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Exercise Training for Patients Pre- and Postsurgically Treated for Non–Small Cell Lung Cancer: A Systematic Review and Meta-analysis

Hui-Juan Ni, MD[1], Bigyan Pudasaini, MD[1], Xun-Tao Yuan, MD[2], He-Fang Li, MD[3], Lei Shi, MD[4], and Ping Yuan, MD[1]

Abstract

Background. This meta-analysis examined the effects of exercise training on length of hospital stay, postoperative complications, exercise capacity, 6-minute walking distance (6MWD), and health-related quality of life (HRQoL) in patients following resection of non–small cell lung cancer (NSCLC). *Methods*. This review searched PubMed, EMBASE, and the Cochrane Collaboration data base up to August 16, 2015. It includes 15 studies comparing exercise endurance and quality of life before versus after exercise training in patients undergoing lung resection for NSCLC. *Results*. This review identified 15 studies, 8 of which are randomized controlled trials including 350 patients. Preoperative exercise training shortened length of hospital stay; mean difference (MD): −4.98 days (95% CI = −6.22 to −3.74, $P < .00001$) and also decreased postoperative complications for which the odds ratio was 0.33 (95% CI = 0.15 to 0.74, $P = .007$). Four weeks of preoperative exercise training improved exercise capacity; 6MWD was increased to 39.95 m (95% CI = 5.31 to 74.6, $P = .02$) .While postoperative exercise training can also effectively improve exercise capacity, it required a longer training period; 6MWD was increased to 62.83 m (95% CI = 57.94 to 67.72) after 12 weeks of training ($P < .00001$). For HRQoL, on the EORTC-QLQ-30, there were no differences in patients' global health after exercise, but dyspnea score was decreased −14.31 points (95% CI = −20.03 to −8.58, $P < .00001$). On the SF-36 score, physical health was better after exercise training (MD = 3 points, 95% CI = 0.81 to 5.2, $P = .007$) while there was no difference with regard to mental health. The I^2 statistics of all statistically pooled data were lower than 30%. There was a low amount of heterogeneity among these studies. *Conclusions*. Evidence from this review suggests that preoperative exercise training may shorten length of hospital stay, decrease postoperative complications and increase 6MWD. Postoperative exercise training can also effectively improve both the 6MWD and quality of life in surgical patients with NSCLC, but requiring a longer training period.

Keywords

exercise training, non–small lung cell cancer, rehabilitation, surgical resection, exercise endurance, health-related quality of life

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Introduction

Lung cancer has been the most common cancer worldwide for several decades. Its incidence is ever increasing[1] and is associated with the highest mortality.[2-4] Patients with lung cancer report poorer health-related quality of life (HRQoL) and a higher prevalence of psychological distress than patients with other types of cancer. The major components of lung cancer treatment are chemotherapy, radiotherapy and surgery.[5]

Non–small cell lung cancer (NSCLC) is common, with surgical resection being the treatment of choice for stage I to III cancers.[6] Exercise training may decrease the length of hospital

[1]Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China
[2]Weifang Traditional Chinese Hospital, Shandong, China
[3]Laian Maternal and Child Health Care and Family Plaining Service Center, Chuzhou, Anhui, China
[4]Zhejiang Cancer Hospital, Hangzhou City, Zhejiang, China

Corresponding Author:
Ping Yuan, Shanghai Pulmonary Hospital, Tongji University, School of Medicine, No. 507 Zhengmin Road, Shanghai 200433, China.
Email: yuanping6766@126.com
And Lei Shi, Zhengjiang Cancer Hospital,No, 38 Guangji Road, Hangzhou 310022, China.
Email: datouerzi_2005@163.com

stay and postoperative complications in such patients.[7] Several studies have already shown that exercise training improved exercise capacity and HRQoL in NSCLC patients who underwent surgery.[8-14] But the research has not disseminated into clinical practice and exercise training following lung resection is not yet routine.[15] Although research on exercise programs in people with surgery for NSCLC suggests exercise interventions are safe and likely to be effective, yet at the same time there is demand for more data from further randomized controlled trials.[16] The National Institute of Health and Clinical Excellence guidelines on lung cancer identified the need for further work to examine rehabilitation programs before and after surgery, stating that outcomes should include mortality, pulmonary complications, pulmonary function, and HRQoL assessment.[17] There are multiple published reports on the benefits of preoperative exercise training in lung cancer patients. It may shorten length of hospital stay, reduce postoperative complications. Postoperative exercise training can improve exercise capacity and quality of life as well. Although the topic is frequently studied it is unfortunate that the studies are varied due to small sample sizes and difference in their approaches. Data on the effects of exercise training prior to or after surgery in NSCLC patients are still limited.

Aims

Thus, this review performed a random effects meta-analysis of available past and current studies on exercise training in surgical NSCLC patients with the aim to ascertain the effectiveness of exercise rehabilitation prior to and after surgery.

Methods

The study was designed according to the standards set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[18]

Data Sources and Search

This review searched PubMed, EMBASE, and the Cochrane Collaboration databases using the key words "exercise training" or "rehabilitation," "physical training" or "physical exercise" and "non-small cell cancer." The search was limited to English language articles published by August 16, 2015.

