Exercise training undertaken by people within 12 months of lung resection for non-small cell lung cancer (Review)

Cavalheri V, Tahirah F, Nonoyama M, Jenkins S, Hill K

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[Intervention Review]

Exercise training undertaken by people within 12 months of lung resection for non-small cell lung cancer

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ABSTRACT

Background

Decreased exercise capacity and impairments in health-related quality of life (HRQoL) are common in people following lung resection for non-small cell lung cancer (NSCLC). Exercise training has been demonstrated to confer gains in exercise capacity and HRQoL for people with a range of chronic conditions, including chronic obstructive pulmonary disease and heart failure, as well as in people with cancers such as prostate and breast cancer. A programme of exercise training for people following lung resection for NSCLC may confer important gains in these outcomes. To date, evidence of its efficacy in this population is unclear.

Objectives

The primary aim of this study was to determine the effects of exercise training on exercise capacity in people following lung resection (with or without chemotherapy) for NSCLC. The secondary aims were to determine the effects on other outcomes such as HRQoL, lung function (forced expiratory volume in one second (FEV_1)), peripheral muscle force, dyspnoea and fatigue as well as feelings of anxiety and depression.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2013, Issue 2 of 12), MEDLINE (via PubMed) (1966 to February 2013), EMBASE (via Ovid) (1974 to February 2013), SciELO (The Scientific Electronic Library Online) (1978 to February 2013) as well as PEDro (Physiotherapy Evidence Database) (1980 to February 2013).

Selection criteria

We included randomised controlled trials (RCTs) in which study participants with NSCLC, who had recently undergone lung resection, were allocated to receive either exercise training or no exercise training.

Data collection and analysis

Two review authors screened the studies and identified those for inclusion. Meta-analyses were performed using post-intervention data for those studies in which no differences were reported between the exercise and control group either: (i) prior to lung resection, or (ii) following lung resection but prior to the commencement of the intervention period. Although two studies reported measures of quadriceps force on completion of the intervention period, meta-analysis was not performed on this outcome as one of the two studies demonstrated significant differences between the exercise and control group at baseline (following lung resection).

Main results

We identified three RCTs involving 178 participants. Three out of the seven domains included in the Cochrane Collaboration's 'seven evidence-based domains' table were identical in their assessment across the three studies (random sequence generation, allocation concealment and blinding of participants and personnel). The domain which had the greatest variation was 'blinding of outcome assessment' where one study was rated at low risk of bias, one at unclear risk of bias and the remaining one at high risk of bias. On completion of the intervention period, exercise capacity as measured by the six-minute walk distance was statistically greater in the intervention group compared to the control group (mean difference (MD) 50.4 m; 95% confidence interval (CI) 15.4 to 85.2 m). No between-group differences were observed in HRQoL (standardised mean difference (SMD) 0.17; 95% CI -0.16 to 0.49) or FEV_1 (MD -0.13 L; 95% CI -0.36 to 0.11 L). Differences in quadriceps force were not demonstrated on completion of the intervention period.

Authors' conclusions

The evidence summarised in our review suggests that exercise training may potentially increase the exercise capacity of people following lung resection for NSCLC. The findings of our systematic review should be interpreted with caution due to disparities between the studies, methodological limitations, some significant risks of bias and small sample sizes. This systematic review emphasises the need for larger RCTs.

PLAIN LANGUAGE SUMMARY

Exercise training following lung resection for people with non-small cell lung cancer

After lung surgery for non-small cell lung cancer (NSCLC), people are less able to exercise and have worse health-related quality of life (HRQoL). Exercise training has been shown to be effective at improving both exercise capacity and HRQoL in people with some chronic lung diseases, such as emphysema and chronic bronchitis, as well as in those with prostate and breast cancer. However, the effects of exercise training in people following lung surgery for NSCLC are unclear.

This review included data from 178 participants in three studies. The overall quality of evidence was poor because of the small number of studies eligible for inclusion as well as limitations in their methodology. Results from our review showed that, after exercise training, exercise capacity was significantly higher in the intervention group compared to the control group (people who did not receive exercise training). However, this review did not show improvements in HRQoL, lung function or the strength of the leg muscles.

Exercise training may improve the exercise capacity of people following lung surgery for NSCLC.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Exercise training for people following lung resection for non-small cell lung cancer

Patient or population: People following lung resection for non-small cell lung cancer
Settings: In-patient or out-patient hospital departments
Intervention: Exercise training

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Exercise training				
Exercise capacity 6-minute walk distance Follow-up: 2 to 3 months	The mean exercise capacity ranged across control groups from **448 to 491 metres**	The mean exercise capacity in the intervention groups was **50.35 higher** (15.45 to 85.24 higher)		139 (3 studies)	⊕⊕◯◯ **low**[1,2]	
Health-related quality of life Follow-up: 2 to 3 months	The mean health-related quality of life ranged across control groups from **42.2 to 73.1**	The mean health-related quality of life in the intervention groups was **0.17 higher** (0.16 lower to 0.49 higher)		147 (3 studies)	⊕⊕◯◯ **low**[1,2]	
Lung function Spirometry (FEV_1 in litres) Follow-up: 2 to 3 months	The mean lung function ranged across control groups from **2.00 to 2.06 litres**	The mean lung function in the intervention groups was **0.13 lower** (0.36 lower to 0.11 higher)		89 (2 studies)	⊕⊕◯◯ **low**[1,2]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval;

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

[1] Some significant risk of bias across the studies
[2] Small sample sizes across the studies

BACKGROUND

Description of the condition

Lung cancer is an important problem worldwide. Data from 2008 indicate that lung cancer is the most commonly diagnosed cancer in men and the fourth most commonly diagnosed cancer in women (Ferlay 2010; Jemal 2008). Mortality from lung cancer is high with a five-year survival of 14%, making it the leading cause of death from malignancy in developed countries such as Australia (AIHW 2010), the United States of America (USA) (Jemal 2008) and the United Kingdom (UK) (Office for National Statistics 2009). Non-small cell lung cancer (NSCLC) is the most common lung cancer, accounting for approximately 85% of all cases (Sher 2008). Survival from NSCLC is considerably better than for small cell lung cancer (SCLC). Approximately 40% of people with NSCLC who undergo complete lung resection of the primary tumour survive five years (Danish Lung Cancer Registry 2009). In contrast, for people with SCLC metastasis is common at the time of diagnosis and lung resection is rarely an option. Thus the median survival ranges from 313 to 388 days (Suzuki 2011).

Since the early 2000s, there has been an increased interest in outcomes other than survival for people diagnosed with NSCLC. Notably, people with this condition who require lung resection perceive physical debility as a far more important and undesirable outcome than pulmonary complications such as lung collapse and pneumonia (Cykert 2000). Earlier work has demonstrated impaired exercise capacity in people with lung cancers (Jones 2007). The reasons are likely to be multifactorial. Tumours in the lungs are thought to disrupt pulmonary mechanics and gas exchange (Travers 2008), resulting in weight loss, anorexia, anaemia, protein catabolism and muscle wasting (Baracos 2010; Murphy 2010). Dyspnoea and fatigue are also common and are likely to result in the adoption of a sedentary lifestyle (O'Driscoll 1999), which serves to further compromise exercise capacity because of skeletal muscle and cardiovascular deconditioning. Treatment for lung cancer compounds the decrements in exercise capacity. Compared with pre-operative measures, the peak rate of oxygen uptake (VO_2peak) has been shown to be reduced by 13% and 28% six months following lobectomy and pneumonectomy, respectively (Nezu 1998). Adjuvant therapy such as chemotherapy initiates a 'deconditioning storm' that further reduces the capacity to deliver or utilise oxygen and metabolic substrate during exercise, thereby contributing to exercise intolerance (Jones 2008a).

