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

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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 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 prostate and breast cancer. A programme of exercise training may also confer gains in these outcomes for people following lung resection for NSCLC. This systematic review updates our 2013 systematic review.

Objectives

The primary aim of this review was to determine the effects of exercise training on exercise capacity and adverse events in people following lung resection (with or without chemotherapy) for NSCLC. The secondary aims were to determine the effects of exercise training on other outcomes such as HRQoL, force-generating capacity of peripheral muscles, pressure-generating capacity of the respiratory muscles, dyspnoea and fatigue, feelings of anxiety and depression, lung function, and mortality.

Search methods

We searched for additional randomised controlled trials (RCTs) in the Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library 2019, Issue 2 of 12), MEDLINE (via PubMed) (2013 to February 2019), Embase (via Ovid) (2013 to February 2019), SciELO (The Scientific Electronic Library Online) (2013 to February 2019), and PEDro (Physiotherapy Evidence Database) (2013 to February 2019).

Selection criteria

We included RCTs in which participants with NSCLC who underwent lung resection were allocated to receive either exercise training, which included aerobic exercise, resistance exercise, or a combination of both, or no exercise training.

Data collection and analysis

Two review authors screened the studies and identified those eligible for inclusion. We used either postintervention values (with their respective standard deviation (SD)) or mean changes (with their respective SD) in the meta-analyses that reported results as mean difference (MD). In meta-analyses that reported results as standardised mean difference (SMD), we placed studies that reported postintervention values and those that reported mean changes in separate subgroups. We assessed the certainty of evidence for each outcome by downgrading or upgrading the evidence according to GRADE criteria.

Main results

Along with the three RCTs included in the original version of this review (2013), we identified an additional five RCTs in this update, resulting in a total of eight RCTs involving 450 participants (180 (40%) females). The risk of selection bias in the included studies was low and the risk of performance bias high. Six studies explored the effects of combined aerobic and resistance training; one explored the effects of combined aerobic and inspiratory muscle training; and one explored the effects of combined aerobic, resistance, inspiratory muscle training and balance training. On completion of the intervention period, compared to the control group, exercise capacity expressed as the peak rate of oxygen uptake ($\text{VO}_{2\text{peak}}$) and six-minute walk distance (6MWD) was greater in the intervention group ($\text{VO}_{2\text{peak}}$: MD 2.97 mL/kg/min, 95% confidence interval (CI) 1.93 to 4.02 mL/kg/min, 4 studies, 135 participants, moderate-certainty evidence; 6MWD: MD 57 m, 95% CI 34 to 80 m, 5 studies, 182 participants, high-certainty evidence). One adverse event (hip fracture) related to the intervention was reported in one of the included studies. The intervention group also achieved greater improvements in the physical component of general HRQoL (MD 5.0 points, 95% CI 2.3 to 7.7 points, 4 studies, 208 participants, low-certainty evidence); improved force-generating capacity of the quadriceps muscle (SMD 0.75, 95% CI 0.4 to 1.1, 4 studies, 133 participants, moderate-certainty evidence); and less dyspnoea (SMD -0.43, 95% CI -0.81 to -0.05, 3 studies, 110 participants, very low-certainty evidence). We observed uncertain effects on the mental component of general HRQoL, disease-specific HRQoL, handgrip force, fatigue, and lung function. There were insufficient data to comment on the effect of exercise training on maximal inspiratory and expiratory pressures and feelings of anxiety and depression. Mortality was not reported in the included studies.

Authors' conclusions

Exercise training increased exercise capacity and quadriceps muscle force of people following lung resection for NSCLC. Our findings also suggest improvements on the physical component score of general HRQoL and decreased dyspnoea. This systematic review emphasises the importance of exercise training as part of the postoperative management of people with NSCLC.

PLAIN LANGUAGE SUMMARY

Exercise training after lung surgery for people with non-small cell lung cancer

Review question

We updated the evidence about the effect of exercise training after lung surgery for non-small cell lung cancer (NSCLC) on fitness level; adverse events; quality of life; strength of the leg, hand, and breathing muscles; breathlessness; fatigue; feelings of anxiety and depression; and lung function.

Background

After lung surgery for NSCLC, people's fitness levels and quality of life decrease. We know that exercise training improves these outcomes in people with chronic lung disease and in those with prostate and breast cancer. In the 2013 version of this review, we demonstrated that exercise training improved fitness level (distance walked on the six-minute walk test) in people after lung surgery for NSCLC. Due to the limited number of studies, the effect of exercise training on quality of life and other outcomes was unclear.

Search date

The evidence is current to February 2019.

Study characteristics

We included three studies from the 2013 review and an additional five new studies from the current review, for a total of eight studies with 450 participants (180 women). The number of participants in the included studies ranged between 17 and 131; the mean age of participants was between 63 and 71 years. Six studies explored the effects of combined aerobic and strengthening exercises; one explored the effects of combined aerobic exercise and inspiratory muscle training; and one explored the effects of combined aerobic exercise, strengthening exercise inspiratory muscle training and balance training. The length of the exercise programmes ranged from four to 20 weeks, with exercises performed twice to five days a week.

Key results

Our results showed that people with NSCLC who exercised after lung surgery had better fitness level (measured using both a cycling test and the six-minute walk test) and strength in their leg muscles compared to those that did not exercise. We also showed initial evidence

for better quality of life and less breathlessness in those who exercised. One adverse event (hip fracture) related to the intervention was reported in one study. The effect of exercise training after lung surgery on grip strength, fatigue, and lung function was uncertain. We found insufficient evidence for improvements in the strength of breathing muscles or feelings of anxiety and depression.

Quality of evidence

Overall the quality (certainty) of evidence for the outcomes was moderate, ranging between very low (for breathlessness) and high (for fitness level measured via the six-minute walk test).

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Exercise group compared to control group for non-small cell lung cancer

Exercise group compared to control group for non-small cell lung cancer

Patient or population: non-small cell lung cancer

Setting: the studies were based in the UK, Denmark, Australia, Norway, Spain, Belgium and the Netherlands

Intervention: Exercise group

Comparison: control group

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N° of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with control group	Risk with Exercise group				
Exercise capacity (VO2peak in mL/kg/min)	The mean exercise capacity (VO2peak in mL/kg/min) ranged from 13.3 to 19.0 mL/kg/min	MD 2.97 mL/kg/min higher (1.93 higher to 4.02 higher)	-	135 (4 RCTs)	⊕⊕⊕⊖ MODERATE ¹	-
Exercise capacity (6MWD in metres)	The mean exercise capacity (6MWD in metres) ranged from 452 to 491 metres	MD 57.3 metres higher (34.3 higher to 80.2 higher)	-	182 (5 RCTs)	⊕⊕⊕⊕ HIGH ^{1 2}	-
Safety of the intervention (adverse events related to the intervention) assessed with: number of events	1 adverse event (a hip fracture) was reported in the intervention group of 1 RCT.		-	202 (4 RCTs)	⊕⊕⊕⊖ MODERATE ³	-
General health-related quality of life (SF-36 - physical component score)	The mean general health-related quality of life (SF-36 - physical component score) ranged from 23.0 to 43.3	MD 5.02 higher (2.3 higher to 7.73 higher)	-	208 (4 RCTs)	⊕⊕⊖⊖ LOW ^{1 4}	-
General health-related quality of life (SF-36 - mental component score)	The mean general health-related quality of life (SF-36 - mental component score) ranged from 46.6 to 51	MD 2.32 lower (11.26 lower to 6.62 higher)	-	208 (4 RCTs)	⊕⊕⊖⊖ LOW ^{1 4}	-
Force-generating capacity of peripheral muscles (quadriceps)	-	SMD 0.75 higher (0.4 higher to 1.11 higher)	-	133 (4 RCTs)	⊕⊕⊕⊖ MODERATE ⁵	Different measurement methods (femoral

					nerve stimulation, maximal isometric force and 1-repetition maximum)
Dyspnoea	-	SMD 0.43 lower (0.81 lower to 0.05 lower)	-	110 (3 RCTs)	⊕⊕⊕⊕ VERY LOW ^{1 3 6} Two different tools used (EORTC QLQ-C30 Dyspnoea and VAS Dyspnoea)

***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).

6MWD: 6-minute walk distance; **CI:** confidence interval; **MD:** mean difference; **RCT:** randomised controlled trial; **SF-36:** Medical Outcomes Study Short Form 36 General Health Survey **SMD:** standardised mean difference; **VAS:** visual analogue scale; **VO₂peak:** peak rate of oxygen uptake.

Minimal clinically important difference (MCID): 6MWD = 22 to 42 metres ([Granger 2015](#)); **SF-36** = 3 to 5 points ([Samsa 1999](#)).

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: 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 certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

¹Some studies rated as having a high risk of detection bias.

²Very large effect, and mean difference reached clinical important difference.

³Outcome reported in only four of the eight included studies.

⁴Some level of inconsistency across results of studies.

⁵Small sample sizes across the studies, some with wide confidence intervals.

⁶Imprecision of pooled estimates.

BACKGROUND

Description of the condition

Lung cancer is an important problem worldwide. Data from 2018 indicate that lung cancer is the most commonly diagnosed cancer in men and the third most commonly diagnosed cancer in women (Bray 2018). Mortality from lung cancer is high, with a five-year survival of 11% to 19%, making it the leading cause of death from malignancy in high-income countries such as Australia (AIHW 2017), the USA (Jemal 2017), and the UK (Office for National Statistics 2015). 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 (Jett 2013).

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 cancer (Jones 2007). The reasons for this are likely to be multifactorial. Over half of all people diagnosed with lung cancer have an underlying chronic lung disease (e.g. chronic obstructive pulmonary disease (COPD)), Mouronte-Roibas 2018, that impairs exercise capacity (McCarthy 2015). Furthermore, people with lung cancer are affected by 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 a decline in physical activity levels (Granger 2014; Granger 2016), as well as the adoption of a sedentary lifestyle (Cavalheri 2016; D'Silva 2018; O'Driscoll 1999). Failure to engage in sufficient physical activity to meet physical activity guidelines has been reported in 88% and 70% of people six months and 3.5 years after lung resection, respectively (Coups 2009), suggesting there is no spontaneous recovery in physical activity following treatment. This decline in physical activity levels results in skeletal muscle and cardiovascular deconditioning and serves to further compromise exercise capacity (Burtin 2017; Cavalheri 2015).

Treatment for lung cancer compounds the decrements in exercise capacity. Compared with preoperative measures, the peak rate of oxygen uptake ($\text{VO}_{2\text{peak}}$) has been shown to be reduced by 13% and 28% six months following lobectomy and pneumonectomy, respectively (Nezu 1998), and it is up to 40% lower compared with healthy age-matched peers (Burtin 2017; Cavalheri 2015). 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 2008 and fatigue, Huang 2015. Of note, the overall incidence of post-treatment fatigue in people with early stage NSCLC is 60% (Huang 2015).

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 (Cavalheri 2015; Myrdal 2003). These impairments were of similar magnitude to those reported by people who have undergone coronary bypass grafting (Myrdal 2003).

Description of the intervention

Exercise training was the intervention studied in this systematic review. Training included aerobic exercises, strengthening (resistance) exercises, or a combination of these, with or without inspiratory muscle training. Earlier studies have shown that supervised exercise training is feasible for people following lung resection for NSCLC (Cesario 2007; Schneider 2007; Spruit 2006), and our original Cochrane Review demonstrated improvements in exercise capacity as measured via the six-minute walk test (6MWT) (Cavalheri 2013a).