Interventions and Outcome Measures

This review includes 15 studies comparing exercise endurance and HRQoL before and after exercise training in patients undergoing lung resection for NSCLC. Study inclusion criteria were the following: length of hospital stay, postoperative complications, 6-minute walk distance (6MWD), the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC-QLQ-C30),[19] and 36-Item Short Form Health Survey (SF-36).[20]

Patients managed in any setting, that is, hospital, community facility, or home were included if they received an exercise-based intervention that included at least an aerobic exercise training component performed by the lower limbs (bicycle, treadmill walking) lasting 1, 4, 12, or 20 weeks, either alone or as part of a comprehensive rehabilitation program defined as also including components of muscle training, breathing exercises, health education, and psychological treatment.

Reviews, editorials, letters, case reports, and conference abstracts were excluded. Studies were excluded if there was an overlap in patients with another study within the same analysis. Thus, if some patients could possibly have been included in both the controlled and uncontrolled study analyses, they were only included once in any given analysis. Therefore, there was no overlap in populations included in our meta-analyses.

Data Extraction and Assessment of Risk of Bias

Two reviewers (HJN, PY) independently extracted data from eligible studies. Disagreements were resolved by consensus. Data pertaining to baseline characteristics of study subjects (number of subjects, age, sex, type of patients), exercise training program, duration and follow up, 6MWD, length of hospital stay, post-operative complication, EORTC-QLQ-C30 score (global Health, dyspnea score) and SF-36 score (physical function and mental health) were extracted.

For randomized controlled trials (RCTs), risk of bias was assessed for the domains as suggested by the Cochrane Handbook of Systematic Reviews,[21] specifically emphasizing on sequence generation, allocation concealment, blinding, outcomes assessment, and selective reporting for the 8 randomized control trials included. For each criterion, risk of bias was assessed as (1) low risk of bias (adequate fulfillment of the respective criterion), (2) unclear (insufficient information to judge about fulfillment or nonfulfillment of the respective criterion), and (3) high risk of bias (inadequate fulfillment or nonfulfillment of the respective criterion).[21,22] Risk of publication bias was assessed for each meta-analysis that included at least 10 studies.[21] So this review did not detect clear publication bias as the numbers of included studies were small. As for the 5 single group trials (SGTs) and 2 controlled trials (CTs) reviewed, we used the Ottawa Quality Assessment Scale Cohort Studies. In the Newcastle-Ottawa Scale, studies are assigned up to 4 stars for selection, 2 for comparability, and 3 for outcome. For uncontrolled studies, the maximum available stars in the Newcastle-Ottawa scale is 3 for selection, 0 for comparability, and 3 for outcome.

Outcomes

The main outcome measure for the present analysis was length of hospital stay and postoperative complication. The

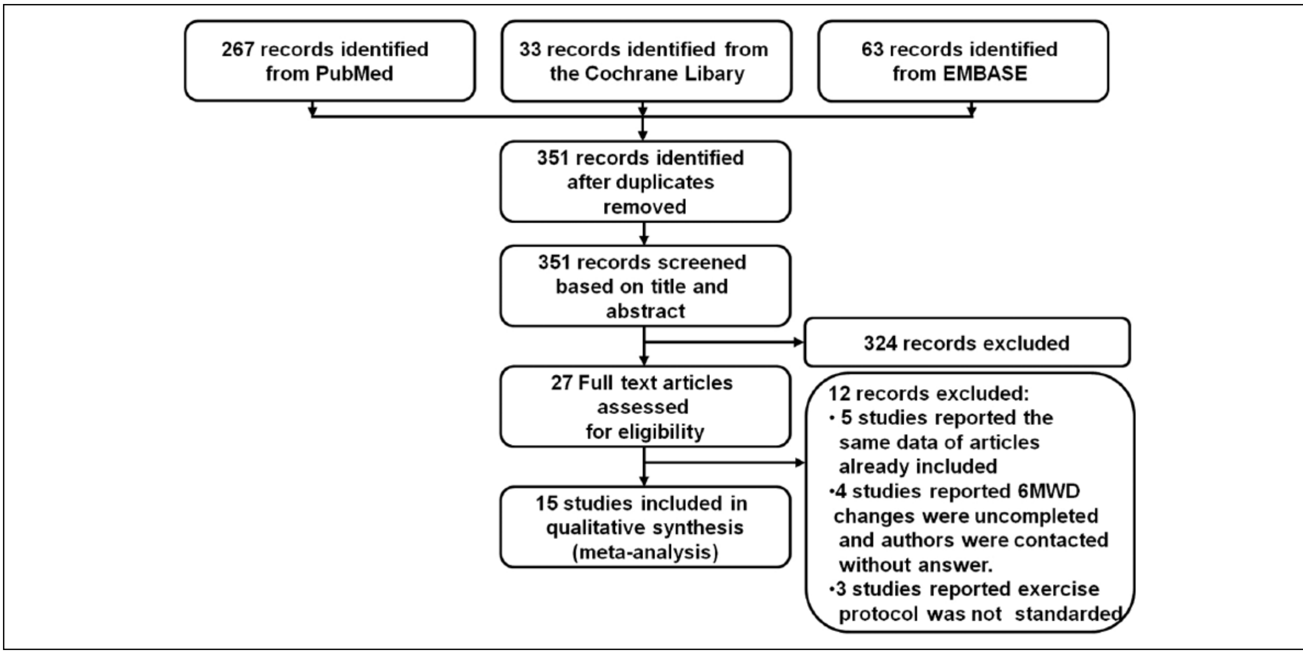

Figure 1. Flowchart showing the progress through the stages of meta-analysis.

following additional secondary parameters which were reported explicitly and clearly in part of the studies were also assessed: 6MWD, EORTC-QLQ-C30 score, and SF-36 score.