Another important outcome for people with lung cancer is health-related quality of life (HRQoL). At the time of diagnosis, people with lung cancer present with impaired HRQoL and considerable psychological distress, such as feelings of anxiety and depression (Dagnelie 2007; Sugimura 2006). People who have undergone lung resection have been shown to have short-term (four months) and long-term (four years) impairments in HRQoL. These impairments were of similar magnitude to those reported by people who have undergone coronary bypass grafting (Myrdal 2003). Aoki 2007 demonstrated that HRQoL scores did not differ significantly at three or 12 months between groups who underwent either video-assisted thoracoscopic or open surgery .

Description of the intervention

Exercise training was the intervention for this systematic review. Training included aerobic or strengthening (resistance) exercise. Preliminary data have shown that supervised exercise training is feasible, safe and may confer benefits in exercise capacity (Cesario 2007; Jones 2008; Schneider 2007; Spruit 2006) and HRQoL (Jones 2008) for people following lung resection for NSCLC.

How the intervention might work

The role of exercise training is well established in many chronic respiratory conditions, including chronic obstructive pulmonary disease (COPD) (Lacasse 2006), interstitial lung disease (Holland 2008) and asthma (Chandratilleke 2012). There is especially strong evidence for people with COPD. In this population, Cochrane reviews have shown that exercise training improves exercise capacity and HRQoL (Lacasse 2006; Puhan 2011), as well as reducing symptoms of dyspnoea and fatigue (Lacasse 2006). There is also evidence to suggest a reduction in healthcare utilisation and a survival benefit (Lacasse 2006; Puhan 2011). The mechanisms underlying improvements in exercise capacity and reductions in dyspnoea on exertion relate to a reduction in exercise-induced lactic acidosis due to improved skeletal muscle oxidative capacity (Casaburi 1991; Maltais 1996). Previous studies have shown that exercise training confers gains in fatigue and HRQoL in people with other forms of cancer, such as prostate and breast cancer (Schwartz 2001; Segal 2009). We hypothesise that exercise training will also be effective in people following treatment for lung cancer.

Why it is important to do this review

The results of this study have the capacity for an immediate and direct impact on clinical practice. If exercise training is shown to be effective for people following lung resection for NSCLC, it will provide a strong evidence base to promote referral to existing pulmonary rehabilitation programmes. This review will also identify the strengths and limitations of the studies in this area, as well as gaps in the literature. Therefore, the results will be of use when designing future randomised controlled trials (RCTs) to determine the effect of exercise training in this population.

OBJECTIVES

The primary aim of this study was to determine the effects of exercise training on exercise capacity in people following lung resection (with or without chemotherapy) for NSCLC. The secondary aims were to determine the effects on other outcomes such as HRQoL, lung function (forced expiratory volume in one second (FEV_1)), peripheral muscle force, dyspnoea and fatigue as well as feelings of anxiety and depression.

METHODS

Criteria for considering studies for this review

Types of studies

This review included RCTs in which the study participants were allocated to receive either exercise training or no exercise training following lung resection for NSCLC. Studies and abstracts published in any language were eligible for inclusion.

Types of participants

Inclusion criteria comprised participants following lung resection for NSCLC, performed via video-assisted thoracoscopic surgery (VATS) or thoracotomy, with or without induction or adjuvant chemotherapy. We included study participants who had undergone lung resection via either approach because earlier work (Gopaldas 2010) has demonstrated that important outcomes such as short-term mortality, length of hospital stay and hospitalisation costs were similar between these groups. This is despite the fact that people who undergo resection via VATS or thoracotomy differ in terms of pain and shoulder dysfunction (Landreneau 1993). Participants who had undergone resections of any type (that is, wedge resection, segmentectomy, lobectomy or pneumonectomy) were eligible for inclusion. However, study participants were excluded if they had received treatment that aimed only at palliation following diagnosis, or had an anticipated survival following diagnosis of less than 12 months. People with SCLC were excluded from this review because metastasis is common at the time of diagnosis and the median survival is usually less than 12 months.

Types of interventions

The intervention comprised exercise training of any type (aerobic exercise, resistance exercise, respiratory muscle training or any combination) started within 12 months of lung resection. Training sessions could be supervised or unsupervised, or a combination of both. Characteristics of the training programme, such as intensity, frequency, duration, type, adherence and extent of supervision, were recorded where possible. Any adverse events were also documented. Control groups received usual care with either no exercise training or only instructions pertaining to exercise training.

Types of outcome measures

Primary outcomes

The primary outcome was any measure of exercise capacity including VO_2peak and the six-minute walk distance (6MWD).

Secondary outcomes

1. HRQoL (e.g. the Medical Outcomes Study Short Form 36 General Health Survey (SF-36), the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire core 30 (EORTC-C30) and the St. George's Respiratory Questionnaire (SGRQ)).
2. Force-generating capacity of peripheral muscles (e.g. measures of upper and lower limb muscle strength).
3. Pressure-generating capacity of respiratory muscles (e.g. maximal inspiratory and expiratory pressures).
4. Dyspnoea (e.g. the Borg category ratio scale) or functional limitation during daily life resulting from dyspnoea (e.g. the Medical Research Council dyspnoea scale).
5. Fatigue (e.g. the Functional Assessment of Chronic Illness Therapy - Fatigue Subscale).
6. Feelings of anxiety and depression (e.g. the Hospital Anxiety and Depression scale).
7. Lung function (e.g. volumes, flows and diffusing capacity).
8. Mortality.
9. Development of a post-operative pulmonary complication (only for studies that initiated the exercise training programme prior to discharge from hospital following surgery).

Search methods for identification of studies

Electronic searches

Trials were identified from electronic bibliographic databases including:

1. the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2013, Issue 2 of 12);
2. MEDLINE (via PubMed) (1966 to February 2013);
3. EMBASE (via Ovid) (1974 to February 2013);
4. SciELO (The Scientific Electronic Library Online) (1978 to February 2013); and
5. PEDro (Physiotherapy Evidence Database) (1980 to February 2013).

The search strategies that were used for MEDLINE and CENTRAL are presented in Appendix 1 and Appendix 2, respectively. The strategy was adapted for use in the other databases.

We also handsearched abstracts from scientific meetings of the American Thoracic Society, the European Respiratory Society and the Thoracic Society of Australia and New Zealand (2002 to February 2013).

Searching other resources

Reference lists of all primary studies and review articles were screened for additional references. Authors of identified trials were contacted and asked to identify further published and unpublished studies.

Data collection and analysis

Selection of studies

Two review authors (VC and FT) independently examined the titles and abstracts of all studies identified using the search strategy to determine eligibility for inclusion. The decisions of the two review authors were recorded and disagreements were resolved by discussion.

Data extraction and management

Two review authors (VC and FT) extracted data using a standardised form. Disagreements were resolved by discussion or, where necessary, by a third review author (KH). Once consensus was reached, data were entered into the software (Review Manager 5.1 (RevMan 2011)) by the first review author (VC). Data included details of the studies, characteristics of the participants and the results. Where applicable, the authors of the included studies were asked to verify the data and provide details of missing data.

Assessment of risk of bias in included studies

The risk of bias for included studies was assessed as high, low or unclear, with the last category indicating either a lack of information or uncertainty regarding the potential for bias. We used the Cochrane Collaboration's 'seven evidence-based domains' tables (random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data, selective reporting and other possible sources of bias). Disagreements were resolved by discussion or, where necessary, by a third review author (KH). We contacted study authors to seek clarification on issues pertaining to bias.