How the intervention might work

The role of exercise training is well established in many chronic respiratory conditions, including COPD (McCarthy 2015), interstitial lung disease (Dowman 2014), and asthma (Carson 2013). There is especially abundant evidence, from over 60 randomised controlled trials (RCTs), for people with COPD. Cochrane Reviews have shown that in this population exercise training improves exercise capacity and HRQoL (McCarthy 2015; Puhan 2016), as well as reducing symptoms of dyspnoea and fatigue (McCarthy 2015). There is also evidence to suggest a reduction in healthcare utilisation (Puhan 2016). The mechanisms underlying improvements in exercise capacity and reductions in dyspnoea on exertion relate, at least in part, to an enhanced skeletal muscle function and a reduction in ventilation requirements at submaximal exercise intensities (Maltais 2014; Porszasz 2005). Previous systematic reviews have shown that exercise training confers reductions in fatigue and improvements in HRQoL in people with other forms of cancer, such as prostate and breast cancer (Lahart 2018; Mishra 2012). We hypothesised that exercise training would also be effective at improving outcomes other than exercise capacity in people following treatment for NSCLC.

Why it is important to do this review

The original version of this review in 2013 was undertaken in order to evaluate the effects of exercise training following lung resection for NSCLC, but also to identify the strengths and limitations of the published studies in this area and gaps in the literature. The original review included three RCTs (Cavalheri 2013a), and we concluded that exercise training conferred an increase in exercise capacity, measured as six-minute walk distance (6MWD), in people following lung resection for NSCLC. We also provided important considerations on how future studies could minimise bias and methodological heterogeneity. Some of the considerations for upcoming studies were to: (i) collect outcome measures immediately before and after the exercise training intervention rather than before lung resection and on completion of the exercise training intervention; (ii) choose disease-specific HRQoL questionnaires; (iii) report the values for each domain that contributes to HRQoL as well as the total score obtained from HRQoL questionnaires; and (iv) report the mean change (and standard deviation of the change) in outcomes collected immediately before and after the exercise training intervention. We

also suggested that researchers explore other variables such as fatigue, dyspnoea, and feelings of anxiety and depression. In the current review we investigated whether exercise training following resection for NSCLC confers benefit in outcome measures other than 6MWD and also whether the certainty of the evidence found has improved compared to the original review.

OBJECTIVES

The primary aim of this review was to determine the effects of exercise training on exercise capacity and adverse events in people following lung resection (with or without chemotherapy) for NSCLC. The secondary aims were to determine the effects of exercise training on other outcomes such as HRQoL, force-generating capacity of peripheral muscles, pressure-generating capacity of the respiratory muscles, dyspnoea and fatigue, feelings of anxiety and depression, lung function, and mortality.

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. Full papers and abstracts published in any language were eligible for inclusion.

Types of participants

Our 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 has demonstrated that important outcomes such as short-term mortality, length of hospital stay, and hospitalisation costs were similar between these groups ([Gopaldas 2010](#)). This is despite the fact that people who undergo resection via VATS or thoracotomy differ in terms of pain, HRQoL, and shoulder dysfunction ([Bendixen 2016](#); [Landreneau 1993](#)). Participants who had undergone resections of any type (i.e. wedge resection, segmentectomy, lobectomy, or pneumonectomy) were eligible for inclusion. We excluded from this review people with SCLC because metastasis is common at the time of diagnosis, and median survival is usually less than 12 months ([Dayen 2017](#)).

Types of interventions

The intervention comprised exercise training that included aerobic exercise, resistance exercise, or a combination of both, and started within 12 months of lung resection. We did not include studies that investigated the effectiveness of inspiratory muscle training alone. Training sessions could be supervised or unsupervised, or a combination of both. Where possible, we recorded characteristics of the training programme, such as frequency, intensity, type, duration, adherence, and extent of supervision. We also documented any adverse events. Control groups received usual care with either no exercise training or only general instruction to exercise.

Types of outcome measures

Primary outcomes

1. Exercise capacity as measured either as VO₂peak during a maximal incremental exercise test or as the 6MWD.
2. Safety of the intervention as measured by numbers of adverse events.

Secondary outcomes

1. General HRQoL (e.g. the Medical Outcomes Study Short Form 36 General Health Survey (SF-36)).
2. Disease-specific HRQoL (e.g. the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire core 30 (EORTC QLQ-C30)).
3. Force-generating capacity of peripheral muscles (e.g. measures of lower limb muscle strength).
4. Pressure-generating capacity of respiratory muscles (e.g. maximal inspiratory and expiratory pressures).
5. Dyspnoea (e.g. the Borg category ratio scale, the visual analogue scale) or functional limitation during daily life resulting from dyspnoea (e.g. the Medical Research Council dyspnoea scale).
6. Fatigue (e.g. the Functional Assessment of Chronic Illness Therapy - Fatigue Subscale (FACIT-fatigue)).
7. Feelings of anxiety and depression (e.g. the Hospital Anxiety and Depression scale (HADS)).
8. Lung function (e.g. volumes and diffusing capacity).
9. Mortality.

Search methods for identification of studies

Electronic searches

We identified trials from electronic bibliographic databases including:

1. the Cochrane Central Register of Controlled Trials (CENTRAL; Issue 2, 2019) in the Cochrane Library (searched 11 February 2019);
2. MEDLINE (via PubMed) (2013 to 11 February 2019);
3. Embase (via Ovid) (2013 to 11 February 2019);
4. SciELO (The Scientific Electronic Library Online) (2013 to 11 February 2019); and
5. PEDro (Physiotherapy Evidence Database) (2013 to 11 February 2019).

The search strategies used for MEDLINE, CENTRAL and Embase are presented in [Appendix 1](#), [Appendix 2](#), and [Appendix 3](#), respectively. The search string for MEDLINE was developed according to the Cochrane Highly Sensitive Search Strategy, sensitivity maximising version (2008 version) as referenced in Section 6.4.11.1 and detailed in box 6.4.b of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We adapted the strategy for use in the other databases.

Searching other resources

We screened the reference lists of all primary studies and review articles for additional references. We contacted the authors of included trials to inquire about further published and unpublished studies.

Data collection and analysis

Selection of studies

Two review authors (VC and CB) independently examined the studies identified by the literature search using Covidence (Covidence 2017). We first excluded studies based on their title and abstract and recorded the reasons for exclusion. We subsequently obtained the full texts of the remaining studies, and the two review authors independently examined these, coding them as (i) 'include'; (ii) 'unclear'; or (iii) 'exclude' based on the review criteria. Any disagreements were resolved by consensus, and a full record was kept of the decisions.

Data extraction and management

Two review authors (VC and VRF) extracted data using a standardised form. Any disagreements were resolved by discussion or by involving a third review author (CB) when necessary. Once consensus was reached, the first review author (VC) entered data into Review Manager 5 software (RevMan 2014). The data entered included study details, participant characteristics, and outcome measures related to the aims of this review. Where applicable, we asked the authors of the included studies to verify the data and provide details of missing data.

Assessment of risk of bias in included studies

Three review authors (VC, CB, and VRF) independently appraised the risk of bias of the included studies using the Cochrane Collaboration's 'Risk of bias' tool. Any disagreements were resolved by consensus. We judged risk of bias as 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. Where applicable, we contacted study authors to seek clarification on issues related to bias. We generated both a 'Risk of bias' graph (i.e. bar chart) and 'Risk of bias' summary (i.e. traffic lights).

Measures of treatment effect

The review did not have dichotomous outcomes. We calculated the mean differences (MD) and standardised mean differences (SMD) together with their corresponding 95% confidence intervals (CIs) for the continuous outcomes. Mean difference was calculated for exercise capacity (VO₂peak and 6MWD), general and disease-specific HRQoL, handgrip force, and lung function (forced vital capacity (FVC)). Standardised mean difference was calculated for force-generating capacity of quadriceps muscle, dyspnoea, fatigue, and lung function (forced expiratory volume (FEV₁)), as the included studies either measured these outcomes using different tools/tests or reported their findings in different ways (e.g. absolute values versus % of predicted values).

We used either postintervention values (with their respective standard deviation (SD)) or mean changes (with their respective SD) in the meta-analyses that reported results as MD. When the SD of the mean change was not reported in the included study, not provided by the authors, or not able to be imputed through calculation, pre-intervention SD was used. In meta-analyses that reported results as SMD, studies that reported postintervention

values (with their respective SD) and those that reported mean changes (with their respective SD) were placed in separate subgroups.

Unit of analysis issues

We planned that for studies that presented postintervention data at two or more time points (e.g. exercise capacity reported immediately postintervention and at three months postoperatively), we would not combine the results from the different time points in a single meta-analysis. We only used data collected immediately after completion of the intervention period.

Dealing with missing data

We contacted the authors of all the included studies to obtain missing data. When the specific data requested were provided, they were included in the meta-analyses. We did not impute any data.

Assessment of heterogeneity

We assessed statistical heterogeneity across the studies using the I² statistic. We considered values of I² greater than 50% as substantial heterogeneity (Higgins 2011). If we detected substantial statistical heterogeneity, we investigated whether clinical or methodological heterogeneity were the potential causes.

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. As the number of studies included in this review was less than 10, we did not generate funnel plots.

Data synthesis

We used Review Manager 5 to conduct the statistical analyses and generate forest plots (RevMan 2014). We initially used a random-effects model for calculating summary estimates. However, if the studies were clinically, methodologically, and statistically homogeneous, we changed to a fixed-effect model. We meta-analysed the results of homogeneous studies using the inverse-variance DerSimonian and Laird method (DerSimonian 1986). Where data aggregation was not possible due to considerable clinical, methodological, or statistical heterogeneity, we provided a narrative discussion of the data only.

GRADE and 'Summary of findings' table

In order to interpret the findings, we created a GRADE Summary of findings table (Summary of findings for the main comparison) in which we included the following outcomes: (i) exercise capacity; (ii) safety of the intervention; (iii) general HRQoL; (iv) force-generating capacity of the peripheral muscles (quadriceps); and (v) dyspnoea (Atkins 2004; Guyatt 2008). We assessed the certainty of evidence for each outcome by downgrading based on the GRADE criteria. We used the methods and recommendations described in Chapter 11 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Sensitivity analysis

We performed sensitivity analyses when we detected substantial heterogeneity (i.e. I² greater than 50%) to investigate the effects of studies rated as having a high or unclear risk of detection or attrition bias.

RESULTS

Description of studies

For complete details of studies classified as included or excluded, see the [Characteristics of included studies](#) and [Characteristics of excluded studies](#) sections.

Results of the search

Our search of all the databases in February 2019 yielded a total of 1380 records: 359 from CENTRAL; 401 from MEDLINE; 590 from

Embase; 29 from PEDro; and one from SciELO. We identified one extra record through other sources, therefore the total number of new records identified was 1381 ([Figure 1](#)). After removal of duplicates, 1106 records remained. Of these we excluded 1082 records based on the title and abstract and assessed 24 full-texts and conference abstracts for eligibility. We included 5 studies (9 records) identified in the current version of the review, in addition to 3 studies (5 records) identified in the original review ([Cavalheri 2013a](#)). We were able to contact authors of three new eligible studies to obtain missing data.