Data Synthesis and Statistical Analysis

The difference in change of length of hospital stay, postoperative complications, 6MWD, and EORTC-QLQ-C30 score and SF-36 score after exercise training versus control was pooled, stratified and analyzed using random-effects meta-analysis models with inverse variance weighting. The magnitude of heterogeneity present was estimated using the I^2 statistic, an estimate of the proportion of the total observed variance that is attributed to between study variance.

Pooled effects on hospital stay, postoperative complication, 6MWD, EORTC-QLQ-C30, score and SF-36 score were presented as weighted mean differences (MDs) or odds ratio (ORs) with corresponding 95% confidence intervals (CIs). This review considered $P < .05$ as significant. Throughout, values are presented as mean ± SD unless otherwise stated. Analyses were performed using the Cochrane Collaboration Review Manager (version 5.2, Cochrane Collaboration, Copenhagen, Denmark).

Results

Characteristics of the Studies

Of 351 articles identified initially, 27 were retrieved for more detailed evaluation, Subsequently, 15 studies (8 randomized controlled trials)[23-37] that included 350 patients were finally included in the analyses (Figure 1). Table 1 summarizes the design and methods of the included studies. The studies included patients with stage I to IV NSCLC. All the patients were adults referred for resection by thoracotomy or video-assisted thoracoscopic surgery. Some of them had chronic obstructive pulmonary disease. Eight studies including 238 patients delivered exercise training after surgery. Seven studies including 112 patients delivered exercise training before surgery. The exercise training program was largely similar, including bicycle, walking, breathing, and so on. Mean duration of the exercise training program was 8 ± 7 weeks (1, 4, 12, or 20 weeks). The mean age of subjects across studies ranged from 54 to 70 years.

For RCTs, evaluation of risk of bias of each trial and assessment of risk of bias by individual trials are illustrated in Figures 2 and 3, respectively. Three trials[23,24,28] had a high drop-out rate in the control group, but failed to address this incomplete outcome with intention-to-treat analysis. Four trials[24,25,27,29] were open to bias with false-positive results because of failure to blind participants in relation to intervention delivery. The risk of bias was low in the other studies; a detailed assessment is available in Table 2.

Effect of Exercise Training on Length of Hospital Stay and Postoperative Complications

Preoperative exercise training shortened the length of hospital stay. In 4 studies,[25-27,32] there was a marked decrease in length of stay of −4.98 days (95% CI = −6.22 to −3.74) after exercise training ($P < .00001$) (Figure 4A). No

Table 1. Participants in Reviewed Trials.

Study/First Author Year	Preoperative/ Postoperative	Type of Study	Control Patients (F), n	Training Patients (F), n	Type of Patients	Age (Years) Control Patients	Age (Years) Training Patients	Exercise Training	Frequency	Length of intervention	Duration and Follow up
Arbane 2011	Post	RCT	26	27	NSCLC, stage I-IV,100% post-surgical(open thoracotomy or VATS)	62.6 (32-47)	65.4 (47-82)	Resistance (weights) + aerobic (walking, marching, and recumbent bike)	2×/day	12 weeks (+5 days)	Aerobic 5-10 min for each component
Granger 2013	Post	RCT	8	7	suspected lung cancer (those confirmed ¼ 10(67%)), stage I-IV, surgery all patients	72.4 ± 12.4	57 ± 16.2	Aerobic (walking + cycling) + resistance (upper and lower) + stretching	2×/day until discharge then twice weekly	Postsurgery to discharge + 8 weeks outpatient	1 h
Stigt 2013	Post	RCT	26	23	NSCLC resectable, thoracotomy 4 weeks post-discharge	63.2 ± 10.3	63.6 ± 10.2	Aerobic (cycling) + resistance	2×/week	12 weeks	1 h
Edvardsen 2015	Post	RCT	31	30	NSCLC, stage I-IV,open thoracotomy or VATS. Stratified for receiving chemotherapy and having COPD	65.9 ± 8.5	64.4 ± 9.3	Aerobic (walking on treadmill) + resistance + muscle training	3×/week	20 weeks	1 h
Arbane 2014	Post	RCT	67	64	NSCLC，stage I-IV, surgery resection by thoracotomy or VATS	68 (11)	67 (11)	strength training + walking	Once daily	4 weeks	30 min
Benzo 2011	Pre	RCT	9	10	lung cancer resection by open thoracotomy or VATS and moderate-severe COPD	72 (6.69)	70.2 (8.61)	Aerobic (treadmill, step and arm ergometer) + resistance + breathing	2×/day over 5 days	1 week	20 min lower extremity + upper, extremity + strength, exercises + breathing, 20 min + education
Pehlivan 2011	Pre	RCT	30	30	NSCLC stageIA-IIIB, surgery (lobectomy/ pneumonectomy)	54.76 ± 8.45	54.1 ± 8.53	Aerobic (walking on treadmill + walking around the center) + breathing	3×/day walking + 2×/day chest physiotherapy	1 week preop until discharge	According to patient's tolerance
Morano 2013	Pre	RCT	12	12	NCSLC stage I-IIIA with pulmonary disease and impaired spirometry, surgical resection by thoracotomy or VATS	68.6 ± 7.3	64.8 ± 8	Strength and endurance + breathing + flexibility	5×/week	4 weeks	10 min increasing to 30 min + resistance training + 10-30 min of IMT