Measures of treatment effect

No dichotomous outcomes have been included in the analysis. The mean differences (MD) and standardised mean differences (SMD) together with their corresponding 95% confidence intervals (CIs) were calculated for continuous outcomes. MD was calculated for exercise capacity (6MWD) and lung function (FEV_1). SMD was calculated for HRQoL as this outcome was measured using questionnaires with different scale directions. For the SF-36 and the EORTC-C30, higher scores indicate less limitation whereas for the SGRQ higher scores indicate more limitation. In order to pool these data, the mean scores of the SGRQ were subtracted from the maximum possible value for its scale (100). Therefore, in this review, higher scores for HRQoL indicate less limitation.

Dealing with missing data

We contacted the authors of all included studies to obtain missing data.

Assessment of heterogeneity

Heterogeneity and the extent of inconsistency between studies were assessed by visual inspection of the forest plots, the Chi^2 test and using the I^2 statistic.

Assessment of reporting biases

In order to reduce publication bias, we conducted a comprehensive literature search that encompassed published and unpublished studies as well as trials registries. As the number of studies included in this review was less than 10, funnel plots were not generated.

Data synthesis

We used Review Manager 5.1 to conduct the statistical analyses and generate forest plots (RevMan 2011). Initially, a random-effects model was used for calculating summary estimates. As the studies were found to be homogeneous, a fixed-effect model was applied. The results of homogeneous studies were meta-analysed using the inverse variance DerSimonian and Laird method (DerSimonian 1986). Where data aggregation was not possible, a narrative discussion of the study results was undertaken.

A GRADE 'Summary of findings' table (Atkins 2004; Guyatt 2008) was created in order to interpret findings. This was achieved by exporting data from RevMan 5.1, preparing the table, and importing it back into RevMan. The outcomes that were included in the 'Summary of findings' table were (i) 6MWD; (ii) HRQoL (SF-36, EORTC-C30 or the SGRQ) and (iii) lung function (FEV_1). Outcomes expressed as numerical data were edited using the 'summary of findings' screen. We assessed the quality of evidence for each outcome by downgrading or upgrading evidence in accordance with the GRADE criteria. Assumed risk for these outcomes was calculated using the post-intervention values across control groups. The corresponding risk (and 95% CI) for these outcomes was expressed as the mean difference (MD) or standardised mean difference (SMD) of the post-intervention values measured in the intervention group minus the assumed risk.

RESULTS

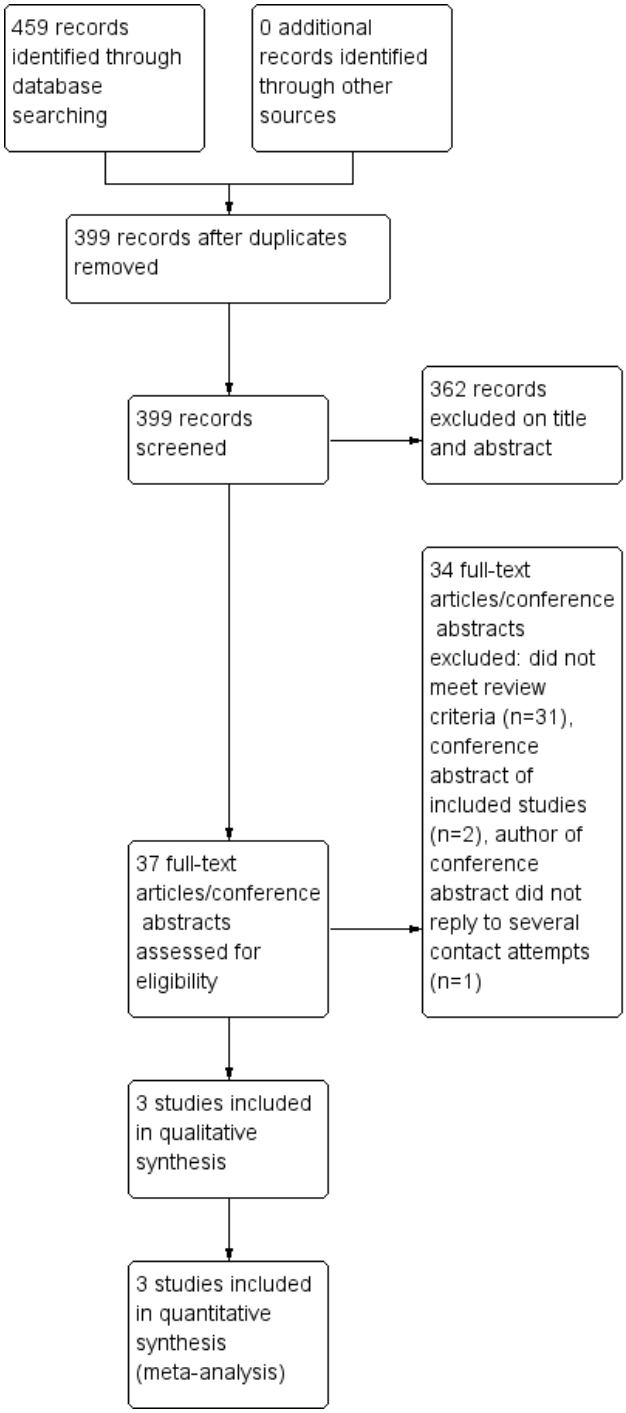
Description of studies

See: Characteristics of included studies; Characteristics of excluded studies. Refer to Characteristics of included studies and Characteristics of excluded studies for complete details of studies which were classified as included or excluded.

Results of the search

The search of all the databases in February 2013 yielded a total of 459 records: 73 from CENTRAL; 297 from MEDLINE; 76 from EMBASE; 10 from PEDro and three from ScIELO. After removing duplicates the total was 399. We excluded 362 based on the title and abstract and assessed 37 full texts and conference abstracts for eligibility. We excluded 34 studies as they did not meet the review criteria (n = 31), were conference abstracts of included studies (n = 2) or the authors did not reply to several contact attempts (n = 1). We were able to contact the authors of the three studies eligible for this review (two full texts and one conference abstract) to obtain missing data (Figure 1).

Figure 1. Study flow diagram.



Included studies

Refer to Characteristics of included studies.

Study

This review comprised three RCTs involving 178 participants (Arbane 2011; Brocki 2010; Stigt 2013).

Population

The three studies included only participants with NSCLC following lung resection. The sample size of the included studies ranged from 49 to 78 with the mean age of the participants ranging from 58 to 65 years. Of the 178 participants, 112 (63%) were male and 66 (37%) were female.

Setting

The studies were based in the UK, Denmark and the Netherlands (Characteristics of included studies). One study is yet to be published (Brocki 2010) and the other two were published in 2011 and 2013, respectively.

Intervention

There was considerable variation in the type, frequency and intensity of the exercise programmes that were investigated. They varied from twice-daily inpatient exercise for five days plus 12 weeks of home-based exercises (Arbane 2011) to out-patient programmes that started four weeks after hospital discharge and were conducted twice a week for 12 weeks (Brocki 2010; Stigt 2013).

Exercise capacity and HRQoL were the only outcomes that were reported in all three studies. Quadriceps force was reported in one study (Arbane 2011). The studies by Brocki 2010 and Stigt 2013 reported lung function as an outcome. Post-operative complications were reported as an outcome in only one study (Arbane 2011).

Control groups received usual care that was comprised of routine out-patient appointments, pain medication prescription (Arbane 2011; Stigt 2013), phone calls (Arbane 2011) as well as instructions regarding exercise (Brocki 2010).

Excluded studies

Of the 37 studies for which the full texts were reviewed, 34 were excluded for the following reasons: (i) lack of randomisation (18 studies); (ii) investigated the role of exercise training started before lung resection (six studies); (iii) an intervention other than exercise training (five studies); (iv) conference abstracts of included studies (two abstracts) and (v) mixed population with few participants (n = 7) who underwent lung resection for NSCLC. Two additional studies were excluded as the authors: (i) were unable to provide the specific data needed for this review (one study) and (ii) did not reply to several contact attempts to obtain the specific data needed for this review (one abstract). These reasons are summarised in Characteristics of excluded studies.

