal catheter.

Study or subgroup	Intervention N	Intervention Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Benzo 2011	9	4.3 (2.1)	8	8.8 (5.3)		26.63%	-4.5[-8.42,-0.58]
Morano 2013	12	4.5 (2.9)	9	7.4 (2.6)		73.37%	-2.9[-5.26,-0.54]
Total ***	**21**		**17**			**100%**	**-3.33[-5.35,-1.3]**
Heterogeneity: Tau^2=0; Chi^2=0.47, df=1(P=0.49); I^2=0%							
Test for overall effect: Z=3.22(P=0)							



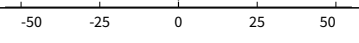
Analysis 1.3. Comparison 1 Intervention group versus control group, Outcome 3 Postoperative length of hospital stay.

Study or subgroup	Intervention N	Intervention Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Benzo 2011	9	6.3 (3)	8	11 (6.3)		6.13%	-4.7[-9.49,0.09]
Lai 2017	30	6.9 (4.4)	30	10.7 (6.4)		18.17%	-3.8[-6.58,-1.02]
Morano 2013	12	7.8 (4.8)	9	12.2 (3.6)		10.87%	-4.4[-7.99,-0.81]
Pehlivan 2011	30	5.4 (2.7)	30	9.7 (3.1)		64.84%	-4.3[-5.77,-2.83]
Total ***	**81**		**77**			**100%**	**-4.24[-5.43,-3.06]**
Heterogeneity: Tau^2=0; Chi^2=0.15, df=3(P=0.99); I^2=0%							
Test for overall effect: Z=7.02(P<0.0001)							



Analysis 1.4. Comparison 1 Intervention group versus control group, Outcome 4 Preoperative exercise capacity (6-minute walk distance).

Study or subgroup	Intervention N	Intervention Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Lai 2017	30	28.6 (18.2)	30	9.4 (27)		69.71%	19.2[7.55,30.85]
Morano 2013	12	50 (26)	9	34 (15)		30.29%	16[-1.68,33.68]
Total ***	**42**		**39**			**100%**	**18.23[8.5,27.96]**
Heterogeneity: Tau^2=0; Chi^2=0.09, df=1(P=0.77); I^2=0%							
Test for overall effect: Z=3.67(P=0)							



Analysis 1.5. Comparison 1 Intervention group versus control group, Outcome 5 Forced vital capacity (% pred).

Study or subgroup	Intervention N	Intervention Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Morano 2013	12	13.2 (11.6)	12	4.9 (16.4)		1.1%	8.3[-3.07,19.67]
Pehlivan 2011	30	19.3 (2.3)	30	16.4 (2.4)		98.9%	2.91[1.71,4.11]
Total ***	**42**		**42**			**100%**	**2.97[1.78,4.16]**
Heterogeneity: Tau^2=0; Chi^2=0.85, df=1(P=0.36); I^2=0%							
Test for overall effect: Z=4.89(P<0.0001)							

ADDITIONAL TABLES

Table 1. Table 1. Results of included studies

Study	Results

Table 1. Table 1. Results of included studies *(Continued)*

Benzo 2011	**Number of patients who developed a postoperative pulmonary complication:** Intervention group (IG): 3 of 9 (33%) Control Group (CG): 5 of 8 (63%) P = 0.23 (between-group) **Number of days patients needed a chest tube:** IG: 4.3 ± 2.1 days CG: 8.8 ± 5.3 days P = 0.03 (between-group) **Postoperative length of hospital stay:** IG: 6.3 ± 3.0 days CG: 11.0 ± 6.3 days P = 0.058 (between-group)
Lai 2017	**Number of patients who developed a postoperative pulmonary complication:** IG: 4 of 30 (13%) CG: 11 of 30 (37%) P = 0.037 (between-group) **Postoperative length of hospital stay:** IG: 6.9 ± 4.4 days CG: 10.7 ± 6.4 days P = 0.01 (between-group) **Exercise capacity**: Six-Minute Walk Distance (6MWD), in metres: IG: 30 participants completed; CG: 30 participants completed; Preoperative measurements: baseline and post-intervention: Mean ± standard deviation (SD): IG: 431.7 ± 102.8 m to 460.3 ± 93.6 m; CG: 434.5 ± 86.2 m to 443.9 ± 88.4 m P = 0.029 (between-group)
Morano 2013	**Number of patients who developed a postoperative pulmonary complication:** IG: 2 of 12 (17%) CG: 7 of 9 (78%) P = 0.01 (between-group) **Number of days patients needed a chest tube:** IG: 4.5 ± 2.9 days CG: 7.4 ± 2.6 days P = 0.03 (between-group)