(continued)

Table 1. (continued)

Study/First Author Year	Preoperative/ Postoperative	Type of Study	Control Patients (F), n	Training Patients (F), n	Type of Patients	Age (Years) Control Patients	Age (Years) Training Patients	Exercise Training	Frequency	Length of intervention	Duration and Follow up
Sekine 2005	Pre	CT	60	22	NSCLC stage I-IV with COPD, thoracotomy	70.4 ± 4.6	69 ± 5.5	Breathing (incentive spirometry, abdominal breathing, huffing, and coughing) + aerobic (walking)	Daily (breathing 5× per day)	2 weeks	Breathing 15 min 5×/day + pulmonary exercises for 30 min and walking more than 5000 steps every day
Cesario 2007	Post	CT	186	25	NSCLC, Surgical (lateral muscle sparing thoracotomy)	NR	NR	Aerobic (cycling, walking) + breathing	5×/week	4 weeks	3 h
Coats 2013	Pre	SGT		13	under investigation for NSCLC (stage I-IV) awaiting surgical resection		59 ± 9	Aerobic (walking + cycling) + resistance	3-5×/week	4 weeks	Aerobic 30 min + muscle strength exercises
Jones 2007	Pre	SGT		25	suspected surgical lung cancer stage I-IIIA		65 ± 10	Aerobic (cycling)	5×/week on consecutive days	Until surgical resection, mean of 30 sessions	20-30 min + 5 min warm up and 5 min cool down
Peddle-McIntyre 2012	Post	SGT		17	94% NSCLC stage I-IIIB and limited stage SCLC, on average 3 and a half years post-surgical		66.7 (50-85)	Resistance + breathing + stretching	3×/week nonconsecutive days	10 weeks (28 sessions)	NR
Reisenberg and Lubbe 2010	Post	SGT		45	NSCLC stage I-IIIB+SCLC (2 limited an 1 extensive), undergone treatment (88% surgical); time since last treatment no more than 14 days		60.2 ± 8.0	Aerobic (cycling)	Daily	28 days	30 min per day interval training (3-5 min)
Jones 2008	Post	SGT		20	NSCLC stage I-IIIB, 80% surgery		62 ± 11	Aerobic (cycling)	3×/week on consecutive days	14 weeks	15-45 min increasing over 14 weeks

Abbreviations: CT, controlled trial; RCT, randomized controlled trial; SGT, single group trial; NSCLC, non–small cell lung cancer; SCLC, small cell lung cancer; COPD, chronic obstructive pulmonary disease; NR, not reported; IMT, inspiratory muscle training; VATS, video-assisted thoracoscopic surgery.

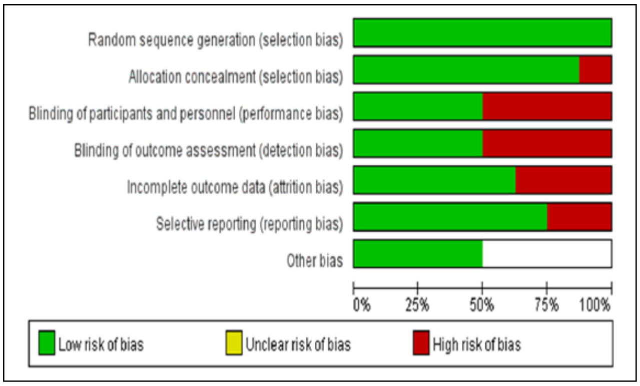

Figure 2. Overall risk of bias assessment using the Cochrane tool.

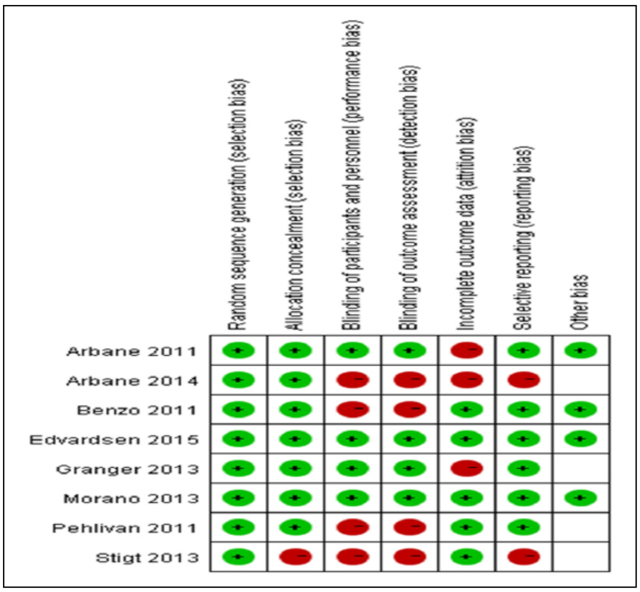

Figure 3. Risk of bias assessment by individual trials.

heterogeneity was apparent among studies (I^2 = 0%). Exercise training in these 4 studies,[25-27,32] also effectively decreased postoperative complications; the OR was 0.33 (95% CI = 0.15 to 0.74, P = .007) (Figure 4B). There was a low heterogeneity (I^2 = 7%) among these studies.

