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Review Article

Effects of exercise prehabilitation and/or rehabilitation on health-related quality of life and fatigue in patients with non-small cell lung cancer undergoing surgery: A systematic review

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ABSTRACT

Background: This systematic review aimed to appraise the current available evidence regarding the effects of exercise prehabilitation and rehabilitation on perceived health-related quality of life (HRQoL) and fatigue in patients undergoing surgery for non-small cell lung cancer (NSCLC).
Methods: Studies were selected according to Cochrane guidelines and assessed for methodological quality and therapeutic quality (the international CONsensus on Therapeutic Exercise aNd Training (i-CONTENT)). Eligible studies included patients with NSCLC performing exercise prehabilitation and/or rehabilitation and postoperative HRQoL and fatigue up to 90-days postoperatively.
Results: Thirteen studies were included. Exercise prehabilitation and rehabilitation significantly improved postoperative HRQoL in almost half of the studies (47%), although none of the studies demonstrated a decrease in fatigue. Methodological quality and therapeutic quality were poor in respectively 62% and 69% of the studies.
Conclusion: There was an inconsistent effect of exercise prehabilitation and exercise rehabilitation on improving HRQoL in patients with NSCLC undergoing surgery, with no effect on fatigue. Due to the low methodological and therapeutic quality of included studies, it was not possible to identify the most effective training program content to improve HRQoL and reduce fatigue. It is recommended to investigate the impact of a high therapeutic qualified exercise prehabilitation and exercise rehabilitation on HRQoL and fatigue in larger studies.

1. Introduction

Lung cancer is the fourth most common type of cancer in the Netherlands with 14,573 newly diagnosed patients in 2020 [1,2]. Non-small cell lung cancer (NSCLC) concerns 85% of all patients with lung cancer [3]. According to European guidelines [4], surgery is advised for relatively fit patients with operable early-stage NSCLC. About half of the patients is aged 70 years or older and this proportion is expected to increase due to aging [5]. Characteristics of patients with NSCLC are smoking-related comorbidities, frailty, poor physical performance status, and long-term physical inactivity [6]. These characteristics can increase postoperative complications, and decrease survival and health-related quality of

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life (HRQoL) [7–9].

In addition, NSCLC and its treatment is often accompanied with physical and psychological symptoms. Pain, fatigue, insomnia, and/or mood disturbances are the four most commonly reported postoperative and distressing symptoms [10,11]. These symptoms can severely reduce perceived HRQoL and daily functioning after surgery [12]. This accounts especially for patients with NSCLC who are physically inactive and/or malnourished and therefore have a low physiological reserve capacity [6]. Prehabilitation (physical exercise training before surgery) and rehabilitation (physical exercise training after surgery) in patients with NSCLC are emerging disciplines, which may positively influence long-term HRQoL, fatigue, and exercise capacity [9,11,13,14]. Previous systematic reviews reported a minimal improvement in HRQoL after prehabilitation and/or rehabilitation in patients with NSCLC [15–17], with a limited number and low quality of evidence of included trials. However, systematic evidence regarding the effects of exercise prehabilitation and rehabilitation on HRQoL and fatigue in patients with NSCLC is scarce. Therefore, the aim of this study was to systematically review the literature regarding the effects of exercise prehabilitation and rehabilitation on perceived HRQoL and fatigue in patients undergoing surgery for NSCLC.

2. Methods

Cochrane and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed. The study protocol was registered at PROSPERO (CRD42018087073).

2.1. Data sources and searches

Articles were systematically searched in PubMed and EMBASE till May 2022. Search terms were related to the research question, including patients with NSCLC performing (a combination of) preoperative and/or postoperative aerobic exercise training, resistance exercise training, and breathing exercises in whom HRQoL and fatigue were assessed (see Supplementary file 1). No filters were applied for study design, and date, as this could eliminate useful articles.

2.2. Study selection

Randomized and non-randomized controlled trials in patients with NSCLC, aged ≥18 years, in which of ≥95% patients with NSCLC underwent elective surgery were included. Search results were combined and duplicates removed. Two reviewers (E.D. and R.R. until March 2018, M.V. and E.D. until May 2022) independently assessed titles, abstracts, and full texts regarding eligibility. Studies were included when patients were diagnosed with stage I-III NSCLC and participated in a physical exercise training intervention (aerobic exercise training, resistance exercise training, and/or breathing exercises) before and/or after surgery, that evaluated the effect on HRQoL and/or fatigue. Furthermore, only randomized controlled trials (RCT), cohort studies, or pilot studies written in English or Dutch were included. Studies were excluded when the physical exercise training intervention was not described or when studies were case reports or systematic reviews. Discrepancies between the three reviewers (M.V., E.D., and R.R.) were discussed until consensus.