Table 1. Table 1. Results of included studies *(Continued)*

	Postoperative length of hospital stay: IG: 7.8 ± 4.8 days CG: 12.2 ± 3.6 days P = 0.04 (between-group) **Exercise capacity**: Six-Minute Walk Distance (6MWD), in metres: IG: 12 participants completed; CG: 12 participants completed; Preoperative measurements: baseline and post-intervention: Mean ± standard deviation (SD): IG: 425.5 ± 85.3 m to 475 ± 86.5 m (P < 0.01); CG: 339.6 ± 107 m to 335 ± 107 m (P > 0.05) P < 0.001 (between-group) **Lung function**: (i) Forced expired volume in one second (FEV_1; % predicted): IG: 12 participants completed; CG: 12 participants completed; Preoperative measurements: baseline and post-intervention: IG: 48.1 ± 13.9% to 54.8 ± 22.4% (P = 0.08); CG: 51.7 ± 9.8% to 58.8 ± 13.0% (P = 0.23) Between-group difference was not calculated (ii) Forced vital capacity (FVC; % predicted): IG: 12 participants completed; CG: 12 participants completed; Preoperative measurements: baseline and post-intervention: Median (interquartile range): IG: 62.5% (49 to 71) to 76% (65 to 79.7); P = 0.02; CG: 62.5% (56 to 92) to 71% (63.2 to 89); P = 0.37 Between-group difference was not calculated
Pehlivan 2011	**Number of patients who developed a postoperative pulmonary complication:** IG: 1 of 30 (3%) CG: 5 of 30 (17%) P = 0.04 (between-group) **Postoperative length of hospital stay:** IG: 5.4 ± 2.7 days CG: 9.7 ± 3.1 days P < 0.001 (between-group) **Lung function**: (i) FEV_1; % predicted: IG: 30 participants completed; CG: 30 participants completed; Preoperative measurements: change from baseline to post-intervention: IG: 15.84 ± 2.10%; CG: 9.92 ± 3.5%

Table 1. Table 1. Results of included studies *(Continued)*

	P = 0.3 (between-group) (ii) FVC; % predicted: IG: 30 participants completed; CG: 30 participants completed; Preoperative measurements: baseline and post-intervention: IG: 19.26 ± 2.33%; CG: 16.3 ± 2.4% P = 0.6 (between-group)
Stefanelli 2013	**Exercise capacity**: Peak rate of oxygen uptake (VO_{2peak}), in ml/kg/min: IG: 20 participants completed; CG: 20 participants completed; Preoperative measurements: baseline and post-intervention: IG: 14.9 ± 2.3 ml/kg/min to 17.8 ± 2.1 ml/kg/min; CG: 14.8 ± 1.4 ml/kg/min to 14.5 ± 1.2 ml/kg/min P < 0.001 (between-group) **Lung function**: FEV_1; % predicted: IG: 20 participants completed; CG: 20 participants completed; Preoperative measurements: baseline and post-intervention: IG: 57.4 ± 19.1% to 59.8 ± 19.2%; CG: 57.6 ± 16.9% to 57.5 ± 17.0% P > 0.05 (between-group)

Intervention group (IG), Control Group (CG)

APPENDICES

Appendix 1. CENTRAL search strategy

#1 lung cancer*

#2 non-small cell*

#3 non small cell*

#4 nonsmall cell*

#5 MeSH descriptor: [Lung Neoplasms] explode all trees

#6 MeSH descriptor: [Carcinoma, Non-Small-Cell Lung] explode all trees

#7 nsclc

#8 #1 or #2 or #3 or #4 or #5 or #6 or #7

#9 exercis*

#10 rehabilitat*

#11 aerobic*

#12 endurance

#13 treadmill

#14 walking

#15 physiother*

#16 physical there*

#17 #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16

#18 #8 and #17

#19 preoperat*

#20 pre-operat*

#21 pre operat*

#22 presurg*

#23 pre-surg*

#24 pre surg*

#25 before surg*

#26 before operat*

#27 #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26

#28 #18 and #27

Appendix 2. MEDLINE (PubMed) search strategy

#1, Carcinoma, Non-Small-Cell Lung[MeSH]

#2, nsclc[Title/Abstract]

#3, lung cancer*[Title/Abstract]

#4, lung carcinoma*[Title/Abstract]

#5, lung neoplasm*[Title/Abstract]

#6, lung tumor*[Title/Abstract]

#7, lung tumour*[Title/Abstract]