Effect of Exercise Training on 6-Minute Walk Distance

Preoperative exercise training improved exercise capacity in 3 studies,[26,33-34] 6MWD was increased to 39.95 m (95% CI = 5.31 to 74.6) after 4 weeks training (P = .02); there was no heterogeneity (I^2 = 0%) among these studies. While postoperative exercise training also effectively improved exercise capacity in the other 6 studies,[23,28,29,31,36,37] 6MWD was increased to 62.83 m (95% CI = 57.94 to 67.72) only after 12 weeks training (P < .00001). There was a low amount of heterogeneity (I^2 = 7%) among these studies. (Figure 5A and B).

Effect of Exercise Training on EORTC-QLQ-30 Score

Four studies reported global health score.[23,28,35,36] There was no alteration in patients' global health after exercise training, cumulative MD 2.4 points (95% CI = −2.9 to 7.7, P = .37).

However, low heterogeneity was apparent among studies (I^2 = 11%) (Figure 6A). Meanwhile, the other 3 studies reported the dyspnea score.[28,30,37] Exercise training decreased the dyspnea score to −14.3 points (95% CI = −20 to −8.6, P < .00001). There was a low heterogeneity (I^2 = 17%) between these studies (Figure 6B).

Effect of Exercise Training on HRQoL Questionnaire SF-36 Score

Four studies reported HRQoL Questionnaire SF-36 score (physical health)[28,30,35,36] and 3 reported the SF-36 score (mental health).[28,35,36] Although the SF-36 score improved with exercise training (MD = 3 points, 95% CI = 0.81 to 5.2, P = .007), there was no alteration in mental health of patients (MD = 1.9 points, 95% CI = −0.5 to 4.4, P = .12) (Figure 7A and B). No heterogeneity was related to both physical health and mental health (I^2 = 0%) (Figure 7A and B).

Discussion

This review aims to evaluate the effects of exercise training on length of hospital stay, postoperative complications, exercise capacity (6MWD) and HRQoL in patients following resection of NSCLC. Preoperative exercise training may shorten length of hospital stay, decrease postoperative complications, and increase the 6MWD. Although postoperative exercise training also effectively improved the 6MWD and quality of life in surgical patients with NSCLC, the time taken for improvement was longer.

Data from 15 studies (8 RCTs) and 350 patients were included, which is still a small number for a meta-analysis. It comprehensively represents, however, most of the published experience of exercise training in patients with NSCLC prior to and after resection. In a meta-analysis, especially when the outcome is continuous, the number of included studies is more important than the number of patients included.

The outcome is clear as the studies show preoperative exercise training shortens the length of hospital stay and decreases postoperative complications. The results show that preoperative exercise training may shorten length of

Table 2. Bias Assessment of Cohort and Uncontrolled Studies[a].

Study	Selection	Comparability	Outcome
Sekine 2005	☆☆☆	☆☆☆	☆☆☆
Cesario 2007	☆☆☆	☆☆	☆☆☆
Coats 2013	☆☆☆		☆☆
Jones 2007	☆☆☆		☆☆
Peddle-McIntyre 2012	☆☆☆		☆☆☆
Reisenberg and Lubbe 2010	☆☆☆		☆☆
Jones 2008	☆☆☆		☆☆

[a]The Ottawa Quality Assessment Scale Cohort Studies. In the Newcastle-Ottawa Scale, studies are assigned up to 4 stars for selection, 2 for comparability, and 3 for outcome. For uncontrolled studies, the maximum available stars in the Newcastle-Ottawa scale is 3 for selection, 0 for comparability, and 3 for outcome.