Figure 1. Study flow diagram.

Included studies

See [Characteristics of included studies](#).

Study

We included the three RCTs, [Arbane 2011](#); 'Brocki 2010'; [Stigt 2013](#), from the 2013 version of this review ([Cavalheri 2013a](#)). We included five new RCTs for this update, therefore a total of eight RCTs (14 records) contributed data to the meta-analyses ([Arbane 2014](#); [Cavalheri 2017](#); [Edvardsen 2015](#); [Messaggi-Sartor 2018](#); [Salhi 2015](#)). The eight RCTs included 450 participants. The study named 'Brocki 2010' in the original version of the review is now named [Brocki 2014](#). The record from 2010 was a conference proceeding, and the final full text of that study, [Brocki 2014](#), was found through the database search for this update review.

Population

Six studies included only participants with NSCLC following lung resection. Two studies also included a small number of participants who either had thoracic cancers other than NSCLC or who did not undergo lung resection ([Brocki 2014](#); [Salhi 2015](#)). We contacted the authors of these two studies, and they provided data specific to the participants with NSCLC who underwent lung resection. The sample size of the included studies ranged between 17 and 131, with the mean age of the participants ranging between 63 and 71 years. Of the 450 participants, 180 (40%) were female. At baseline, the intervention and control groups in all included studies were balanced for age. Both baseline VO_{2peak} and baseline 6MWD were also balanced between the intervention and control groups in the studies that included these measures (VO_{2peak} : [Cavalheri 2017](#); [Edvardsen 2015](#); [Messaggi-Sartor 2018](#); [Salhi 2015](#). 6MWD: [Arbane 2011](#); [Brocki 2014](#); [Cavalheri 2017](#); [Salhi 2015](#); [Stigt 2013](#)). Six studies reported on extent of lung resection (i.e. wedge resection, lobectomy/bilobectomy, pneumonectomy) and demonstrated balanced numbers between groups ([Arbane 2011](#); [Brocki 2014](#); [Edvardsen 2015](#); [Messaggi-Sartor 2018](#); [Salhi 2015](#); [Stigt 2013](#)). Four studies reported on type of surgical procedure (i.e. VATS or thoracotomy) ([Arbane 2011](#); [Arbane 2014](#); [Cavalheri 2017](#); [Messaggi-Sartor 2018](#)); three of these studies demonstrated no between-group difference in type of surgical procedure ([Arbane 2014](#); [Cavalheri 2017](#); [Messaggi-Sartor 2018](#)). One study mentioned that only two participants had undergone VATS ([Arbane 2011](#)), but did not report the group allocation of these participants.

Setting

The studies were based in the UK ([Arbane 2011](#); [Arbane 2014](#)), Denmark ([Brocki 2014](#)), Australia ([Cavalheri 2017](#)), Norway ([Edvardsen 2015](#)), Spain ([Messaggi-Sartor 2018](#)), Belgium ([Salhi 2015](#)), and the Netherlands ([Stigt 2013](#)). The studies were published between 2011 and 2018.

Intervention

There was considerable variation in length, type, frequency, and intensity of the exercise programmes that were investigated. Interventions ranged in length from four weeks, [Arbane 2014](#), to 20 weeks, [Edvardsen 2015](#). The exercise programmes in all studies had a supervised component, whilst in four studies they also

had a home-based component ([Arbane 2011](#); [Arbane 2014](#); [Brocki 2014](#); [Cavalheri 2017](#)). The setting for the supervised component was varied, including hospital-based outpatient programmes ([Brocki 2014](#); [Cavalheri 2017](#); [Messaggi-Sartor 2018](#); [Stigt 2013](#)), fitness centre-based programmes ([Edvardsen 2015](#)), and inpatient programmes ([Arbane 2011](#); [Arbane 2014](#)). In two studies ([Arbane 2011](#); [Arbane 2014](#)), home-based exercise was the main component of the exercise training programme.

The interventions consisted of combined aerobic and resistance exercise in six studies ([Arbane 2011](#); [Arbane 2014](#); [Brocki 2014](#); [Cavalheri 2017](#); [Salhi 2015](#); [Stigt 2013](#)); combined aerobic exercise and inspiratory muscle training in one study ([Messaggi-Sartor 2018](#)); and combined aerobic exercise, resistance exercise, inspiratory muscle training and balance training in one study ([Edvardsen 2015](#)). The frequency of the exercise training programme varied from twice a week to five days a week. The intensity of the aerobic exercise was variably reported, ranging between 60% to 90% of maximum heart rate or baseline peak work rate, 80% of the average speed achieved on the 6MWT, or an intensity that elicited scores between 11 to 15 on rating of perceived exertion scale. The intensity of the resistance training was not reported in three studies ([Arbane 2014](#); [Brocki 2014](#); [Stigt 2013](#)); was set at a specific initial weight (e.g. 2 lb; 1.5 kg) in two studies ([Arbane 2011](#); [Cavalheri 2017](#)); and was reported as 50% 1 repetition-maximum (RM) in one study, [Salhi 2015](#), and 6 to 12 RM in one study, [Edvardsen 2015](#). [Edvardsen 2015](#) did not report the intensity of inspiratory muscle training, whereas [Messaggi-Sartor 2018](#) reported starting inspiratory muscle training at 50% of the maximal inspiratory pressure (after one familiarisation session at 30% of the maximal inspiratory pressure).

The control groups received usual care that comprised routine outpatient appointments and pain medication prescription ([Arbane 2011](#); [Arbane 2014](#); [Cavalheri 2017](#); [Edvardsen 2015](#); [Messaggi-Sartor 2018](#); [Stigt 2013](#)), phone calls ([Arbane 2011](#); [Cavalheri 2017](#)), breathing exercises and mobilisation ([Arbane 2014](#)), and instructions regarding exercise ([Brocki 2014](#)). Participants in two studies were advised to perform physical activity ([Brocki 2014](#); [Messaggi-Sartor 2018](#)), whilst those in one study were discouraged from undertaking supervised exercise training ([Salhi 2015](#)).

Excluded studies

In this update, of the 24 records for which the full texts were reviewed, 15 were excluded for the following reasons: (i) did not meet review criteria ($n = 12$); and (ii) authors did not reply to several contact attempts to obtain the specific data needed for this review ($n = 3$). These reasons are summarised in the [Characteristics of excluded studies](#) section.

Risk of bias in included studies

Three out of the seven domains included in the Cochrane Collaboration's 'Risk of bias' tool were identical across the eight included studies (random sequence generation, allocation concealment, and blinding of participants and personnel). For details regarding risk of bias in the included studies, see [Characteristics of included studies](#); [Figure 2](#); [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.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Arbane 2011	+	+	-	-	+	?	-
Arbane 2014	+	+	-	-	+	+	+
Brocki 2014	+	+	-	+	?	+	+
Cavalheri 2017	+	+	-	+	+	-	+
Edvardsen 2015	+	+	-	-	+	-	+
Messaggi-Sartor 2018	+	+	-	+	-	-	+
Salhi 2015	+	+	-	-	+	-	+
Stigt 2013	+	+	-	?	-	-	-

Allocation

All eight included studies reported using a process of randomly allocating participants to the two groups, and in all studies this

randomisation sequence was concealed. We therefore judged all the included 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 the included studies as at high risk of performance bias. Regarding detection bias, in three studies blinding of the outcome assessor was fully ensured (Brocki 2014; Cavalheri 2017; Messaggi-Sartor 2018), therefore these studies were rated as at low risk of detection bias. As the study by Stigt 2013 did not describe blinding of outcome assessors, and as the authors did not reply to our email specifically asking about this issue, we rated the risk of detection bias as unclear. We rated the other four studies as at high risk of detection bias (Arbane 2011; Arbane 2014; Edvardsen 2015; Salhi 2015).

Incomplete outcome data

We rated five studies as at low risk of bias due to incomplete outcome data (Arbane 2011; Arbane 2014; Cavalheri 2017; Edvardsen 2015; Salhi 2015), as missing outcome data were balanced between the intervention and control groups in numbers, with similar reasons for missing data across groups. Although Brocki 2014 analysed their data according to the intention-to-treat principle, details about the missing cases were insufficient to permit a judgement of low or high risk of bias, therefore we rated this study as at unclear risk of bias due to incomplete outcome data. We rated two studies as at high risk of bias (Messaggi-Sartor 2018; Stigt 2013), mainly due to investigators performing 'as-treated' rather than intention-to-treat analysis, Messaggi-Sartor 2018, and a large loss to follow-up, with some postintervention data reported in only 40% to 60% of participants (Stigt 2013).

Selective reporting

We judged two studies as having a low risk of reporting bias (Arbane 2014; Brocki 2014). We judged one study as at unclear risk of reporting bias due to insufficient information to judge this item

(i.e. no access to trial registration) (Arbane 2011). We reviewed the trial registration of five studies (Cavalheri 2017; Edvardsen 2015; Messaggi-Sartor 2018; Salhi 2015; Stigt 2013), and noticed that one to two prespecified outcomes were not reported in the published paper, therefore we rated these five studies as at high risk of reporting bias.

Other potential sources of bias

We rated two studies as at high risk of other potential sources of bias (Arbane 2011; Stigt 2013). The potential sources of bias were as follows: (i) both studies did not collect all outcome measures at identical time points; (ii) in Arbane 2011 the control group 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. We rated the remaining studies as at low risk of other potential sources of bias.

Effects of interventions

See: [Summary of findings for the main comparison Exercise group compared to control group for non-small cell lung cancer](#)

We included data pertaining to exercise capacity, HRQoL, force-generating capacity of the peripheral muscles, dyspnoea, fatigue, and lung function in the meta-analyses.

I. Primary outcome: exercise capacity

Four studies reported the VO₂peak as their measure of exercise capacity (Cavalheri 2017; Edvardsen 2015; Messaggi-Sartor 2018; Salhi 2015). On completion of the intervention period, VO₂peak was significantly higher in the intervention group compared to the control group (mean difference (MD) 2.97 mL/kg/min, 95% confidence interval (CI) 1.93 to 4.02 mL/kg/min, I² = 0%, 4 studies, 135 participants, moderate-certainty evidence) (Analysis 1.1; Figure 4).

Figure 4. Forest plot of comparison: 1 Exercise group versus control group, outcome: 1.1 Exercise capacity (VO₂peak in mL/kg/min).

Five studies reported the 6MWD as their measure of exercise capacity (Arbane 2011; Brocki 2014; Cavalheri 2017; Salhi 2015;

Stigt 2013). On completion of the intervention period, 6MWD was significantly higher in the intervention group compared to the

control group (MD 57 m, 95% CI 34 to 80 m, $I^2 = 22\%$, 5 studies, 182 participants, high-certainty evidence) (Analysis 1.2; Figure 5). The magnitude of the effect found (MD = 57 m) exceeded the minimal

important difference (MID) of the 6MWD reported for people with lung cancer (i.e. 22 to 42 m) (Granger 2015).

Figure 5. Forest plot of comparison: 1 Exercise group versus control group, outcome: 1.2 Exercise capacity (6MWD in metres).

I. Primary outcome: safety of the intervention

Four of the eight included studies reported data on safety of the intervention (i.e. adverse events related to the intervention) (Brocki 2014; Edvardsen 2015; Messaggi-Sartor 2018; Salhi 2015). Three of these four studies reported no adverse events (Brocki 2014; Messaggi-Sartor 2018; Salhi 2015), whereas one reported a hip fracture during balance training (Edvardsen 2015).