Risk of bias in included studies

Three out of the seven domains included in the Cochrane Collaboration's 'seven evidence-based domains' table were identical across the three studies (random sequence generation, allocation concealment and blinding of participants and personnel). None of the studies reported blinding participants or personnel and the domain which had the greatest variation was 'blinding of outcome assessment' where one study was rated at low risk of bias (Brocki 2010), one at unclear risk of bias (Stigt 2013) and the remaining one at high risk of bias (Arbane 2011). Intention-to-treat analysis was only reported by Brocki 2010. Further details can be found in the section titled Characteristics of included studies as well as 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.

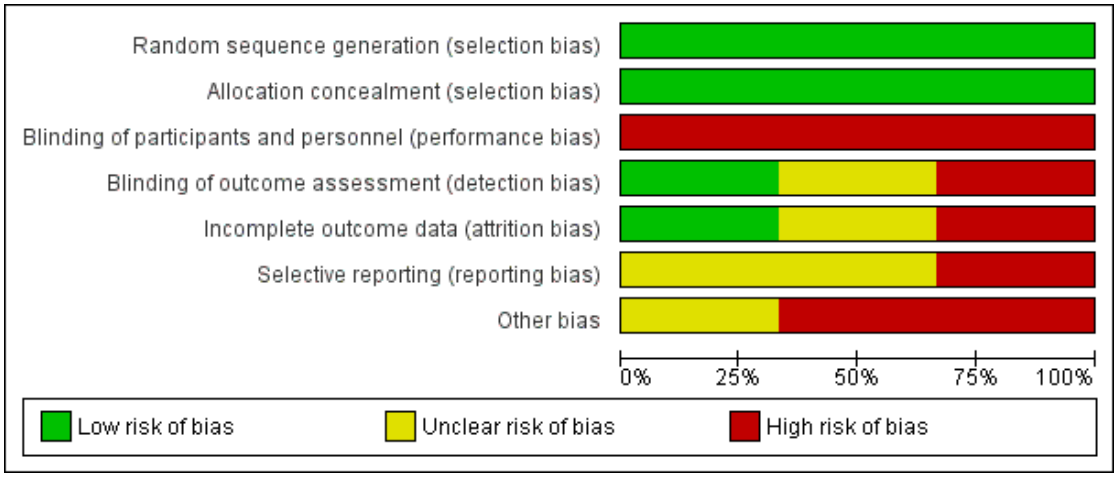


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Allocation

All three studies reported using a process of randomly allocating participants to the two groups. In all studies, this randomisation sequence was concealed. Therefore we judged all the studies to be at low risk of selection bias.

Blinding

Neither the participants nor the personnel responsible for implementing the intervention were blind to group allocation in any of the included studies. This lack of blinding could have influenced the results as the participants may have been influenced by a placebo effect. Hence, we rated all studies at a high risk of performance bias. Regarding detection bias, in one study (Brocki 2010) blinding of the outcome assessor was fully ensured and the study was rated as at low risk of detection bias. As the study by Stigt 2013 did not describe blinding of outcome assessors, the risk of detection bias was rated as unclear. In the other study (Arbane 2011), partial blinding of the outcome assessors was reported. Specifically, in about 10 participants the same therapist performed the assessments and provided the intervention and thus this study was judged as high risk of bias.

Incomplete outcome data

We rated one study at low risk of bias due to incomplete outcome data (Arbane 2011). This was because missing outcome data were balanced in numbers between the intervention and control groups, with similar reasons for missing data across groups. Although Brocki 2010 analysed their data according to the intention-to-treat principle, we did not have sufficient details about the missing cases to permit judgement of low or high risk of bias. Therefore, this study was rated at unclear risk of bias due to incomplete outcome data. One study was rated at high risk of bias (Stigt 2013) mainly due to a large loss to follow-up, with some post-intervention data (see Table 1) reported on only 40% to 60% of participants.

Selective reporting

Two studies (Arbane 2011; Brocki 2010) were judged to be at unclear risk of bias due to selective reporting because there was insufficient information to judge this item (that is, no access to trial's registry). The trial registration of the study by Stigt 2013 (http://clinicaltrials.gov/show/NCT01136083) was reviewed and not all of the pre-specified outcomes were reported. Therefore, the study was rated at high risk of bias due to selective reporting.

Other potential sources of bias

The two published studies were rated at high risk of bias due to other sources of bias. The potential sources of bias were as follows: (i) two studies (Arbane 2011; Stigt 2013) did not collect all outcome measures at identical time points; (ii) the control group of the first study (Arbane 2011) had five participants classified as stage IV disease whereas the intervention group had none in this stage; and (iii) Stigt 2013 had more participants following chemotherapy randomised to the intervention group and there was a higher attrition rate for those who had chemotherapy compared to those who did not.

Effects of interventions

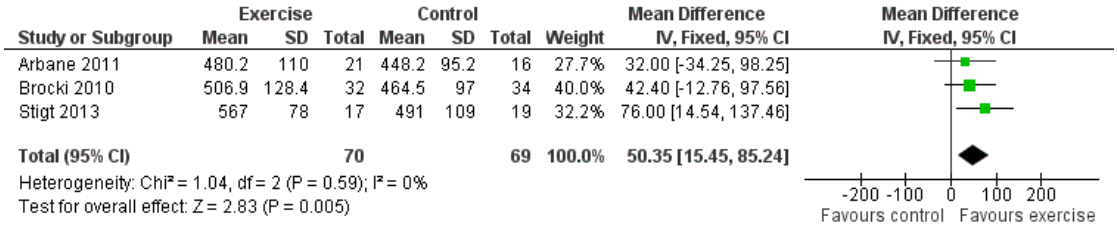
See: **Summary of findings for the main comparison** Exercise training for people following lung resection for non-small cell lung cancer

The means and standard deviations for differences in outcome measures collected at baseline (that is, following lung resection but before starting the intervention) and post-intervention were not available in any of the studies. Therefore, the meta-analysis was performed using post-intervention data for those studies in which no significant differences between the control group and intervention group were reported either: (i) before lung resection, or (ii) following lung resection but before the start of the intervention period. Exercise capacity, HRQoL and lung function (FEV_1) data were included in the meta-analysis. We presented a narrative summary for quadriceps force and development of post-operative complications.

I. Primary outcome: exercise capacity

All three studies reported the 6MWD as their measure of exercise capacity (Table 1). On completion of the intervention period, exercise capacity was significantly higher in the intervention group compared to the control group (MD 50 m; 95% CI 15 to 85 m) (Figure 4).

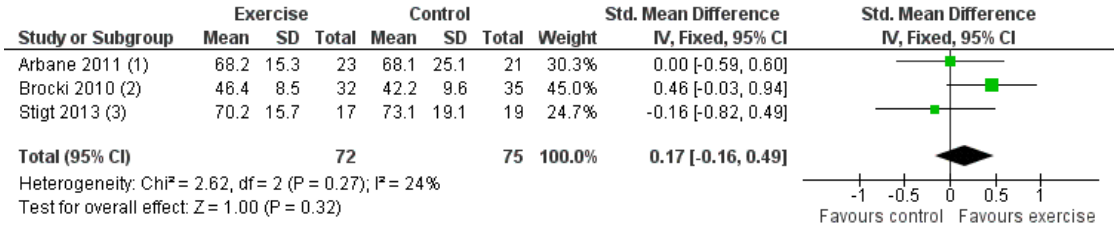
Figure 4. Forest plot of comparison: 1 Exercise group versus control group, outcome: 1.1 Exercise capacity (6MWD in metres).