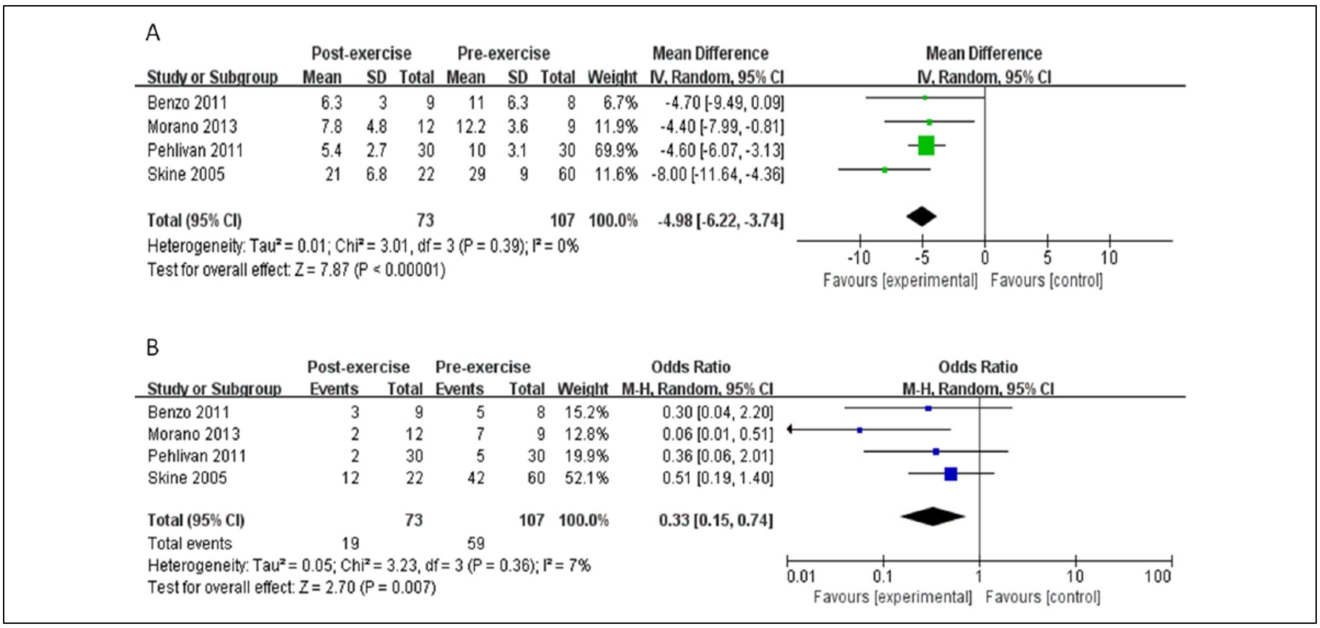

Figure 4. Meta-analysis of length of hospital stay and postoperative complication. (A) Changes of length of hospital stay after exercise training. (B) Changes of postoperative complication. CI, confidence interval(s); IV, inverse variance; SD, standard deviation; M-H, Mueller-Hinton.

hospital stay by −4.98 days. Arbane et al[23] reported that postoperative exercise training may shorten length of hospital stay by −2.1 days. Although more data are warranted, these results further strengthen the fact that preoperative exercise is more effective in shortening the length of hospital stay. Shortened hospital stay after exercise training may be associated with increased exercise capacity, increased muscle strength, reduced fatigue and improved pulmonary function.

The 6MWD was increased to 39.95 m after 4 weeks training (P = .02) in patients with preoperative exercise training, while postoperative exercise training also effectively improved the 6MWD to 62.83 m after 12 weeks training (P < .00001). This is consistent with the study of Cavalheri et al,[38] which showed that postoperative exercise training improves the 6MWD. This meta-analysis demonstrates that both preoperative and postoperative exercise training can increase exercise capacity. These very positive effects on recovery of patients may relate to the improvement of their cardiopulmonary function, leading to an improved exercise tolerance in these patients. Furthermore, our meta-analyses shows that postoperative exercise training was more effective than preoperative exercise training. This may indicate that early postoperative exercise training is more likely to prompt recovery of pulmonary function and motor function in patients than preoperative exercise training.

This review also suggests that exercise training conferred an improved quality of life for patients following lung resection for NSCLC including the EORTC-QLQ-30