II. Secondary outcome: general HRQoL

Four studies reported general HRQoL using the SF-36 (higher scores indicate better HRQoL) (Arbane 2014; Brocki 2014; Cavalheri 2017; Edvardsen 2015). On completion of the intervention period, the physical component score of the SF-36 was significantly higher in the intervention group compared to the control group (MD 5.0 points, 95% CI 2.3 to 7.7 points, $I^2 = 44\%$, 4 studies, 208 participants, low-certainty evidence) (Analysis 1.3; Figure 6). On completion

of the intervention period, there was an uncertain effect for the mental component score of the SF-36 (MD -2.3 points, 95% CI -11.3 to 6.6 points, $I^2 = 87\%$, 4 studies, 208 participants, low-certainty evidence) (Analysis 1.4). Heterogeneity was substantial in the meta-analysis for the mental component score of the SF-36 ($I^2 = 87\%$), therefore we undertook sensitivity analyses. Both the uncertain effect and the substantial heterogeneity were maintained when (i) the two studies rated as having a high risk of detection bias were excluded (MD -5.3 points, 95% CI -12.1 to 1.6 points, $I^2 = 72\%$) (Arbane 2014; Edvardsen 2015); and (ii) the study rated as having an unclear risk of attrition bias was excluded (MD -3.2 points, 95% CI -17.9 to 11.6 points, $I^2 = 91\%$) (Brocki 2014). When the two studies rated as having a high risk of reporting bias were excluded (Cavalheri 2017; Edvardsen 2015), the uncertain effect was maintained (MD -3.7 points, 95% CI -11.4 to 4.0 points), and there was no substantial heterogeneity ($I^2 = 21\%$).

Figure 6. Forest plot of comparison: 1 Exercise group versus control group, outcome: 1.3 General health-related quality of life (SF-36 - physical component score).

III. Secondary outcome: disease-specific HRQoL

Four studies reported disease-specific HRQoL using the EORTC QLQ-C30 (Arbane 2011; Cavalheri 2017; Messaggi-Sartor 2018; Salhi 2015). The four studies reported the global health component score of the EORTC QLQ-C30; two studies reported scores for the functional and symptom scales of the EORTC QLQ-C30 (Arbane 2011; Cavalheri 2017); and two studies reported the physical functioning component score of the EORTC QLQ-C30 (Messaggi-Sartor 2018; Salhi 2015). Higher scores indicate better HRQoL for the global health and physical functioning components. Conversely, for symptoms, higher scores indicate worse symptoms. On completion of the intervention period, there was an uncertain effect on all components of disease-specific HRQoL (global health: MD -0.14 points, 95% CI -7.24 to 6.96 points, $I^2 = 0\%$, 4 studies, 111 participants (Analysis 1.5); functional scales: MD -0.82 points, 95% CI -8.81 to 7.17 points, $I^2 = 0\%$, 2 studies, 60 participants (Analysis 1.6); symptom scales: MD -3.05 points, 95% CI -10.58 to 4.47 points, $I^2 = 0\%$, 2 studies, 60 participants (Analysis 1.7); physical functioning: MD 2.05 points, 95% CI -3.50 to 7.59 points, $I^2 = 0\%$, 2 studies, 51 participants (Analysis 1.8)).

IV. Secondary outcome: force-generating capacity of peripheral muscles

Four studies measured force-generating capacity of the quadriceps muscle (Arbane 2011; Cavalheri 2017; Edvardsen 2015; Salhi 2015). This outcome measure was assessed using different techniques/measures in the four studies. Furthermore, two studies reported postintervention values (Arbane 2011; Edvardsen 2015), whereas the other two studies reported mean change values (Cavalheri 2017; Salhi 2015). Consequently, we have presented the final result as standardised mean difference (SMD), and subgroups (studies that reported postintervention values; studies that reported mean change values) were included in the meta-analysis. Overall, on completion of the intervention period, force-generating capacity of the quadriceps muscle was significantly higher in the intervention group compared to the control group (SMD 0.75, 95% CI 0.4 to 1.1, $I^2 = 0\%$, 4 studies, 133 participants, moderate-certainty evidence) (Analysis 1.9). There was no different between the results of the subgroups ($P = 0.78$; $I^2 = 0\%$).

Two studies measured handgrip force (Cavalheri 2017; Edvardsen 2015). On completion of the intervention period, there was an uncertain effect on handgrip force (MD 3.19 kg, 95% CI -1.14 to 7.52 kg, $I^2 = 0\%$, 2 studies, 75 participants) (Analysis 1.10).

V. Secondary outcome: pressure-generating capacity of respiratory muscles

Only one study measured the pressure-generating capacity of inspiratory and expiratory muscles (Messaggi-Sartor 2018). On completion of the intervention period, there was no significant difference between the intervention and control in both maximal inspiratory pressure (MD 13 % predicted, 95% CI -37 to 11 % predicted) and maximal expiratory pressure (MD 10 % predicted, 95% CI -27 to 8 % predicted).

VI. Secondary outcome: dyspnoea

Three studies measured dyspnoea (Edvardsen 2015; Messaggi-Sartor 2018; Salhi 2015). Two of these studies reported the dyspnoea component score of the EORTC QLQ-C30 (Edvardsen 2015; Messaggi-Sartor 2018), whereas one used the visual analogue scale (Salhi 2015). In both tools, higher scores indicate worse dyspnoea. Furthermore, two studies reported postintervention values (Edvardsen 2015; Salhi 2015), whereas the remaining study reported mean change values (Messaggi-Sartor 2018). Consequently, we have presented the final result as SMD, and subgroups (studies that reported postintervention values; study that reported mean change values) were included in the meta-analysis. Overall, on completion of the intervention period, dyspnoea was significantly less in the intervention group compared to the control group (SMD -0.43, 95% CI -0.81 to -0.05, $I^2 = 37\%$, 3 studies, 110 participants, very low-certainty evidence) (Analysis 1.11). In the subgroup of studies that reported postintervention values, dyspnoea was significantly less in the intervention group compared to the control group (SMD -0.59, 95% CI -1.02 to -0.16, $I^2 = 0\%$, 2 studies, 87 participants). No between-group difference was demonstrated in the study that reported mean change values (SMD 0.15, 95% CI -0.67 to 0.98, 1 study, 23 participants).

VII. Secondary outcome: fatigue

Three studies measured fatigue (Cavalheri 2017; Messaggi-Sartor 2018; Salhi 2015). Two studies measured fatigue using the FACIT-fatigue (Cavalheri 2017; Salhi 2015), whereas one study used the fatigue component score of the EORTC QLQ-C30 (Messaggi-Sartor 2018). For the FACIT-fatigue, lower scores indicate greater fatigue, whereas for the EORTC QLQ-C30 higher scores indicate greater fatigue. In order to pool these data, we changed the direction of the mean change in scores of the EORTC QLQ-C30 (i.e. negative values were made positive). On completion of the intervention period, there was an uncertain effect on fatigue (SMD -0.05, 95% CI -0.52 to 0.43, $I^2 = 0\%$, 3 studies, 68 participants) (Analysis 1.12).

VIII. Secondary outcome: feelings of anxiety and depression

Only one study measured feelings of anxiety and depression using the HADS (Cavalheri 2017). On completion of the intervention period in this study, there was no significant difference between the intervention and control groups in feelings of anxiety (mean $\pm$ SD intervention group: 3 ± 2 points to 5 ± 4 points and control group: 2 ± 2 points to 4 ± 5 points; $P = 0.17$) and depression (mean $\pm$ SD intervention group: 2 ± 2 points to 4 ± 5 points and control group: 3 ± 3 points to 4 ± 3 points; $P = 0.40$).

IX. Secondary outcome: lung function

Four studies reported measures of FEV₁ (Brocki 2014; Cavalheri 2017; Edvardsen 2015; Stigt 2013). One study reported FEV₁ as a % of predicted values (Edvardsen 2015), whereas three studies reported FEV₁ in absolute value (litres) (Brocki 2014; Cavalheri 2017; Stigt 2013). Furthermore, two studies reported postintervention values (Edvardsen 2015; Stigt 2013), whilst the other two studies reported mean change values (Brocki 2014; Cavalheri 2017). Consequently, we have presented the final result as SMD, and subgroups (studies that reported postintervention values; studies that reported mean change values) were included in the meta-analysis. Overall, on completion of the intervention period, there was an uncertain effect on FEV₁ (SMD -0.06, 95% CI -0.37 to 0.25, $I^2 = 0\%$, 4 studies, 166 participants) (Analysis 1.13). There was no difference between the results of the subgroups ($P = 0.59$; $I^2 = 0\%$).

Two studies reported measures of FVC (Brocki 2014; Cavalheri 2017). On completion of the intervention period, there was an uncertain effect on FVC (MD -0.06 L, 95% CI -0.26 to 0.15 L, $I^2 = 0\%$, 2 studies, 83 participants) (Analysis 1.14).

V. Secondary outcome: mortality

Data were not available for this outcome.

DISCUSSION

Summary of main results

This review provides moderate- to high-certainty evidence that, in people following lung resection for NSCLC, exercise training increased VO₂peak (MD 2.97 mL/kg/min, 95% CI 1.93 to 4.02 mL/kg/min); 6MWD (MD 57 m, 95% CI 34 to 80 m); and quadriceps muscle force (SMD 0.75, 95% CI 0.4 to 1.1). One adverse event (hip fracture) related to the intervention was reported in one of the included studies. Low-certainty evidence also suggested that exercise training improved the physical component score of general HRQoL (MD 5.0 points, 95% CI 2.3 to 7.7 points) and relieved

dyspnoea (SMD -0.43, 95% CI -0.81 to -0.05) in people following lung resection for NSCLC. We observed uncertain effects for disease-specific HRQoL, handgrip force, fatigue, and lung function. Data were insufficient to comment on the effect of exercise training on maximal inspiratory and expiratory pressures and feelings of anxiety and depression. The included studies did not report on mortality.

Overall completeness and applicability of evidence

The update of this systematic review was warranted as we were able to include five additional studies, almost tripling the number of studies in the original review (Cavalheri 2013a), and providing a 2.5-fold increase on the number of participants (178 to 450). The updated meta-analyses investigating the effects of exercise training following lung resection for NSCLC on exercise capacity were able to provide novel, moderate-certainty evidence for improvements in VO₂peak as well as confirm and strengthen the certainty of the previous finding of improvements in 6MWD. Exercise capacity in people with NSCLC is adversely affected by several factors including the tumour itself, coexisting 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). Of note, earlier work that assessed several outcomes such as exercise capacity, HRQoL, muscle force, lung function, and feelings of anxiety and depression reported that, compared to healthy controls, the greatest impairment demonstrated in people following lung resection for NSCLC was in exercise capacity (Cavalheri 2015). In fact, 15 of the 21 participants (i.e. 71%) had a VO₂peak below the lower limit of normal established in healthy controls (Cavalheri 2015). Our findings of improved exercise capacity are particularly relevant because both VO₂peak and 6MWD are valuable prognostic indicators in this population (Jones 2010; Zarogoulidis 2012). For example, a longitudinal study that followed 398 participants with NSCLC for 30.8 months demonstrated that each 1 mL/kg/min increase in VO₂peak was associated with a 4% reduction in all-cause mortality (Jones 2010). Regarding the 6MWD, the magnitude of the effect found in this update (MD = 57 m) exceeded the minimal important difference (MID) of the 6MWD reported for people with lung cancer (i.e. 22 to 42 m) (Granger 2015). In addition to being statistically significant, the magnitude of improvement in exercise capacity was therefore also clinically important. We did not investigate maintenance of improvements in exercise capacity in this review, and future studies should investigate strategies to maintain these gains.