#8, non-small cell*[Title/Abstract]

#9, nonsmall cell*[Title/Abstract]

#10, (#3 OR #4 OR #5 OR #6 OR #7) AND (#8 OR #9)

#11, #1 OR #2 OR #10

#12, exercise[MeSH Terms]

#13, exercis*[Title/Abstract]

#14, rehabilitation[MeSH Terms]

#15, rehabilitat*[Title/Abstract]

#16, aerobic*[Title/Abstract]

#17, endurance[Title/Abstract]

#18, treadmill[Title/Abstract]

#19, walking[MeSH Terms]

#20, walk*[Title/Abstract]

#21, breathing exercises[MeSH Terms] OR respiratory muscle training[Text Word]

#22, bicycl*[Title/Abstract] OR cycling*[Title/Abstract]

#23, physiotherap*[Title/Abstract] OR physical therap*[Title/Abstract]

#24, #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23

#25, #11 AND #24

#26, preop*[Title/Abstract] OR pre-op*[Title/Abstract]

#27, presurg*[Title/Abstract] OR pre-surg*[Title/Abstract]

#28, before surg*[Title/Abstract] OR before operat*[Title/Abstract]

#29, #26 or #27 or #28

#30, #25 and #29

Appendix 3. Embase Ovid search strategy

#32 #22 AND #31

#31 #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30

#30 'before operat*':tn,lnk,ab,ti

#29 'before surg*':tn,lnk,ab,ti

#28 'pre surg*':tn,lnk,ab,ti

#27 'presurg*':tn,lnk,ab,ti

#26 'presurg*':tn,lnk,ab,ti

#25 'pre operat*':tn,lnk,ab,ti

#24 'preoperat*':tn,lnk,ab,ti

#23 'preoperat*':tn,lnk,ab,ti

#22 #10 AND #21

#21 #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20

#20 'physical activit*':tn,lnk,ab,ti

#19 'physical therapy':tn,lnk,ab,ti

#18 'physiotherapy'/exp

#17 'walking'/exp

#16 'treadmill'/exp

#15 'endurance'/exp

#14 'aerobic*':tn,lnk,ab,ti

#13 'rehabil*':tn,lnk,ab,ti

#12 'rehabilitation'/exp

#11 'exercise'/exp

#10 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9

#9 'nsclc':tn,lnk,ab,ti

#8 'thoracic cancer':tn,lnk,ab,ti

#7 'lung neoplasm':tn,lnk,ab,ti

#6 'lung carcinoma'/exp

#5 'lung tumor'/exp

#4 'nonsmall cell':tn,lnk,ab,ti

#3 'nonsmall cell':tn,lnk,ab,ti

#2 'non small cell lung cancer'/exp

#1 'lung cancer'/exp

WHAT'S NEW

Date	Event	Description
8 June 2017	Amended	Correction in figure 4

CONTRIBUTIONS OF AUTHORS

Vinicius Cavalheri: initiation, writing of protocol, organisation of protocol into RevMan, selection of studies, extraction of data from studies, conduct of the analysis, and writing of the final review paper.

Catherine Granger: initiation, writing of protocol and protocol development, selection of studies, extraction of data from studies, and writing of the final review paper.

DECLARATIONS OF INTEREST

Vinicius Cavalheri: none known

Catherine Granger: none known

SOURCES OF SUPPORT

Internal sources

- School of Physiotherapy and Exercise Science, Faculty of Health Sciences, Curtin University, Australia.
- Department of Physiotherapy, The University of Melbourne, Australia.
- Department of Physiotherapy, Royal Melbourne Hospital, Australia.
- Institute for Respiratory Health, Sir Charles Gairdner Hospital, Perth, Australia.

External sources

- Cancer Council Western Australia, Australia.

  Vinicius Cavalheri is supported by a Cancer Council Western Australia Postdoctoral Fellowship
- Victorian Cancer Agency, Australia.

  Catherine Granger is supported by a Victorian Cancer Agency Clinical Research Fellowship

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We did not perform subgroup or sensitivity analyses due to the small number of studies included in the meta-analyses, as well as their small sample sizes.

INDEX TERMS

Medical Subject Headings (MeSH)

*Physical Conditioning, Human; Carcinoma, Non-Small-Cell Lung [*surgery]; Chest Tubes [statistics & numerical data]; Length of Stay [statistics & numerical data]; Lung Neoplasms [*surgery]; Postoperative Complications [*prevention & control]; Randomized Controlled Trials as Topic; Time Factors; Vital Capacity; Walk Test

MeSH check words

Aged; Humans; Middle Aged