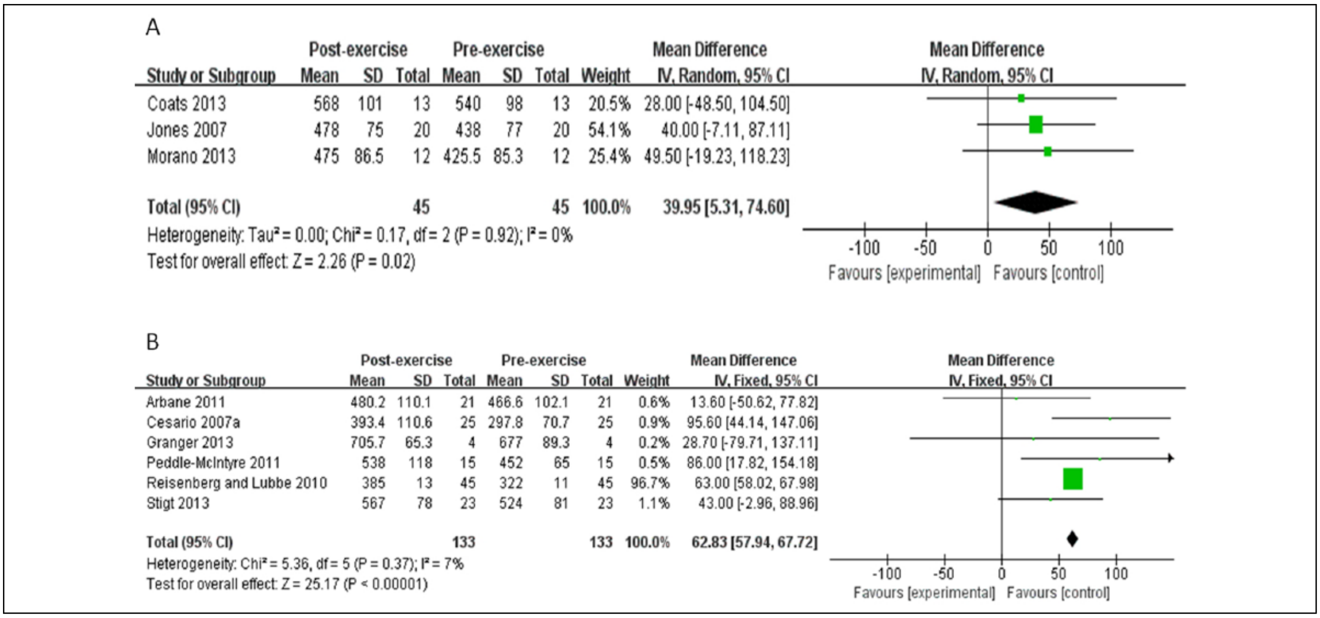

Figure 5. Meta-analysis of 6-minute walk distance (6WMD). It shows the changes of 6MWD stratified by follow-up time after exercise training. A demonstrates shows the changes of 6WMD in preoperative exercise training patients. B shows the changes of 6WMD in postoperative exercise training patients. CI, confidence interval; IV, inverse variance; SD, standard deviation.

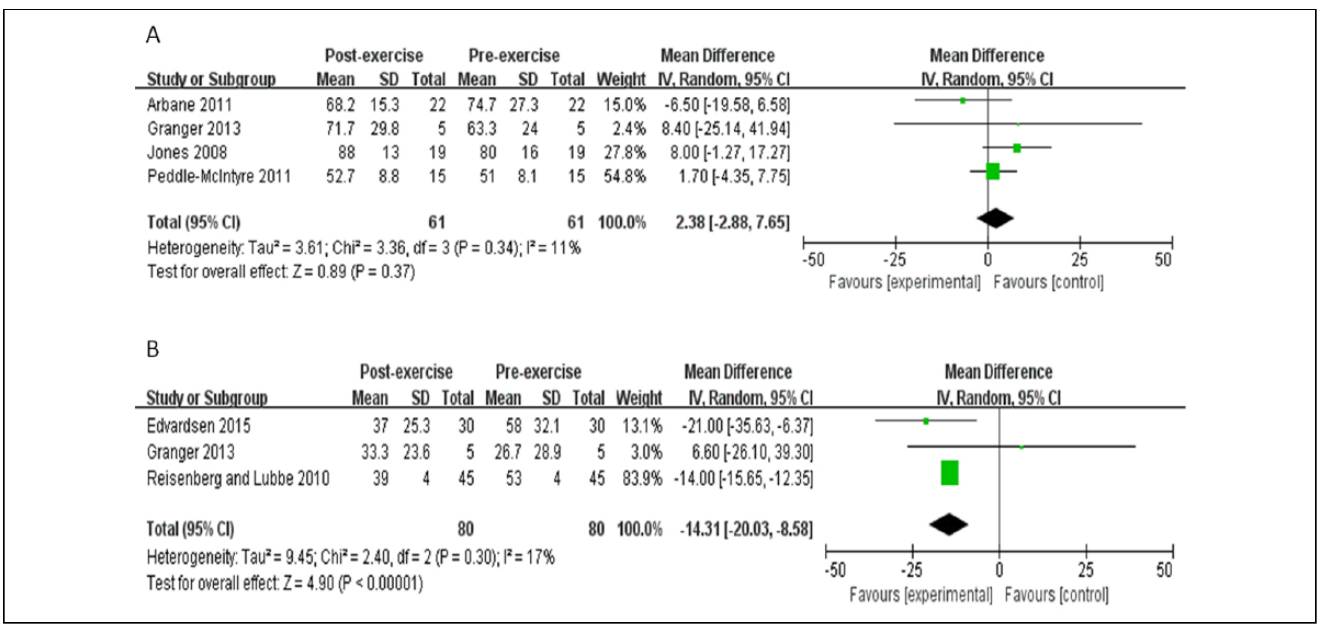

Figure 6. Meta-analysis of Quality of Life Questionnaire. (A) Changes of EORTC-QLQ-30 in global health. (B) Changes of EORTC-QLQ-30 in dyspnea score. CI, confidence interval; IV, inverse variance; SD, standard deviation.

and the SF-36 scores. On the EORTC-QLQ-30, global health was no different after exercise, but the dyspnea score was lower (MD = −14.3 points, 95% CI = −20 to −8.6, $P <$ .00001) after exercise. This demonstrates that exercise training improved dyspnea in postoperative patients. It is known that resistance training can increase peak oxygen uptake, especially in severely deconditioned adults.[39] Hagerman et al[40] showed that cancer patients' regained muscle mass, improved their performance of daily life activities, reduced cancer-related fatigue and improved HRQoL after whole-body resistance training. One of the possible reasons perhaps is that exercise training decreased