Three of the four included studies reporting on adverse events found no adverse events during exercise training (Brocki 2014; Messaggi-Sartor 2018; Salhi 2015). Edvardsen 2015 reported the occurrence of a hip fracture during balance training, a type of training that was only conducted in that study. When needed, balance training should therefore be performed under close supervision, and in proximity to a railing or other secure support (Beck 2017).

Our review suggests that exercise training improved the physical component score of general HRQoL, as measured by the SF-36, in people following lung resection for NSCLC. This finding is important because, compared to pre-surgical scores, people with NSCLC present with a worse physical component score for HRQoL at six months following lung resection, with little change up to two years afterwards (Poghosyan 2013). Furthermore,

the magnitude of the between-group difference in the physical component score of HRQoL found in the current review was 5 points, which exceeded the MID for the SF-36 (i.e. 3 to 5 points) (Samsa 1999). This improvement in HRQoL following a programme of exercise training is in agreement with findings of systematic reviews in people with chronic lung diseases such as COPD, McCarthy 2015; Puhan 2016, and interstitial lung disease, Dowman 2014, as well as in women with breast cancer, Lahart 2018. Conversely, improvements in the mental component score of general HRQoL were not demonstrated in the current review. The meta-analysis undertaken for this outcome was the only one that presented substantial heterogeneity. However, both the lack of improvement in the mental component score of general HRQoL and the substantial heterogeneity were unresolved by sensitivity analyses. It is possible that this lack of improvement may be attributable to minimal impairment in this domain and, therefore, little scope for improvement with exercise training. However, it is also likely that exercise training alone has no effect on the mental component of HRQoL, and that a combination of exercise training with other interventions provided by a multidisciplinary team including psychologists and other health professionals needs to be considered. Our finding of no between-group difference in disease-specific HRQoL, measured using the EORTC QLQ-C30, may reflect that the meta-analyses lacked statistical power to detect changes in disease-specific HRQoL, especially for the subscales of physical functioning, function, and symptoms. The number of participants in the meta-analyses for the disease-specific HRQoL subscales ranged between 51 and 60, a sample size much lower than that for the physical component score of general HRQoL ($n = 208$). Larger RCTs are needed to further investigate the effects of exercise training on disease-specific HRQoL in people following lung resection for NSCLC.

A novel finding of the current review is that exercise training improved force-generating capacity of the quadriceps muscle. We included four studies in the meta-analysis (Arbane 2011; Cavalheri 2017; Edvardsen 2015; Salhi 2015), and, despite assessing force-generating capacity of the quadriceps muscle using different methods (e.g. femoral nerve stimulation, maximal isometric force, and one-repetition maximum), results were similar across the four studies, and the I^2 in the meta-analysis was 0%. A previous cross-sectional study in 64 people following lung resection for NSCLC demonstrated that force-generating capacity of the muscle is only modestly reduced in this population (Burtin 2017), that is the average isometric quadriceps force was $89 \pm 25\%$ of predicted (Burtin 2017). However, as discussed by the authors of that study, the high SD (i.e. 25%) suggests substantial heterogeneity in isometric quadriceps muscle force across the population, with muscle weakness being more pronounced in those patients with lower exercise capacity. Some people with NSCLC may therefore present with significant reduction in isometric quadriceps muscle force following lung resection, and the improved force-generating capacity of the quadriceps muscle after exercise training demonstrated in the current review is specifically relevant to this group.

We did not find changes in handgrip force following exercise training. This finding was expected, as one principle of exercise training is specificity, and training of the hand muscles was not part of the exercise training programmes in the two studies that measured this outcome (Cavalheri 2017; Edvardsen 2015). The only study that measured the pressure-generating capacity of

inspiratory and expiratory muscles did not show improvement in these outcomes following exercise training (Messaggi-Sartor 2018). The reasons for the lack of improvement in these outcomes may relate to an ineffective training programme as well as lack of statistical power to detect small changes.

We demonstrated in this review that exercise training may reduce dyspnoea in people following lung resection for NSCLC. Dyspnoea is a common symptom amongst people with lung cancer. A previous study in 142 people following lung resection for NSCLC (median time from surgery = 10 years) showed that 90 (63%) reported chronic dyspnoea, and 45 (32%) had to stop due to breathlessness when walking at their own pace (Sarna 2004). Similarly, a cross-sectional survey of 342 people following lung resection for NSCLC (assessed 1 to 6 years following the resection) demonstrated that 205 (60%) reported significant dyspnoea at the time they responded to the survey (Feinstein 2010). The 2013 evidence-based clinical practice guidelines (CPG) of the American College of Chest Physicians (ACCP) discuss the importance of managing dyspnoea in people with lung cancer as "it creates significant worsening to a patient's HRQoL" (Simoff 2013). This CPG was based on a previous integrative review of systematic reviews related to the management of breathlessness in respiratory illnesses (Bailey 2010). It concluded that it is important to focus future research on promising non-pharmacological interventions to manage dyspnoea, as pharmacological treatments do not completely alleviate symptoms and have the added burden of side effects. Our review suggests that exercise training may be a promising non-pharmacological intervention to manage dyspnoea in people following lung resection for NSCLC.

Our meta-analysis did not show differences in fatigue following exercise training. Fatigue is a common symptom in people with early stage (i.e. stages I to IIIA) NSCLC (Huang 2015). However, the mean time taken following lung resection for people with NSCLC to recover from symptoms of fatigue is 62 days (95% CI 52 to 72 days) (Fagundes 2015). The lack of between-group difference in fatigue demonstrated in this review is therefore likely to be related, at least in part, to a natural recovery in this outcome in both the intervention and control groups.

The only study that measured feelings of anxiety and depression did not show improvement in these outcomes following exercise training (Cavalheri 2017). However, the participants in that study presented with low scores for feelings of anxiety and depression (i.e. HADS anxiety and depression scores ≤ 7) at baseline. This result is in agreement with a study of pulmonary rehabilitation in people with COPD that found that people with baseline HADS scores for feelings of anxiety and depression of ≤ 7 did not have a significant change in symptoms following pulmonary rehabilitation (Harrison 2012). As lung resection is the treatment that offers the best chance of cure of NSCLC (Brunelli 2013), further investigation is needed to explore the extent to which feelings of anxiety and depression are present in this population, and, if so, whether they are best managed with a combination of exercise training and other interventions provided by a multidisciplinary team.

We did not demonstrate changes in lung function following exercise training in this review. This finding was expected and is in agreement with the literature on the effect of pulmonary rehabilitation on lung function for people with COPD (McCarthy 2015).

Quality of the evidence

We rated the quality (certainty) of the evidence provided by the studies included in the analysis as moderate, ranging between very low (e.g. dyspnoea) and high (e.g. exercise capacity measure as the 6MWD). We assessed all included studies as having a high risk of performance bias. However, blinding of participants and personnel is particularly challenging in RCTs investigating the effectiveness of exercise training. The reasons for rating the evidence for the outcomes dyspnoea and HRQoL as very low and low certainty, respectively, were mainly due to high risk of detection bias and some level of inconsistency (for HRQoL and dyspnoea) and imprecision of pooled estimates (dyspnoea). We rated the evidence for the outcome exercise capacity (VO₂peak) as moderate certainty because two of the four studies included in the meta-analysis had a high risk of detection bias (i.e. lack of blinding of the outcome assessors) for that specific outcome measure. We judged the evidence for the outcome quadriceps muscle force as of moderate certainty due to small sample size across the studies. Finally, we rated the evidence for the outcome exercise capacity (6MWD) as of high certainty due to the very large size of the effect, which showed marginal increase compared to the original version of the review (Cavalheri 2013a). We believe that further research is very unlikely to change our confidence in the estimate of effect for 6MWD.

Potential biases in the review process

Our review was strengthened by a number of methodological processes used to ensure rigour and completeness. These included an extensive electronic search, a search strategy with no language limitation, the use of two review authors to independently examine and select studies, and our success in contacting authors of the included studies to provide additional data. In the previous version of the review we attempted to contact authors of two other studies; one did not reply, and the other did not have access to the requested data. In this update, we attempted to contact the authors of another study, but we did not receive a reply to our several contact attempts. Exclusion of these three studies is a potential source of selection bias.

Agreements and disagreements with other studies or reviews

The first published systematic review on the effects of exercise training for people with NSCLC included randomised and non-randomised controlled trials (Granger 2011). However, of 16 studies (two RCTs) included in this earlier review, only one RCT initiated exercise training following lung resection for NSCLC (Arbane 2011), whilst all the others explored the effect of preoperative exercise training. Based on the results of 11 non-RCTs, the authors concluded that in people with NSCLC exercise training in this population was safe and may confer positive benefits on exercise capacity and some domains of HRQoL. Reviews of preoperative exercise training in people with NSCLC have since been published following that first review (Cavalheri 2017a; Pouwels 2015; Sebio Garcia 2016). Only one of the three reviews reported results of a meta-analysis for the outcome 6MWD (Cavalheri 2017a), and, in agreement with the current review, demonstrated improved 6MWD in the intervention group compared with the control group (MD 18 m, 95% CI 9 to 28 m). Similarly, a recently published review that investigated the effects of exercise training in people with advanced lung cancer (i.e. stages IIIB to IVB) demonstrated improved 6MWD

in the intervention group compared with the control group (MD 63 m, 95% CI 4 to 123 m) (Peddle-McIntyre 2019). Regarding reviews on exercise training following lung resection for NSCLC, the original version of our Cochrane Review, Cavalheri 2013a, as well as two other reviews, Crandall 2014; Sommer 2018, have been published. The review by Crandall 2014 included both RCTs and non-RCTs that investigated the effectiveness of exercise training for people with NSCLC before as well as after lung resection. However, the authors did not perform meta-analysis. The review by Sommer 2018 included only four RCTs (Arbane 2011; Brocki 2014; Edvardsen 2015; Salhi 2015). In agreement with our review, Sommer 2018 reported higher exercise capacity in the intervention group compared with the control group (SMD 0.48, 95% CI 0.04 to 0.93). However, in contrast to our review, which analysed VO₂peak and 6MWD separately, Sommer 2018 pooled results of VO₂peak and 6MWD together in the meta-analysis. Consistent with our findings, Sommer 2018 reported better scores for the physical component of HRQoL in the intervention group compared with the control group (SMD 0.50, 95% CI 0.19 to 0.82). However, instead of analysing general HRQoL and disease-specific HRQoL separately, Sommer 2018 pooled results of the SF-36 physical component score and EORTC QLQ-C30 physical functioning score together in the meta-analysis. Of note, our review is the first to report findings of meta-analysis for outcomes such as force-generating capacity of peripheral muscles, pressure-generating capacity of respiratory muscles, dyspnoea, and fatigue.