2.3. Assessment of methodological quality

Three reviewers (M.V., E.D., and R.R.) independently assessed the methodological quality of included studies by means of the Cochrane risk of bias tool for randomized controlled trials II (RoB2) [18] and non-randomized controlled trials of interventions for non-RCTs (ROBINS-I) tool [19]. The RoB2 reviews six domains and the ROBINS-I tool reviews seven domains. In the RoB2 tool, each item was rated as 'high', 'low', or 'some'. In the ROBINS-I tool, each item was rated as 'low', 'moderate', serious', 'critical', or 'no information'. Discrepancies were resolved by consensus. If no consensus was reached, a fourth person acted as an adjudicator (M.J.).

2.4. Therapeutic quality

Therapeutic quality of exercise prehabilitation programs was assessed independently by the same reviewers (M.V., E.D.) using the international Consensus on Therapeutic Exercise aNd Training (i-CONTENT) tool [20]. Using the i-CONTENT tool, the following eight items were substantively described: 1) patient selection, 2) dosage of the exercise program, 3) type of the exercise program, 4) qualified supervisor, 5) type and timing of outcome assessment, 6) safety of the exercise program, and 7) adherence to the exercise program. A score could be given as low or high risk for ineffectiveness on each of the seven items. An overall risk of ineffectiveness was calculated based on the weight per item that applies to estimate the content of an exercise prehabilitation and/or rehabilitation program. The used criteria for grading the overall risk of ineffectiveness are shown in Table 1.

2.5. Data extraction

Information collected included the name of the first author, year of publication, number of participants, study design, used exercise intervention, age of participants, comorbidity, type of surgery, type and dosage of the exercise program (e.g., frequency, intensity, time, and type), qualified supervisor of the exercise program, type and timing of the outcome assessment, adherence to the physical exercise training sessions, and safety of the exercise program. The outcome measures HRQoL and fatigue were presented as reported in the original studies. A meta-analysis was intended to be performed by use of the Review Manager (version 5.4; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

3. Results

3.1. Study characteristics

3.1.1. Study selection

The PubMed and EMBASE search provided respectively 380 and 232 hits, and 247 hits were found through other sources. After removal of duplicates, there were 756 unique hits. The reasons for exclusion based on title, abstract, and full-text analyses are described in the PRISMA flow diagram (Fig. 1). After full-text review, thirteen studies [21–33] were included. Study designs included eight RCTs [22,25,26,28–30,32,33] and five cohort studies [21,23,24,27,31]. A total of 633 patients with lung cancer were included (98% NSCLC), consisting of patients with (pathological) stage I (33%), II (14%), III (4%), IV (1%), I-II (28%), I-IIIa (3%), or unknown stage of disease (15%). The sample size ranged from 9 to 101 participants, with an overall age-range between 44 and 79 years. Medical treatment consisted of surgery (99%) [21,22,24–33], whereas two studies included (palliative) chemotherapy and one study palliative chemoradiotherapy after surgery as well [23]. General characteristics of the included studies are described in Table 2. A meta-analysis could not be performed due to a lack of accurate reporting of HRQoL and fatigue outcomes and heterogeneity of the content of physical exercise training programs in the included studies.

Table 1
Interpretation of therapeutic quality of exercise prehabilitation, rehabilitation program, or a combination of prehabilitation and rehabilitation for patients with NSCLC scheduled for surgery, based on the i-CONTENT tool [20].