II. Secondary outcome: health-related quality of life (HRQoL)

All three studies reported measures of HRQoL (Table 1); one used the EORTC-C30 (Arbane 2011), one used the SGRQ (Stigt 2013) and one used the SF-36 (Brocki 2010). On completion of the intervention period, there was no significant difference in HRQoL between the intervention and control groups (SMD 0.17; 95% CI -0.16 to 0.49) (Figure 5).

Figure 5. Forest plot of comparison: 1 Exercise group versus control group, outcome: 1.2 Health-related quality of life.

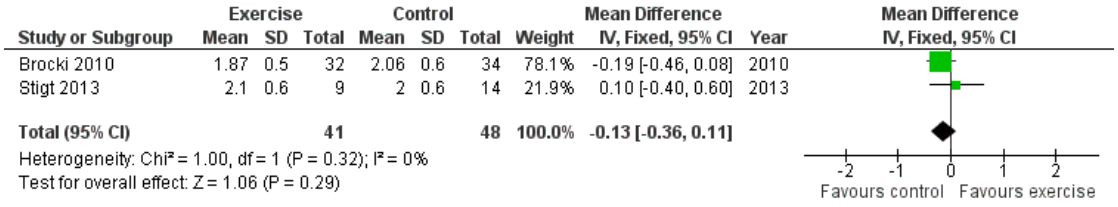


(1) Global function of the EORTC-C30
(2) Physical component SF-36
(3) Total score of the SGRQ. Mean scores subtracted from 100. Therefore, higher scores indicate less limitation.

III. Secondary outcome: lung function (FEV_1)

Two studies reported measures of lung function (Brocki 2010; Stigt 2013) (Table 1). On completion of the intervention period, there was no significant difference in FEV_1 between the intervention and control groups (MD -0.13 L; 95% CI -0.36 to 0.11 L) (Figure 6).

Figure 6. Forest plot of comparison: 1 Exercise group versus control group, outcome: 1.3 Lung function (FEV1 in litres).



IV. Secondary outcome: quadriceps force

Only one study (Arbane 2011) measured quadriceps force (Table 1). Arbane 2011 measured quadriceps force as twitch force elicited via magnetic stimulation of the femoral nerve. This study demonstrated no differences between groups on completion of the 12-week intervention (Table 1).

V. Development of a post-operative pulmonary complication

Only one study commenced the intervention period during the in-patient stay immediately following lung resection (Arbane 2011). This was the only study to report post-operative complications. There were two complications following lung resection in the intervention group and three in the control group; the nature of these complications was not specified in the paper.

VI. Secondary outcomes: pressure-generating capacity of respiratory muscles, dyspnoea, fatigue, feelings of anxiety and depression, and mortality

Data were not available for these outcomes.

DISCUSSION

This review aimed to determine the effects of exercise training on exercise capacity, HRQoL, FEV_1 and quadriceps force in people following lung resection for NSCLC. Data from three RCTs and 178 participants were included. The meta-analyses demonstrate that exercise training conferred an increase in exercise capacity, measured as 6MWD (MD 50 m; 95% CI 15 to 85 m), in this population. However, there was no statistical difference in HRQoL or lung function. There were insufficient data to comment on the effect of exercise training on quadriceps force. The findings of our systematic review should be interpreted with caution due to disparities between the studies, methodological limitations, some significant risks of bias and small sample sizes.

The exercise capacity of people with NSCLC is adversely affected by several factors including the tumour itself, co-existing lung disease as well as treatment for the condition, which may include resection of the tumour with or without adjuvant chemotherapy or radiotherapy (Jones 2009). Deconditioning is triggered by disruption in pulmonary mechanics and gas exchange (Travers 2008), weight loss, protein catabolism and muscle wasting. Consequently, people with any type of cancer tend to live very inactive lifestyles (Blanchard 2008). Several single-group interventional studies, published in the past seven years, have shown that exercise training is safe, feasible and may confer benefit for people following resection for lung cancer (Andersen 2011; Cesario 2007; Jones 2008; Schneider 2007; Spruit 2006). These studies have recommended that large RCTs are undertaken to provide more conclusive evidence regarding the role of exercise training in this population.

In this review, we were able to include two recently published RCTs as well as data from one unpublished study. Even though there was disparity in both the timing and nature of the exercise training, as well as the time points at which outcome measures were assessed, pooled analysis demonstrated a statistically significant effect of exercise training on exercise capacity, measured as the 6MWD (MD 50 m; 95% CI 15 to 85 m). In people with NSCLC, the minimal clinically important difference (MCID) for the 6MWD has not been published. Nevertheless, a MD of 50 metres exceeds the MCID for 6MWD in people with COPD (30 to 35 m) (Polkey 2013; Puhan 2008) and parenchymal lung disease (29 to 34 m) (Holland 2009) and, therefore, may be considered important by people following lung resection for NSCLC. An increase in 6MWD following exercise training is an important finding because this measure appears to be a valuable prognostic indicator for people with NSCLC (Zarogoulidis 2012).

Our review suggests that exercise training has little effect on HRQoL for people following lung resection for NSCLC. This contrasts with earlier work in people with COPD (Lacasse 2006; Puhan 2011) and interstitial lung disease (Holland 2008) in which improvements in HRQoL have been demonstrated following exercise training. Nonetheless, the lack of improvement in HRQoL

seen in this review is consistent with studies in people with other types of cancer. That is, Markes 2006 demonstrated limited evidence for the effectiveness of exercise training to change HRQoL for people undergoing treatment for breast cancer. Although it is possible that exercise training is not effective at improving HRQoL in breast or lung cancer, these findings might also relate to limitations in the way HRQoL was assessed. In our review, two included studies did not use disease-specific HRQoL questionnaires, which are likely to be more responsive to changes in this outcome compared with generic HRQoL questionnaires. Our finding may also reflect that our meta-analysis lacked statistical power to detect small changes in HRQoL. Larger RCTs using disease-specific HRQoL questionnaires are needed to further investigate the effects of exercise training on HRQoL in people following lung resection for NSCLC.

Changes in lung function (FEV_1) following exercise training were not demonstrated in this review. This is in agreement with the literature on the effect of pulmonary rehabilitation on lung function for people with COPD (Lacasse 2006).

Summary of main results

This review showed that, for people who required lung resection for NSCLC, exercise training conferred a statistically significant improvement in exercise capacity (MD 50 m; 95% CI 15 to 85 m). However, this review did not find any evidence that exercise training improved other outcomes such as HRQoL, lung function and quadriceps force.

Overall completeness and applicability of evidence

A recent survey that described pre- and post-operative physiotherapy management for people with lung cancer across Australia and New Zealand (Cavalheri 2013) reported that only a small proportion of people were referred to pulmonary rehabilitation programmes following lung resection. Our review suggests that healthcare professionals should consider referring people following lung resection for NSCLC to an exercise training programme, particularly those with marked decrements in exercise capacity. Exercise training has the potential to interrupt the 'deconditioning storm' (Jones 2008a) induced by the disease and its treatment.

Quality of the evidence

The quality of the evidence provided by the studies included in the analysis has been rated as poor, mainly because of some significant risks of bias and small sample sizes. Specifically, blinding of outcome assessors was only described in one of the studies (Brocki 2010). All the studies were rated as having a high risk of performance bias. However, blinding study participants to treatment allocation in RCTs of exercise training is very difficult, as even with 'sham' training participants are often aware of whether or not they are exercising. Likewise, study personnel implementing the intervention are aware of whether or not the participants are exercising. The low number of studies also adversely affected the quality of the evidence. The inclusion of data from future RCTs will improve the statistical power and precision of our estimates for the impact of exercise in this population.

Potential biases in the review process

The strengths of this review are the extensive electronic search, the search strategy with no language limitation and use of two review authors to independently examine and select studies, as well as our success with contacting the authors of the four included studies to provide additional data. Although we attempted to contact authors from two other studies, one did not reply and the other did not have access to the data we requested. Exclusion of these studies is a potential source of bias.