AUTHORS' CONCLUSIONS

Implications for practice

Our meta-analyses provided moderate- to high-certainty evidence that exercise training, which included aerobic and resistance exercises, improved exercise capacity and quadriceps muscle force of people following lung resection for non-small cell lung cancer (NSCLC). The improvement in exercise capacity was clinically important. Lower-certainty evidence from our meta-analyses also suggested that exercise training improved the physical component score of general health-related quality of life (HRQoL) and decreased dyspnoea in people following lung resection for NSCLC. The improvement in the physical component score of general HRQoL was clinically important. A survey that described the management of people with lung cancer across Australia and New Zealand reported that only a small proportion of people were referred to exercise training programmes following lung resection (Cavalheri 2013). Our review suggests that referrals to exercise programmes could be considered for people following lung resection for NSCLC. Exercise training has the potential to interrupt the 'deconditioning storm' induced by the disease and its treatment (Jones 2008). Importantly, balance training, when needed, should be performed under close supervision and in proximity to a railing or other secure support (Beck 2017).

Implications for research

In the original review we provided important considerations for minimising bias and methodological heterogeneity in upcoming studies. We were pleased to see that these considerations were addressed in the five studies added to this review (Arbane 2014; Cavalheri 2017; Edvardsen 2015; Messaggi-Sartor 2018; Salhi 2015). Specifically, these studies: (i) collected outcome measures immediately before and after the exercise training intervention rather than before lung resection and on completion of the

exercise training intervention; (ii) chose disease-specific HRQoL questionnaires; and (iii) reported the values for each domain that contributed to HRQoL as well as the total score obtained from HRQoL questionnaires. Reporting of data could be optimised by reporting the mean change in outcomes collected immediately before and after the exercise training intervention.

The current systematic review strengthens the message that exercise training improves exercise capacity in people following lung resection for NSCLC. It also highlights the need for larger randomised controlled trials (RCTs) to confirm or investigate the effects of exercise training following lung resection for NSCLC on outcomes other than exercise capacity, including different aspects of quality of life and symptoms. The effect of combining exercise training with other interventions provided by a multidisciplinary team (e.g. dietitians, occupational therapists, psychologists, and others) needs to be considered. Although blinding of study participants and personnel in RCTs of exercise training is very difficult, even with 'sham' training, future studies should strive to blind outcome assessors. Upcoming studies should consider intention-to-treat analysis, as well as attempts to minimise losses

to follow-up. The addition of longer-term follow-up measures is also important for future trials. Furthermore, a comparison of the effects of exercise training in people who underwent video-assisted thoracoscopic surgery (VATS) and those who underwent thoracotomy could be included as an exploratory aim in future RCTs to evaluate their influence on maximal inspiratory and expiratory pressures as well as other outcomes.

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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	<p>Randomised controlled trial</p> <p>Setting: St George's Hospital, London, UK</p> <p>Study duration: 5 days (inpatient) + 12 weeks of home-based intervention. Assessments were performed preoperatively, 5 days postoperatively, and after the 12 weeks of intervention following discharge.</p>
Participants	<p>67 participants with NSCLC, referred for lung resection via open thoracotomy or VATS, were screened. 53 agreed to participate in the study and were randomised before any formal testing. 2 were excluded. 51 participants (median (range) age 63 (32 to 87) years – control group; 65 (47 to 82) years – exercise group) completed the study.</p>
Interventions	<p>Control (n = 25): Pain medication as relevant via patient-controlled analgesia on day 1 postoperatively, thereafter orally as needed. Usual care comprising routine inpatient physiotherapy treatment (airway clearance techniques, mobilisation as able, and upper limb activities) once daily from day 1 post-surgery to discharge and monthly phone calls after discharge.</p> <p>Exercise (n = 26): Same as control group plus twice-daily additional strength and mobility training from day 1 to day 5 postsurgery as well as 12 weeks of home-based non-supervised exercise programme (walking + home-adapted strengthening exercises) including 3 home visits.</p>
Outcomes	<p>Exercise capacity (6-minute walk distance), health-related quality of life (EORTC QLQ-C30 version 2.0), maximal quadriceps force (femoral nerve stimulation), and postoperative complications</p>
Notes	<p>Control group: stage I (10 participants), stage II (6 participants), stage IV (5 participants), and 4 participants described as "other".</p> <p>Active group: stage I (15 participants), stage II (6 participants), stage III (2 participants), and data were unavailable for 3 participants.</p> <p>Missing data provided on number of males/females in each group.</p>

Arbane 2011 (Continued)

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: 5-day postoperative assessment did not include quality of life questionnaire. Also, the control group had 5 participants categorised at stage IV, whereas the exercise group had no participants with this categorisation.

Arbane 2014

Methods Randomised controlled trial

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

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Arbane 2014 (Continued)

Setting: teaching hospital, London, UK

Study duration: 5 days (inpatient) + 4 weeks of home-based intervention. Assessments were performed preoperatively, 5 days postoperatively (or sooner if discharge was earlier), and 4 weeks postoperatively.

Participants	131 participants with NSCLC were randomised before lung resection (via open thoracotomy or VATS). Following randomisation, 29 participants (22%) were withdrawn according to predefined criteria, and 24 participants (18%) were unavailable for assessment 4 weeks after lung resection. The mean (SD) age was 68 (11) years for the control group and 67 (11) years for the exercise group.
Interventions	<p>Control (n = 67): standard medical care including routine physiotherapy treatments, airway clearance techniques where indicated, mobilisation, and upper limb activities.</p> <p>Exercise (n = 64): structured, physiotherapy-led cycle ergometry strength-training programme once a day during inpatient stay. This training included a warm-up phase during 0 to 2 minutes consisting of unloaded pedaling at 50 to 60 rpm. Intensity of cycling was increased steadily during the third minute to achieve max 60% to 90% heart rate reserve. Participants were advised to exercise at an intensity of 3 to 4 in the Borg dyspnoea scale or 13 to 15 on the Borg Rating of Perceived Exertion (RPE). The aim was to complete > 5 minutes on postoperative day 1, increasing to maximal duration of 30 minutes on day 5. Furthermore, the exercise group undertook a 4-week home walking programme (with bi-weekly phone calls). The aim was to achieve 30 minutes of walking per day.</p>
Outcomes	Exercise capacity (incremental shuttle walk test), health-related quality of life (SF-36 and EORTC QLQ-LC13), and quadriceps force (maximum voluntary contraction)
Notes	Subgroup analysis was undertaken with data from the 63 participants that had airflow obstruction (defined as $FEV_1/FVC < 0.7$).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote:</p> <p>"This was a dual centre, stratified, randomised controlled trial..." and "...data were added to the online randomisation service provided by the Mental Health and Neurosciences Clinical Trials Unit supplied by King's College London (http://www.ctu.co.uk/)."</p>
Allocation concealment (selection bias)	Low risk	<p>Quote:</p> <p>"The allocation sequence was concealed from the researcher who enrolled and assessed the participants."</p>
Blinding of participants and personnel (performance bias) All outcomes	High risk	<p>Quote:</p> <p>"The study was open labelled; neither the participants nor the researchers were blinded."</p> <p>Comment:</p> <p>No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding.</p>
Blinding of outcome assessment (detection bias) All outcomes	High risk	<p>Comment:</p> <p>Author contacted - "I can clarify that the person who assessed Physical Activity, Exercise Tolerance and Quadriceps Muscle Strength was not blinded to group allocation"</p>

Arbane 2014 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: “The primary efficacy analysis was intention to treat, and imputed data were included assuming no change where data were missing.” Comment: Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	Comment: The study protocol is available, and all of the study’s prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way.
Other bias	Low risk	Comment: The study appears to be free of other sources of bias.

Brocki 2014

Methods	Randomised controlled trial Setting: Aalborg University Hospital, Denmark Study duration: 4 months. Intervention started 3 weeks following lung resection. Assessments were performed 3 weeks following lung resection and after 4 and 12 months.
Participants	294 people with NSCLC were screened for eligibility and 171 were approached; 92 declined to participate and 1 person failed to perform the 6MWT. 78 people (mean (SD) age 65 (9) years – control group; 64 (10) years – exercise group) agreed to participate in the study and were randomised.
Interventions	Control (n = 37): 1 individual instruction session on home exercises (strength training at least twice a week and a daily 30-minute walk or a bicycle ride with an intensity of 11 to 12 on the Borg scale) and usual postoperative nurse counselling consisting of up to 3 individual 1-hour sessions performed in the period of 3 weeks to 4 months after surgery. Exercise (n = 41): 1 individual instruction session on home exercises (as described above), usual post-operative nurse counselling (described above), and supervised outpatient exercise training sessions, 1 hour once a week for 10 weeks. The sessions were based on aerobic exercises with target intensity of 60% to 80% of work capacity, resistance training, and dyspnoea management.
Outcomes	Exercise capacity (6MWD), health-related quality of life SF-36, and lung function (spirometry)
Notes	4 of the 41 participants in the exercise group (10%) and 6 of the 37 participants in the control group (16%) had secondary lung cancer. Author was contacted and kindly provided specific data (gender, age, type of surgical procedure, SF-36, 6MWD, FEV ₁ and FVC) for the participants that had primary NSCLC. 12-month follow-up not included in this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
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Brocki 2014 (Continued)

Random sequence generation (selection bias)	Low risk	Quote: “Computer-generated randomization tables, stratified for pneumonectomy (expected low performance status) were used.”
Allocation concealment (selection bias)	Low risk	Quote: “Individual allocations were placed in consecutively numbered and sealed opaque envelopes by an external person.”
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: “Group allocation was revealed to the patients by the main investigator.” Comment: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “Assessors were blinded to the patient’s group allocation.”
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: There are differential losses to follow-up between groups, and differences between completers/no completers that could be related to the outcomes, therefore we could not make an assessment of low risk of attrition bias. Since the main analysis results at 4 months were mostly of no effect (except for the bodily pain domain), and the more conservative sensitivity analysis (the best case for control) reached similar conclusions, it seems that the overall analysis is robust and there is no suggestion of relevant bias derived from attrition of participants. For this reason, we also could not make an assessment of high risk of attrition bias.
Selective reporting (reporting bias)	Low risk	Comment: ClinicalTrials.gov Identifier: NCT01048762 (not reported in the published paper) - all of the study’s prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way.
Other bias	Low risk	Comment: The study appears to be free of other sources of bias.

Cavalheri 2017

Methods	Randomised controlled trial Setting: 2 tertiary hospitals, Perth, Australia Study duration: 8 weeks of intervention. Measurements were collected at baseline (i.e. 6 to 10 weeks after lobectomy, or for those who required postoperative chemotherapy, 4 to 8 weeks after their last chemotherapy cycle) and following completion of the intervention.
Participants	96 patients with NSCLC undergoing lung resection (via open thoracotomy or VATS) were screened. 17 patients (mean (SD) age 68 (9) years – control group; 66 (10) years – exercise group) agreed to participate in the study and were randomised.