	Low risk of ineffectiveness	High risk of ineffectiveness
1. Patient selection	A VO_{2peak} < 20 mL/kg/min and/or a predicted postoperative VO_{2peak} < 10 mL/kg/min for prehabilitation or other selection criteria with a clear rationale for prehabilitation and/or rehabilitation.	No preselection or selection (described).
2. Dosage of the exercise program	Intensity and duration of the physical exercise training program must be clearly described and/or based on existing literature relevant to the target population of operable patients with NSCLC and/or an adequate exercise test (e.g., steep ramp test, CPET).	Intensity and duration of the physical exercise training program is not (adequately) described and/or no physiological improvement can be expected due to a low training dosage (frequency, intensity, time).
3. Type of the exercise program	At least aerobic training with or without resistance training.	An intervention inconsistent with the goal of training therapy for patients undergoing surgery for lung cancer.
4. Qualified supervisor (if applicable)	Guidance of a physical therapist who is specialized in supervising adult clinical populations.	Supervision or guidance is not reported or supervision or guidance was provided by a professional other than a physical therapist.
5. Type and timing of outcome assessment	Follow-up for HRQoL and/or fatigue before and after exercise prehabilitation and/or before and after exercise rehabilitation.	Follow-up for HRQoL and/or fatigue was not clearly described.
6. Safety of the exercise program	Adverse events related to the exercise program are described and acceptable as would be expected in the studied population.	Adverse events related to the exercise program are higher than would be expected in the studied population or adverse events were not described.
7. Adherence to the exercise program	Adherence was determined separately for training frequency and deemed good in case of ≥80%.	Adherence to the training frequency was <80%.

Abbreviations: CPET = cardiopulmonary exercise test; HRQoL = health-related quality of life; i-CONTENT = the international Consensus on Therapeutic Exercise aNd Training; NSCLC = non = small cell lung cancer; VO_{2peak} = oxygen uptake at peak exercise.