Agreements and disagreements with other studies or reviews

We found only one published systematic review on the effects of exercise training for people with NSCLC (Granger 2011). This previous review included randomised and non-randomised controlled trials and considered studies that provided an exercise intervention to people with NSCLC before as well as after lung resection. Only one RCT of exercise training following lung resection for NSCLC was included in this earlier review (Arbane 2011). Based mainly on the results of 11 non-randomised controlled trials, Granger et al concluded that for people with NSCLC, exercise training implemented before and after cancer treatment was safe and that exercise training may confer positive benefits on exercise capacity and some domains of HRQoL. Our systematic review is the first to show the effects of exercise training following lung resection for NSCLC using higher level evidence.

AUTHORS' CONCLUSIONS

Implications for practice

Evidence from our meta-analysis suggests that exercise training that included aerobic and resistance exercises may increase the exercise capacity of people following lung resection for NSCLC. Although the quality of the evidence is low, referrals to exercise training or pulmonary rehabilitation programmes should be considered for this population. This is especially true for those with

impaired exercise capacity. Larger RCTs with good methodological quality and intention-to-treat analyses are needed to confirm the efficacy of exercise intervention in people with NSCLC.

Implications for research

This systematic review emphasises the need for larger RCTs and ongoing investigation of the effects of exercise training following lung resection for NSCLC. As blinding study participants and personnel in RCTs of exercise training is very difficult, even with 'sham' training, efforts have to be made to at least ensure blinding of outcome assessors. Intention-to-treat analysis as well as attempts to minimise losses to follow-up should be considered in upcoming studies.

In order to minimise methodological heterogeneity and advance knowledge in this field, future RCTs should consider: (i) collecting outcome measures immediately before and after the exercise training intervention rather than before lung resection and on completion of the exercise training intervention; (ii) choosing disease-specific HRQoL questionnaires; (iii) reporting the values for each domain that contributes to HRQoL as well as the total score obtained from HRQoL questionnaires; and (iv) reporting the mean change (and standard deviation of the change) in outcomes collected immediately before and after the exercise training intervention. Exploring other variables such as fatigue, dyspnoea, and anxiety and depression are also likely to be of value.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Arbane 2011

Methods	Randomised controlled trial Setting: St George's Hospital, London, United Kingdom Study duration: Five days (in-patient) + 12 weeks of home-based intervention. Assessments were performed pre-operatively, five days post-operatively and after the 12 weeks of intervention following discharge
Participants	67 participants with non-small cell lung cancer (NSCLC), referred for lung resection via open thoracotomy or Video Assisted Thoracotomy (VATs), were screened. 53 agreed to participate in the study and were randomised before any formal testing. Two were excluded. 51 participants (median [range] age 63 [32 to 87] years - control group; 65 [47 to 82] years - exercise group) completed the study
Interventions	Control (n = 25): Pain medication as relevant via patient controlled analgesia on day one post-operative, thereafter orally as needed. Usual care comprising routine in-patient physiotherapy treatment (airway clearance techniques, mobilisation as able and upper limb activities) once daily from day one post-surgery to discharge and monthly phone calls after discharge Exercise (n =26): Same as control group plus twice daily additional strength and mobility training from day one to day five post-surgery as well as 12 weeks of home-based non-supervised exercise programme (walking + home-adapted strengthening exercises) including three home visits
Outcomes	Exercise capacity (six-minute walk distance), maximal quadriceps force (femoral nerve stimulation), health-related quality of life (EORTC-C30 version 2.0) and post-operative complications
Notes	Control group - Stage I (10 participants), Stage II (six participants), Stage IV (five participants) and four participants described as "other" Active group - Stage I (15 participants), Stage II (six participants), Stage III (two participants) and for three participants the data was unavailable

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "…performed using computer generated tables …"
Allocation concealment (selection bias)	Low risk	Quote: "…Randomisation codes were kept by an independent member of the team and released after consent…" Comment:

		Investigators enrolling participants could not foresee assignment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "…Study was single blinded with the therapist performing assessments unaware of the randomisation although weekend treatments meant that in about 10 participants the same therapist performed the assessment and treatment…" Comment: No blinding of participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "…Study was single blinded with the therapist performing assessments unaware of the randomisation although weekend treatments meant that in about 10 participants the same therapist performed the assessment and treatment…" Comment: Partial blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: Numbers for each outcome were reported. Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
Selective reporting (reporting bias)	Unclear risk	Comment: No protocol available. Insufficient information to permit judgement of 'Low risk' or 'High risk'
Other bias	High risk	Comment: Five-day post-operative assessment did not include quality of life questionnaire Also, the control group had five participants categorised at stage IV whereas the exercise group had none

Brocki 2010

Methods	Randomised controlled trial Setting: Outpatient clinic, Aalborg Hospital, Denmark Study duration: Three months of intervention. Assessments were performed before and after intervention period
Participants	78 participants with lung cancer were included (46M, 32F) and randomised to either the control (mean age 65 ± 9 years) or the exercise group (mean age 64 ± 10 years)
Interventions	Control (n = 37): Usual care and one individual instruction about exercise training Exercise (n = 41): Aerobic exercise, resistance training and dyspnoea management. Target intensity was set at 60% to 80% of participant's peak work capacity. Exercise programme initiated following the assessments which took place three weeks after discharge
Outcomes	Exercise capacity (six-minute walk distance), quality of life (SF-36) and lung function (spirometry)
Notes	Non-published data All the information for the assessment of risk of bias as well as the data for the analysis were informed by the first author

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "We used two computer-generated randomisation tables, stratified for pneumonectomy, since we expected the latter to present with low performance status."
Allocation concealment (selection bias)	Low risk	Quote: "Individual allocations were placed by an external person in consecutively numbered and sealed opaque envelopes."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "No blinding of participants and trainers"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Assessors were blinded to the individual group allocation and patients were instructed not to reveal their individual group allocation."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Exercise group: Nine participants lost to follow-up (two deceased; two withdrew for not wanting to receive intervention; five

		withdrew consent for other reasons); 32 completed Control group: One participant lost to follow-up (deceased); 36 completed. 6MWT n = 34; SF-36 n = 35; spirometry n = 34 Intention-to-treat analysis was done." Comment: Insufficient details about missing cases to permit judgement of 'Low risk' or 'High risk'
Selective reporting (reporting bias)	Unclear risk	Comment: Insufficient information to permit judgement of 'Low risk' or 'High risk'
Other bias	Unclear risk	Comment: Insufficient information to permit judgement of 'Low risk' or 'High risk'

Stigt 2013

Methods	Randomised controlled trial Setting: Teaching Hospital in Zwolle, the Netherlands. Study duration: 12 weeks of intervention and 1-year follow-up. Assessments were performed before surgery and post-operatively at 1, 3, 6 and 12 months
Participants	81 participants with NSCLC, eligible for thoracotomy, were invited. 60 accepted but 57 were randomised before surgery. 49 participants completed (exercise group: n = 23 (21M), mean age 63.6 ± 10.2 years and control group: n = 26 (19M), mean age 63.2 ± 10.3 years)
Interventions	Control (n = 26): Usual care consisting of routine outpatient appointments at 1, 3, 6 and 12 months following surgery. Pain medication prescribed by their pulmonologist or general practitioner Exercise (n = 23): Four weeks after discharge, twice a week, participants exercised at 60-80% of their peak cycling load and performed muscle training for 12 weeks. An anaesthesiologist adjusted pain treatment according to the World Health Organization analgesic ladder
Outcomes	Exercise capacity (six-minute walk distance), health-related quality of life (SGRQ and SF-36), pain (MPQ-DLV) and pulmonary function (spirometry)
Notes	Only "open thoracotomy" included The number of participants who had adjuvant chemotherapy was 10 in the exercise group and six in the control group
Risk of bias	