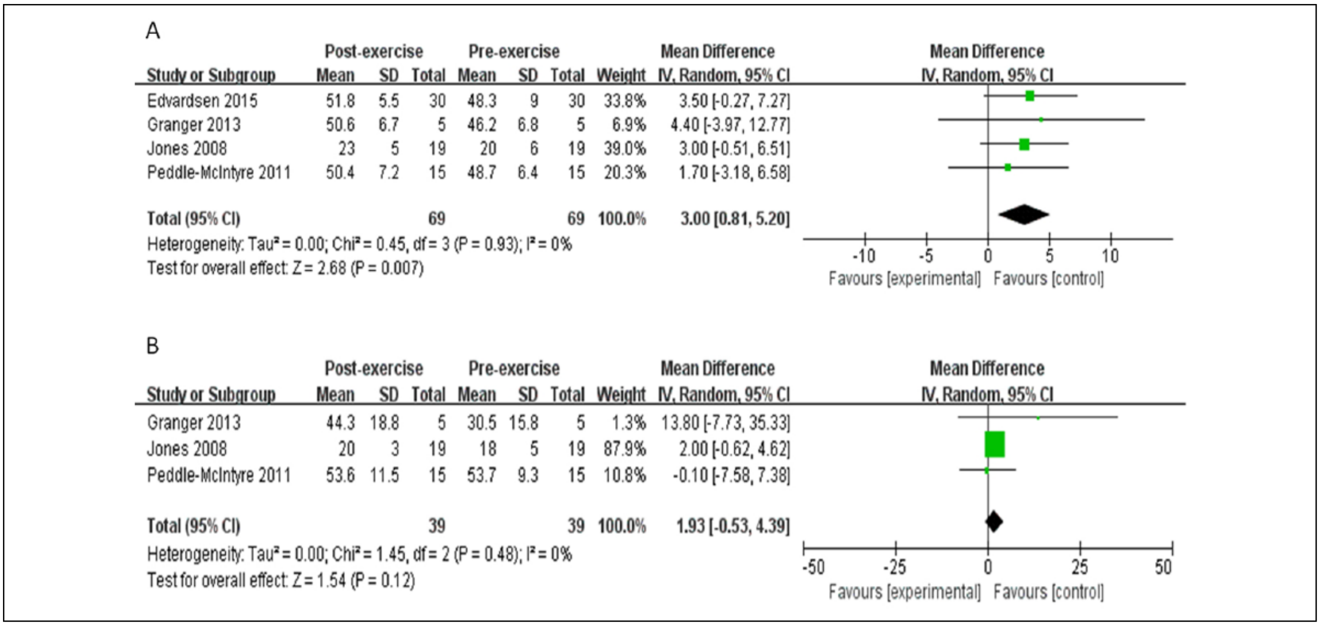

Figure 7. Meta-analysis of Quality of Life Questionnaire. (A) Changes of SF-36 score in physical health. (B) Changes of SF-36 score in mental health. CI, confidence interval; IV, inverse variance; SD, standard deviation.

the dyspnea score. The SF-36 score showed an improved physical health but had no effective in mental health of patients undergoing lung resection after exercise training. This outcome is different from that of Cavalheri et al.[38] They suggest that exercise training had little effect on HRQoL for people following lung resection for NSCLC. The article by Cavalheri et al[38] reviewed 3 studies measuring the HRQoL. One used the EORTC-QLQ-C30 (Arbane et al[23]), one used the St George's Respiratory Questionnaire (Stigt et al[29]), and one used the SF-36 (Brocki et al[41]). HRQoL in our article used the same measured parameter. The increased HRQol following exercise training may be related to increased muscle strength, reduced fatigue, and improved daily life activities. We recommend that future RCTs use equal measurement parameters in the relevant patient population.

Some of the included studies exposed some methodological flaws, thereby introducing high risk of biases into these trials, that is, some trials failed to blind research subjects, intervention delivery, and outcome assessors and some trials included insufficient sample sizes, which meant there was a potential risk of overestimating positive outcomes. Despite the difficulties, studies should blind the outcome assessors to minimize potential methodological biases. Therefore, the reliability of the evidence presented here is clearly limited.

Additionally, there were some other limitations to be considered when interpreting the results of this meta-analysis. First, there were not enough randomized controlled trials providing sufficient data on 6MWD and HRQoL. Second, inclusion was restricted to published studies and may therefore be affected by publication bias. Third, the follow-up rate was quite limited in many of the included studies. Most studies were short-term follow-ups of less than 3 months. Fourth, the exercise training programs was similar. However, the duration, intensity, frequency, and modality of exercise training varied between trials. The generalizability of our findings may therefore be limited. To improve generalizability, future exercise intervention trials should include larger, long-term, multicenter randomized controlled exercise training studies, which should include more data of quadriceps strength, forced expiratory volume in 1 second (FEV_1), and so on. Few of the included studies reported the actual level of exercise training undertaken by participants.

Conclusion

Preoperative exercise training may shorten length of hospital stay, decrease postoperative complications, and increase the 6WMD while postoperative exercise training effectively improves 6MWD and improves HRQoL in surgical patients with NSCLC. Larger RCTs with long-term follow-up are needed to confirm the sustained efficacy and safety of exercise training in such a patient population.

Declaration of Conflicting Interests

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