Cavalheri 2017 (Continued)

Interventions	<p>Control (n = 8): instructed to continue to perform their usual activities during the period of the study. Participants received weekly phone calls from a research assistant that consisted of general conversation as well as standardised questions about their health and well-being.</p> <p>Exercise (n = 9): participants in the exercise group underwent an 8-week exercise training programme aimed at improving aerobic capacity and muscle strength. The programme comprised individual, supervised training 3 times per week delivered by senior physical therapists. Each session was 60 minutes in duration. In the event that a participant could only attend 2 supervised sessions per week, they were provided with a cycle ergometer to use at home for 1 training session per week. Each class comprised aerobic (walking/cycling) and resistance training (upper/lower limbs). For corridor walking, the initial average speed was set at 80% of the average 6MWT speed. Cycling consisted of 10 min of endurance training (initial work rate was set at 60% of the Wmax) and 2 periods of 2 min of power training (initial work rate was set at 80% of the Wmax).</p>
Outcomes	Exercise capacity (6MWD and VO ₂ peak), health-related quality of life (SF-36, FACT-L, and EORTC QLQ-C30), peripheral muscle force (isometric handgrip force, isometric quadriceps force), fatigue (FACIT-Fatigue), feelings of anxiety and depression (HADS), and lung function (spirometry)
Notes	Stage I (14 participants), stage II (2 participants), stage III (1 participant)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomization sequence was generated and managed by an independent researcher using a computer..."
Allocation concealment (selection bias)	Low risk	Quote: "... concealed using sequentially numbered opaque envelopes."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "This study was a pilot single-blinded..." Comment: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The primary investigator, who was responsible for the baseline and post-intervention period assessments, was not aware of whether a participant had been allocated to the EG or the CG."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Intention-to-treat analysis was undertaken."
Selective reporting (reporting bias)	High risk	Comment: Australian New Zealand Clinical Trials Registry Identifier: AC-TRN12611000864921 - pressure-generating capacity of respiratory muscles was included in the clinical trial registry but was not reported in the published paper.
Other bias	Low risk	Comment:

Cavalheri 2017 (Continued)

The study appears to be free of other sources of bias.

Edvardsen 2015

Methods	<p>Randomised controlled trial</p> <p>Setting: Oslo University Hospital in Norway</p> <p>Study duration: 20 weeks, starting 5 to 7 weeks after surgery. Assessments were performed by exercise physiologists before surgery, 4 to 6 weeks after surgery, and immediately after the 20-week intervention.</p>
Participants	<p>A total of 106 patients were screened for participation, and 69 patients were enrolled before lung resection. Following lung resection, 8 participants were not randomised because of postoperative mortality (n = 3) or unexpected events. 61 patients (mean (SD) age 66 (9) years – control group; 64 (9) years – exercise group) agreed to participate in the study and were randomised.</p>
Interventions	<p>Control (n = 31): the control group received standard postoperative care.</p> <p>Exercise (n = 30): the exercise programme was individualised and included a cardiovascular warm-up, interval training, progressive resistance training (PRT), and daily inspiratory muscle training. The intervention focused on high-intensity training, mainly by walking uphill on a treadmill at 80% to 95% of the maximum heart rate and by PRT in 3 series of 6- to 12-repetition maximum of the leg press, leg extension, back extension, seat row, bicep curls, and chest-and-shoulder press. Each session lasted 60 min, and exercise was performed 3 times per week for 20 weeks.</p>
Outcomes	<p>Exercise capacity (VO₂peak), health-related quality of life (SF-36 and EORTC QLQ-C30), and peripheral muscle force (isometric handgrip force by using a dynamometer, isometric quadriceps force by 1-repetition maximum) and lung function (spirometry)</p>
Notes	<p>Stage I (33 participants), stage II (19 participants), stage III (10 participants), stage IV (1 participant)</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote:</p> <p>“The randomisation was done in blocks with varying block size (4–6 subjects)...”</p>
Allocation concealment (selection bias)	Low risk	<p>Quote:</p> <p>“... put into sealed opaque envelopes generated by an external statistician.”</p>
Blinding of participants and personnel (performance bias) All outcomes	High risk	<p>Quote:</p> <p>“We conducted a single-blind randomised controlled trial.”</p> <p>Comment:</p> <p>No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding.</p>
Blinding of outcome assessment (detection bias) All outcomes	High risk	<p>Quote:</p> <p>“Furthermore, we cannot rule out the possibility that the technicians were not blinded during the last data collection.”</p>

Edvardsen 2015 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: “Effects were evaluated on an intention-to-treat basis.”
Selective reporting (reporting bias)	High risk	Comment: ClinicalTrials.gov Identifier: NCT01748981 - 1 prespecified outcome (physical activity) was not reported in the published study.
Other bias	Low risk	Comment: The study appears to be free of other sources of bias.

Messaggi-Sartor 2018

Methods	Pilot randomised controlled trial Setting: outpatient cardiopulmonary rehabilitation unit of 2 university hospitals in Barcelona, Spain Study duration: 8 weeks of intervention and 2-year follow-up
Participants	70 patients with NSCLC were screened to participate. 37 patients (mean (SD) age 65 (9) years – control group; 64 (8) years – exercise group) agreed to participate in the study and were randomised.
Interventions	Control (n = 21): usual postoperative care (standard medical treatment and periodic monitoring). Participants were advised to perform physical activity such as leisure time physical activity (walking, dancing, hiking, or swimming), transportation (walking or cycling), occupational (if still in the workforce), household chores, play, games and sports, or planned exercise. Exercise (n = 16): continuous aerobic training and high-intensity respiratory muscle training (24 supervised sessions, 3 per week, 8 weeks). Continuous aerobic training was performed on an ergometric bicycle, initial intensity was 60% of baseline peak workload and increased by 5 watts weekly if the participant was able to tolerate the set load for 30 min. High-intensity respiratory muscle training consisted of 5 sets of 10 repetitions followed by 1 to 2 min of unloaded recovery breathing, twice a day, 3 days per week, for 8 weeks.
Outcomes	Exercise capacity (VO ₂ peak), health-related quality of life (EORTC QLQ-C30), and respiratory muscle strength (maximal inspiratory and expiratory pressure)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “Eligible patients were randomly assigned to the exercise and control groups. Randomization was performed by a staff member blinded to patient identify, who assigned the anonymized patient record to one of the study groups using a random number generator program.”
Allocation concealment (selection bias)	Low risk	Quote: “Randomization was performed by a staff member blinded to patient identify, who assigned the anonymized patient record to one of the study groups.”

Messaggi-Sartor 2018 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "A two-centre, prospective, single-blind..." Comment: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The researchers assessing the main outcomes were blinded to the group assignments."
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "The main outcomes measures were analysed per protocol." Comment: 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation.
Selective reporting (reporting bias)	High risk	Comment: ClinicalTrials.gov Identifier: NCT01771796 - the prespecified outcomes peripheral muscle strength and sMICA (biomarker) are not reported in the published paper. Furthermore, respiratory muscle strength and quality of life are reported in the paper but are not included in the registration.
Other bias	Low risk	Comment: The study appears to be free of other sources of bias.

Salhi 2015

Methods	Randomised controlled trial Setting: University hospital in Belgium Study duration: 12-week intervention. Participants were evaluated before, after radical treatment, and after completing the 12-week intervention.
Participants	121 consecutive patients with respiratory cancer were recruited. 86 patients completed the assessments before radical treatment. 16 additional patients dropped out following radical treatment. 70 radically treated patients were randomly assigned to 1 of 3 groups: control (n = 24), conventional resistance training (CRT) (n = 24), or whole-body vibration training group (n = 22). Only data pertaining to the control group (median (range) age 64 (51 to 79) years) and CRT group (63 (29 to 76) years) were used in the current review.
Interventions	Control (n = 24): participants were discouraged from undertaking supervised exercise training. Exercise (CRT) (n = 24): 3 times per week for 12 weeks. 20 min of aerobic training on the bicycle and treadmill at 70% of the respective maximal workload (Wmax) and speed; resistance training on multi-gym equipment starting with 3 sets of 8 repetitions for each exercise at 50% 1-repetition-maximum.
Outcomes	Exercise capacity (6MWD and VO ₂ peak), quadriceps muscle force (isometric handheld dynamometer), health-related quality of life (EORTC QLQ-C30), fatigue (FACIT-F), and dyspnoea (VAS dyspnoea)

Salhi 2015 (Continued)

Notes	<p>3-arm trial. Only data from the control and CRT groups were used in the current review.</p> <p>6 of the 24 participants in the control group (25%) and 6 of the 24 participants in the CRT group (25%) did not undergo lung resection.</p> <p>Author was contacted and kindly provided specific data for the participants that underwent lung resection (gender, age, lung cancer stage, VO₂peak, 6MWD, quadriceps force, EORTC QLQ-C30, dyspnoea, fatigue, and FEV₁).</p>
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote:</p> <p>"Patient randomisation was conducted by a blinded, web-based platform using a minimisation technique..."</p>
Allocation concealment (selection bias)	Low risk	<p>Quote:</p> <p>"Patient randomisation was conducted by a blinded, web-based platform using a minimisation technique with random allocation to either a control group (CON), a CRT-group and a WBVT-group."</p> <p>Comment:</p> <p>Central allocation.</p>
Blinding of participants and personnel (performance bias) All outcomes	High risk	<p>Comment:</p> <p>No blinding, and the outcome is likely to be influenced by lack of blinding.</p>
Blinding of outcome assessment (detection bias) All outcomes	High risk	<p>Quote:</p> <p>"The investigator was unblinded for the intervention and its evaluation."</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>Comment:</p> <p>3/24 (control group), 4/24 (resistance group), and 5/22 (whole-body vibration training group) were lost to follow-up. Intention-to-treat and per-protocol analysis performed. Missing data imputation was performed.</p>
Selective reporting (reporting bias)	High risk	<p>Comment:</p> <p>ClinicalTrials.gov Identifier: NCT00752700 (not included in the published paper) – prespecified outcomes such as muscle mass, body composition, and anxiety and depression were not reported in the published paper.</p>
Other bias	Low risk	<p>Comment:</p> <p>The study appears to be free of other sources of bias.</p>

Stigt 2013

Methods	Randomised controlled trial
	Setting: Teaching Hospital in Zwolle, the Netherlands

Stigt 2013 (Continued)

Study duration: 12 weeks of intervention and 1-year follow-up. Assessments were performed before surgery and postoperatively at 1, 3, 6, and 12 months.

Participants	81 patients with NSCLC who were eligible for thoracotomy were invited. 60 patients accepted, but 57 were randomised before surgery. 49 participants completed (exercise group: n = 23 (21 males), mean age 63.6 ± 10.2 years and control group: n = 26 (19 males), 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): 4 weeks after discharge, twice a week, participants exercised at 60% to 80% of their peak cycling load and performed muscle training for 12 weeks. An anaesthesiologist adjusted pain treatment according to the World Health Organization (WHO) analgesic ladder.
Outcomes	Exercise capacity (6MWD), health-related quality of life (SGRQ and SF-36), and pulmonary function (spirometry)
Notes	Only “open thoracotomy” included. The number of participants who had adjuvant chemotherapy was 10 in the exercise group and 6 in the control group.

Risk of bias

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: 3 months postdischarge, 6MWD and lung function data were 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 (clinicaltrials.gov/show/NCT01136083) was reviewed, and not all of the prespecified outcomes were reported in the published paper.

Stigt 2013 (Continued)

Other bias

High risk

Comment:

More participants who had chemotherapy were randomised to the training group, and Table 3 shows a higher dropout in attendance rate for participants who had chemotherapy compared to those who did not.