Stigt 2013 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "…patients were randomised to the active (rehabilitation) group or control group using a computer minimization system…"
Allocation concealment (selection bias)	Low risk	Quote: "…using a computer minimization system initiated by the treating chest physician…" Comment: Investigators enrolling participants could not foresee assignment
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: The study did not address this outcome
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: Three months post-discharge six-minute walk distance and lung function data reported for less than 40% and 60% of participants, respectively. Reasons reported as follows: "… because they dropped out or felt unable to perform the test…"
Selective reporting (reporting bias)	High risk	Comment: The trial registration of the study (http://clinicaltrials.gov/show/NCT01136083) was reviewed and not all of the pre-specified outcomes were reported in the published paper
Other bias	High risk	Comment: More patients who had chemotherapy were randomised to the training group and table 3 shows a higher dropout in attendance rate for patients who had chemotherapy compared to patients who did not

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

Study	Reason for exclusion
Adamsen 2012	Not post-operative patients
Andersen 2011	Not an RCT
Arbane 2009	Conference abstract of an included study
Arbane 2009a	Conference abstract of an included study
Barinow-Wojewodzki 2008	Not post-operative patients
Barinow-Wojewodzki 2008a	Not post-operative patients
Barton 2010	Not exercise training
Bradley 2011	Not post-operative patients
Cesario 2007	Not an RCT
Dimeo 2004	Mixed population. No access to specific data
Glattki 2012	Not an RCT
Granger 2011	Not an RCT
Hwang 2012	Mixed population with few participants (n = 7) who underwent lung resection
Jones 2008	Not an RCT
Jones 2009	Not an RCT
Jones 2010	Not an RCT
Jones 2011	Not an RCT
Kiziltas 2006	Did not reply to several contact attempts
Licker 2011	Not exercise training
Lin 2013	Not exercise training
Lubbe 2001	Not an RCT
Maddocks 2009	Not post-operative patients
Nazarian 2004	Not an RCT

(*Continued*)

Nici 2008	Not an RCT
Oldervoll 2004	Not an RCT
Parsons 2012	Not exercise training
Peddle-McIntyre 2012	Not an RCT
Peddle-McIntyre 2013	Not an RCT
Riesenberg 2010	Not an RCT
Shannon 2010	Not an RCT
Shannon 2011	Not an RCT
Spruit 2006	Not an RCT
Weiner 1997	Not post-operative patients
Woods 1999	Not NSCLC

DATA AND ANALYSES

Comparison 1. Exercise group versus control group

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Exercise capacity (6MWD in metres)	3	139	Mean Difference (IV, Fixed, 95% CI)	50.35 [15.45, 85.24]
2 Health-related quality of life	3	147	Std. Mean Difference (IV, Fixed, 95% CI)	0.17 [-0.16, 0.49]
3 Lung function (FEV1 in litres)	2	89	Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.36, 0.11]

Analysis 1.1. Comparison 1 Exercise group versus control group, Outcome 1 Exercise capacity (6MWD in metres).

Review: Exercise training undertaken by people within 12 months of lung resection for non-small cell lung cancer

Comparison: 1 Exercise group versus control group

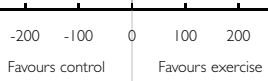
Outcome: 1 Exercise capacity (6MWD in metres)

Study or subgroup	Exercise N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Arbane 2011	21	480.2 (110)	16	448.2 (95.2)		27.7 %	32.00 [-34.25, 98.25]
Brocki 2010	32	506.9 (128.4)	34	464.5 (97)		40.0 %	42.40 [-12.76, 97.56]
Stigt 2013	17	567 (78)	19	491 (109)		32.2 %	76.00 [14.54, 137.46]
Total (95% CI)	**70**		**69**			**100.0 %**	**50.35 [15.45, 85.24]**

Heterogeneity: Chi^2 = 1.04, df = 2 (P = 0.59); I^2 =0.0%

Test for overall effect: Z = 2.83 (P = 0.0047)

Test for subgroup differences: Not applicable

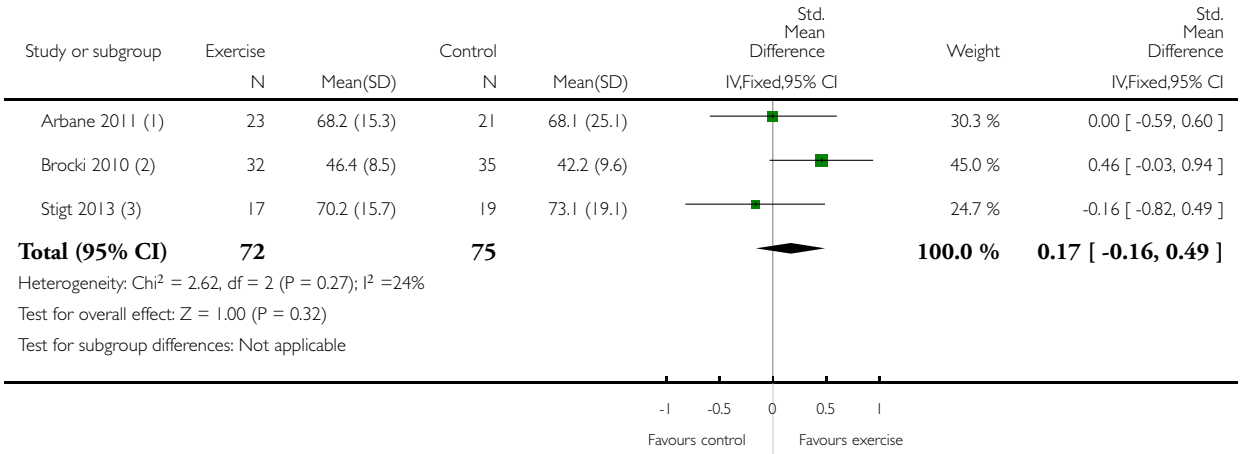


Analysis 1.2. Comparison 1 Exercise group versus control group, Outcome 2 Health-related quality of life.

Review: Exercise training undertaken by people within 12 months of lung resection for non-small cell lung cancer

Comparison: 1 Exercise group versus control group

Outcome: 2 Health-related quality of life



(1) Global function of the EORTC-C30

(2) Physical component SF-36

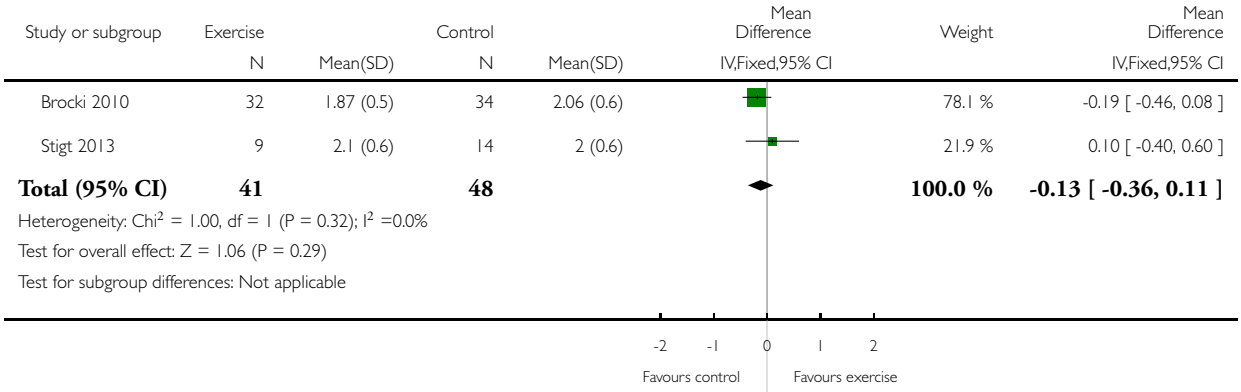
(3) Total score of the SGRQ. Mean scores subtracted from 100. Therefore, higher scores indicate less limitation.

Analysis 1.3. Comparison 1 Exercise group versus control group, Outcome 3 Lung function (FEV1 in litres).

Review: Exercise training undertaken by people within 12 months of lung resection for non-small cell lung cancer

Comparison: 1 Exercise group versus control group

Outcome: 3 Lung function (FEV1 in litres)



ADDITIONAL TABLES

Table 1. Study results

Study	Results
Arbane 2011	***Exercise capacity*** *: Six-Minute Walk Distance (6MWD), in metres* Exercise group (EG): 21 participants completed; control group (CG): 16 participants completed; Measurements 5 days and 12 weeks (post-intervention) post-operatively: Mean ± SD: EG: 336.7 ± 84.1 m to 480.2 ± 110.0 m; CG: 308.7 ± 124.8 m to 448.2 ± 95.1 m ***Health-related quality of life*** *: EORTC QLQ-C30 questionnaire* EG: 22 participants completed; CG: 21 participants completed; Groups were similar pre-operatively. No post-operative baseline measures. Measurements 12 weeks post-operative (post-intervention): *EORTC-C30 (functional):* EG: 79.1 ± 19.1; CG: 76.7 ± 22.7 *EORTC-C30 (symptom):* EG: 18.5 ± 15.2; CG: 21.0 ± 16.4 *EORTC-C30 (global health):* EG: 68.2 ± 15.3; CG: 68.1 ± 25.1 ***Quadriceps force*** *: Magnetic stimulation of femoral nerve, in kg* EG: 17 participants completed; CG: 13 participants completed; Measurements 5 days and 12 weeks (post-intervention) post-operatively EG: 37.6 ± 27.1 kg to 34.2 ± 9.4 kg; CG: 21.5 ± 7.7 kg to 26.4 ± 9.7 kg ***Post-operative complications*** EG: 2; CG: 3

Table 1. Study results (*Continued*)

Brocki 2010 (unpublished data)	***Exercise capacity*** *: Six-Minute Walk Distance (6MWD), in metres* EG: 32 participants completed; CG: 34 participants completed; Post-operative measurements: baseline and post-intervention: Mean ± SD: EG: 426.8 ± 123.6 m to 506.9 ± 128.4 m; CG: 407.2 ± 101.5 m to 464.5 ± 97 m ***Health-related quality of life*** *: SF-36 questionnaire* EG: 32 participants completed; CG: 35 participants completed; Post-operative measurements: baseline and post-intervention: *SF-36 (physical component):* EG: 38.9 ± 7 to 46.4 ± 8.5; CG: 39 ± 10 to 42.2 ± 9.6 *SF-36 (mental component):* EG: 45.7 ± 10 to 50.8 ± 8.8; CG: 44.9 ± 8.9 to 50.2 ± 9.1 ***Lung function*** *: FEV_1* EG: 32 participants completed; CG: 34 participants completed; Post-operative measurements: baseline and post-intervention: EG: 1.75 ± 0.5 L to 1.87 ± 0.5 L; CG: 1.9 ± 0.6 L to 2.06 ± 0.6 L
Stigt 2013	***Exercise capacity*** *: Six-Minute Walk Distance (6MWD), in metres* EG: 8 participants; CG: 11 participants; No post-operative baseline measures. Measurements three months post-operative (post-intervention): Mean ± SD: EG: 567 ± 78 m; CG: 491 ± 109 m [a] ***Health-related quality of life: Saint George Respiratory Questionnaire (SGRQ)*** EG: 22 participants; CG: 22 participants; Post-operative measurements: baseline and post-intervention: EG: 34.6 ± 18.4 to 29.8 ± 15.7; CG: 30.7 ± 20.7 to 26.9 ± 19.1 [a] ***Lung function: FEV_1 in litres*** EG: 9 participants completed; CG: 14 participants completed; Groups were similar preoperatively. No post-operative baseline measures. Measurements three months post-operative (post-intervention): EG: 2.1 ± 0.6 L; CG: 2 ± 0.6 L

[a] Data provided by the author.

APPENDICES

Appendix 1. MEDLINE (via PubMed) search strategy

#1 ((((lung cancer*[Title/Abstract]) OR non-small cell[Title/Abstract]) OR non small cell[Title/Abstract]) OR Lung Neoplasms[MeSH Terms]) OR Carcinoma, Non-Small-Cell Lung[MeSH Terms]
#2 (((((((((exercis*[Title/Abstract]) OR rehabilitat*[Title/Abstract]) OR aerobic*[Title/Abstract]) OR endurance[Title/Abstract]) OR strength*[Title/Abstract]) OR inspiratory muscle*[Title/Abstract]) OR respiratory muscle*[Title/Abstract]) OR treadmill[Title/Abstract]) OR walking[Title/Abstract]) OR cycl*[Title/Abstract]
#3 (training*[Title/Abstract]) OR program*[Title/Abstract]
#4 ((#1) AND #2) AND #3

Appendix 2. CENTRAL search strategy

#1 (lung cancer*):ti,ab,kw in Clinical Trials
#2 (non-small cell):ti,ab,kw in Clinical Trials
#3 (non small cell):ti,ab,kw in Clinical Trials
#4 MeSH descriptor Lung Neoplasms, this term only
#5 MeSH descriptor Carcinoma, Non-Small-Cell Lung, this term only
#6 (#1 OR #2 OR #3 OR #4 OR #5)
#7 (exercis*):ti,ab,kw in Clinical Trials
#8 (rehabilitat*):ti,ab,kw in Clinical Trials
#9 (aerobic*):ti,ab,kw in Clinical Trials
#10 (endurance):ti,ab,kw in Clinical Trials
#11 (strength*):ti,ab,kw in Clinical Trials
#12 (inspiratory muscle*):ti,ab,kw in Clinical Trials
#13 (respiratory muscle*):ti,ab,kw in Clinical Trials
#14 (treadmill):ti,ab,kw in Clinical Trials
#15 (walking):ti,ab,kw in Clinical Trials
#16 (cycl*):ti,ab,kw in Clinical Trials
#17 (#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16)
#18 (training*):ti,ab,kw in Clinical Trials
#19 (program*):ti,ab,kw in Clinical Trials
#20 (#18 OR #19)
#21 (#6 AND #17 AND #20)

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.

Fatim Tahirah: protocol development, selection of studies and extraction of data from studies.

Mika Nonoyama: methodological topics, critical appraisal of the last protocol version, conduct of the analysis and critical appraisal of the final review paper.

Sue Jenkins: critical appraisal of the protocol versions and of the final review paper.

Kylie Hill: critical appraisal of the protocol versions, selection of studies and extraction of data from studies, and critical appraisal of the final review paper.

DECLARATIONS OF INTEREST

VC, KH and SJ are conducting a study which may be included in future updates of this review.

SOURCES OF SUPPORT

Internal sources

- Curtin University, Perth, Australia.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

As one of the studies included in this review measured HRQoL using the St. George's Respiratory Questionnaire (SGRQ), we added this instrument to our list of questionnaires used to assess HRQoL (see secondary outcomes). We did not calculate risk difference as no meta-analysis of dichotomous data was performed. We did not perform subgroup analysis 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)

*Exercise Therapy; Carcinoma, Non-Small-Cell Lung [*rehabilitation; surgery]; Exercise Tolerance [*physiology]; Forced Expiratory Volume [physiology]; Health Status; Lung Neoplasms [*rehabilitation; surgery]; Muscle Strength [physiology]; Postoperative Care [methods]; Quadriceps Muscle [physiology]; Quality of Life; Randomized Controlled Trials as Topic

MeSH check words

Humans