6MWD: 6-minute walk distance

6MWT: 6-minute walk test

EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire core 30

EORTC QLQ-LC13: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, Lung Cancer subscale

FACIT-F: Functional Assessment of Chronic Illness Therapy - Fatigue Subscale

FACT-L: Functional Assessment of Cancer Therapy - Lung

FEV₁/FVC: Forced expiratory volume in one second / Force vital capacity

HADS: Hospital Anxiety and Depression scale

NSCLC: Non-small cell lung cancer

rpm: Revolutions per minute

SD: Standard deviation

SF-36: Medical Outcomes Study Short Form 36 General Health Survey

SGRQ: St. George's Respiratory Questionnaire

VATS: Video assisted thoracotomy

Wmax: Maximum work rate

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Brocki 2016	Not exercise training
Chen 2015	Mixed population. No access to specific data
Chen 2016	Mixed population. No access to specific data
Granger 2013	Not specifically NSCLC
Hoffman 2017	Qualitative analysis only
Hsiao 2017	Includes preoperative intervention
Jakobsen 2013	Did not reply to contact attempts
Karvinen 2014	Mixed population. No access to specific data
Ledderer 2013	Mixed population with few participants with NSCLC
Liu 2015	Intervention delivered more than 12 months following lung resection.
Novoa 2017	Conference abstract. No access to specific data
Tenconi 2017	Conference abstract. No access to specific data
Wang 2013	Intervention delivered more than 12 months following lung resection.
Weiner 1997	Not postoperative patients
Yorke 2015	Not postoperative exercise training

NSCLC: non-small cell lung cancer

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 (VO ₂ peak in mL/kg/min)	4	135	Mean Difference (IV, Fixed, 95% CI)	2.97 [1.93, 4.02]
2 Exercise capacity (6MWD in metres)	5	182	Mean Difference (IV, Fixed, 95% CI)	57.26 [34.34, 80.18]
3 General health-related quality of life (SF-36 - physical component score)	4	208	Mean Difference (IV, Fixed, 95% CI)	5.02 [2.30, 7.73]
4 General health-related quality of life (SF-36 - mental component score)	4	208	Mean Difference (IV, Random, 95% CI)	-2.32 [-11.26, 6.62]
5 Disease-specific health-related quality of life (EORTC QLQ-C30 - global health)	4	111	Mean Difference (IV, Fixed, 95% CI)	-0.14 [-7.24, 6.96]
6 Disease-specific health-related quality of life (EORTC QLQ C30 - functional scales)	2	60	Mean Difference (IV, Fixed, 95% CI)	-0.82 [-8.81, 7.17]
7 Disease-specific health-related quality of life (EORTC QLQ-C30 - symptoms scales)	2	60	Mean Difference (IV, Fixed, 95% CI)	-3.05 [-10.58, 4.47]
8 Disease-specific health-related quality of life (EORTC QLQ-C30 - physical functioning)	2	51	Mean Difference (IV, Fixed, 95% CI)	2.05 [-3.50, 7.59]
9 Force-generating capacity of peripheral muscle (quadriceps)	4	133	Std. Mean Difference (IV, Fixed, 95% CI)	0.75 [0.39, 1.10]
9.1 Studies that reported postintervention values	2	97	Std. Mean Difference (IV, Fixed, 95% CI)	0.72 [0.30, 1.13]
9.2 Studies that reported mean change values	2	36	Std. Mean Difference (IV, Fixed, 95% CI)	0.83 [0.14, 1.52]
10 Force-generating capacity of peripheral muscles (handgrip)	2	75	Mean Difference (IV, Fixed, 95% CI)	3.19 [-1.14, 7.52]
11 Dyspnoea	3	110	Std. Mean Difference (IV, Fixed, 95% CI)	-0.43 [-0.81, -0.05]
11.1 Studies that reported postintervention values	2	87	Std. Mean Difference (IV, Fixed, 95% CI)	-0.59 [-1.02, -0.16]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.2 Study that reported mean change value	1	23	Std. Mean Difference (IV, Fixed, 95% CI)	0.15 [-0.67, 0.98]
12 Fatigue	3	68	Std. Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.52, 0.43]
13 Lung function (FEV ₁)	4	166	Std. Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.37, 0.25]
13.1 Studies that reported postintervention values	2	83	Std. Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.41, 0.46]
13.2 Studies that reported mean change values	2	83	Std. Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.58, 0.29]
14 Lung function (FVC)	2	83	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.26, 0.15]

Analysis 1.1. Comparison 1 Exercise group versus control group, Outcome 1 Exercise capacity (VO₂peak in mL/kg/min).

Analysis 1.2. Comparison 1 Exercise group versus control group, Outcome 2 Exercise capacity (6MWD in metres).

Analysis 1.3. Comparison 1 Exercise group versus control group, Outcome 3 General health-related quality of life (SF-36 - physical component score).

Analysis 1.4. Comparison 1 Exercise group versus control group, Outcome 4 General health-related quality of life (SF-36 - mental component score).

Analysis 1.5. Comparison 1 Exercise group versus control group, Outcome 5 Disease-specific health-related quality of life (EORTC QLQ-C30 - global health).

**Analysis 1.6. Comparison 1 Exercise group versus control group, Outcome 6
Disease-specific health-related quality of life (EORTC QLQ C30 - functional scales).**

**Analysis 1.7. Comparison 1 Exercise group versus control group, Outcome 7
Disease-specific health-related quality of life (EORTC QLQ-C30 - symptoms scales).**

Analysis 1.8. Comparison 1 Exercise group versus control group, Outcome 8 Disease-specific health-related quality of life (EORTC QLQ-C30 - physical functioning).

**Analysis 1.9. Comparison 1 Exercise group versus control group,
Outcome 9 Force-generating capacity of peripheral muscle (quadriceps).**

Analysis 1.10. Comparison 1 Exercise group versus control group, Outcome 10 Force-generating capacity of peripheral muscles (handgrip).

Analysis 1.11. Comparison 1 Exercise group versus control group, Outcome 11 Dyspnoea.

Analysis 1.12. Comparison 1 Exercise group versus control group, Outcome 12 Fatigue.

Analysis 1.13. Comparison 1 Exercise group versus control group, Outcome 13 Lung function (FEV₁).

Analysis 1.14. Comparison 1 Exercise group versus control group, Outcome 14 Lung function (FVC).

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)

Appendix 3. Embase (via Ovid) search strategy

1. "lung cancer*".m_titl.

2. limit 1 to human

3. non-small cell.mp.

4. limit 3 to human

5. non small cell.mp.

6. limit 5 to human

7. Lung Neoplasms.mp.

8. limit 7 to human

9. Carcinoma, Non-Small-Cell Lung.mp.

10. limit 9 to human

11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10

12. exercis*.mp.

13. limit 12 to human

14. rehabilitat*.mp.

15. limit 14 to human

16. aerobic*.mp.

17. limit 16 to human

18. endurance/

19. limit 18 to human

20. strength*.mp.

21. limit 20 to human

22. inspiratory muscle*.mp.

23. limit 22 to human

24. respiratory muscle*.mp.

25. limit 24 to human

26. treadmill/

27. limit 26 to human

28. walking/

29. limit 28 to human

30. cycling/

31. limit 30 to human
32. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
33. training/
34. limit 33 to human
35. program*.mp.
36. limit 35 to human
37. 33 or 34 or 35 or 36
38. 11 and 32 and 37

FEEDBACK

Lack of reporting on adverse events, 4 April 2019

Summary

The Cochrane Lung Cancer consumer (André Stoop) as well as the Statistician (Marta Roque) the lack of reporting on adverse effects or harms related to the intervention.

Reply

We added "safety of the intervention" as a primary outcome as suggested in the document "Standards for planning, conduct and reporting of UPDATES of Cochrane Intervention reviews (U1-11, UR1-7)".

Contributors

All authors.

WHAT'S NEW

Date	Event	Description
10 April 2019	Feedback has been incorporated	New primary outcome included: safety of the intervention (i.e. adverse events related to the intervention).
11 February 2019	New search has been performed	Literature search ran on 11 February 2019.
11 February 2019	New citation required but conclusions have not changed	Five new studies included (Arbane 2014 ; Cavalheri 2017 ; Edvardsen 2015 ; Messaggi-Sartor 2018 ; Salhi 2015), resulting in a total of eight included studies. Background, analysis, 'Summary of findings' table, and conclusions updated. We have excluded the outcome 'development of a postoperative pulmonary complication' from the 2019 update. Two new authors added.

HISTORY

Protocol first published: Issue 7, 2012

Review first published: Issue 7, 2013

Date	Event	Description
21 July 2015	Amended	Contact details updated.

CONTRIBUTIONS OF AUTHORS

Vinicius Cavalheri: selection of studies, 'Risk of bias' assessment, data extraction, conduct of the analysis, and writing the final review paper.

Chris Burtin: selection of studies, 'Risk of bias' assessment, and writing the final review paper.

Vittoria R Formico: selection of studies, 'Risk of bias' assessment, data extraction, conduct of the analysis, and critical appraisal of the final review paper.

Mika L Nonoyama: methodological topics and critical appraisal of the final review paper.

Sue Jenkins: critical appraisal of the final review paper.

Martijn A Spruit: critical appraisal of the final review paper.

Kylie Hill: critical appraisal of the final review paper.

DECLARATIONS OF INTEREST

VC, KH, and SJ conducted a study that was included in this review ([Cavalheri 2017](#)). Consequently, the 'Risk of bias' assessment for that study was performed by CB and VRF.

Vinicius Cavalheri: none known

Chris Burtin: none known

Vittoria R Formico: none known

Mika L Nonoyama: none known

Sue Jenkins: none known

Martijn A Spruit: Prof Spruit discloses receiving personal remuneration for consultancy and/or lectures from Boehringer Ingelheim, AstraZeneca, and GSK outside the submitted work.

Kylie Hill: is a member of the Editorial Board for the *Journal of Physiotherapy*.

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Internal sources

- Curtin University, Perth, Australia.

External sources

- Cancer Council Western Australia, Australia.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We presented the results of the primary outcome 'exercise capacity' in a separate meta-analysis: one that included peak rate of oxygen uptake (VO₂peak) and a second one that included six-minute walk distance (6MWD). We added 'safety of the intervention' as a primary outcome as suggested in the document 'Standards for planning, conduct and reporting of UPDATES of Cochrane Intervention reviews (U1-11, UR1-7)' ([Chandler 2016](#)). We did not calculate risk difference, as no meta-analysis of dichotomous data was performed. We excluded the outcome 'development of a post-operative pulmonary complication' from the 2019 update, as we understand that postoperative exercise training in this population commences days or weeks after hospital discharge and hence cannot have an effect on the development of postoperative pulmonary complications. We added the visual analogue scale as a measure of dyspnoea. We divided the outcome health-related quality of life (HRQoL) into 'general HRQoL' and 'disease-specific HRQoL'. Due to changes such as separate meta-analysis for VO₂peak and 6MWD; the inclusion of 'safety of the intervention' as a primary outcome; the division of HRQoL into general HRQoL and disease-specific HRQoL; and the new findings of significant between-group difference in force-generating capacity of the peripheral muscles (quadriceps) and dyspnoea, new outcomes have been included in the 'Summary of findings' table. These include: (i) exercise capacity (both as VO₂peak and 6MWD); (ii) safety of the intervention; (iii) general HRQoL; (iv) force-generating capacity of the peripheral muscles (quadriceps); and (v) dyspnoea.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Female; Humans; Male