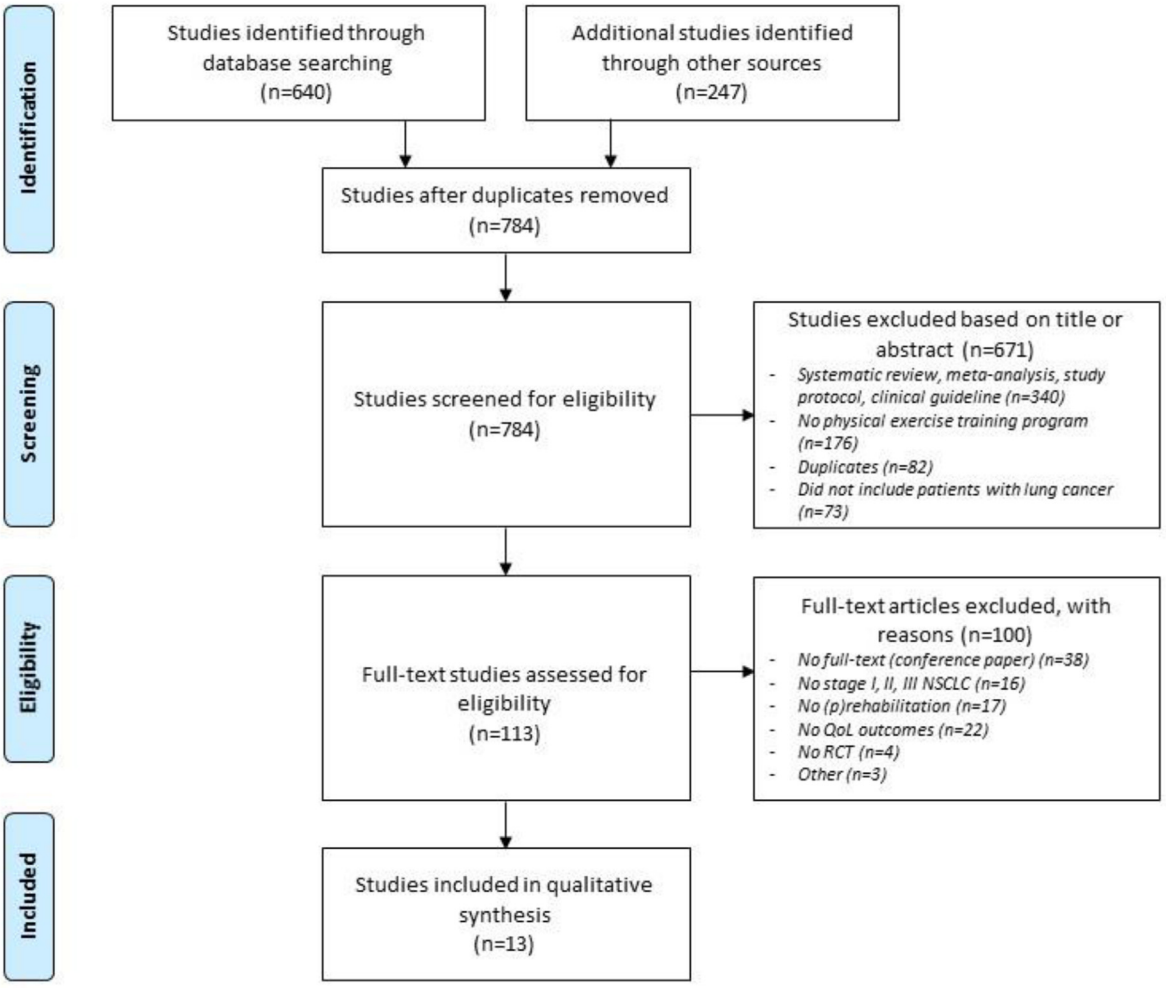

Fig. 1. PRISMA flow diagram displaying the selection of studies and reasons for exclusion.

Table 2
General characteristics of the included studies.

First author, year	Number of participants, n Study design Intervention	Stage of disease, n	Mean age, year, ±SD (range)	Comorbidity, n	Type of surgery, n	Outcome measures
Exercise prehabilitation						
Coats [23], 2013	• 13 • Prospective cohort • Aerobic exercises, resistance exercises	• I: 5 II: 4 IV: 2 Unknown: 2	59 ± 9	• COPD: 5 (38%)	• Awaiting surgery: 10 • CT: 1 • Postoperative palliative CT: 1 • Postoperative palliative RT and CT: 1	• HRQoL • Fatigue
Huang [25], 2017	• IG: 30, UC: 30 • RCT • Aerobic exercises, breathing exercises	• I: IG: 16, UC: 17 II: IG: 10, UC: 11 III: IG: 4, UC: 2	IG: 63.0 ± 8.7 UC: 63.6 ± 6.5	• ASA score >3: IG: 3 (10%), UC: 2 (7%), p = 1.00 • COPD: IG: 5 (17%), UC: 2 (7%), p = 0.49	• VATS: IG: 17, UC: 9 • Open surgery: IG: 13, UC: 11	• HRQoL • Fatigue
Lai [28], 2016	• IG: 30, UC: 30 • RCT	• I: IG: 16, UC: 18 II: IG: 10, UC: 10 III: IG: 3, UC: 2 IV: IG: 1, UC: 0	IG: 72.5, ±3.4 UC: 71.6, ±1.9 p = 0.23	• ASA score: IG: 3 (10%) UC: 3 (10%) (p 1.00) • COPD: IG: 5 (17%) UC: 4 (13%), p = 1.00	• VATS: IG: 21, UC: 20 • Open surgery: IG: 9, UC: 10	• HRQoL
Lai [29], 2017	• IG: 51, UC: 50 • RCT • Aerobic exercises, breathing exercises	• I: IG: 30, UC: 20 II: IG: 14, UC: 25 III: IG: 6, UC: 5 IV: IG: 1, UC: 0	IG: 63.8 ± 8.2 UC: 64.6 ± 6.6 p = 0.58	• Charlson comorbidity index 0−2: IG: 32 (63%), UC: 43 (86%), p = 1.00 • Charlson comorbidity ≥3: IG 18 (35%), UC: 7 (14%), p = 1.00	• VATS: IG: 32, UC: 34 • Open surgery: IG: 19, UC: 16	• HRQoL • COPD: IG: 9 (28%), UC: 11 (34%), p = 0.61
Lai [30], 2019	• IG: 32, UC: 32 • RCT • Aerobic exercises, breathing exercises	• I: NR	IG: 64.2 ± 6.8 UC: 63.4 ± 8.2 p = 0.67	• Hypertension: IG: 8 (25%), UC: 3 (9%), p = 1.00 • DM II: IG: 3 (9%), UC: 1 (3%), p = 0.61	• VATS	• HRQoL • Fatigue
Peddle [21], 2009	• 9 • Prospective cohort • Aerobic exercises, resistance exercises, breathing exercises	• NSCLC: 6 Kidney: 1 Hamartoma: 1 Spindle cell sarcoma: 1	64 ± 8 p = NR	• COPD: 3 (33%) • Charlson comorbidity index >3: (100%)	• Lobectomy: 6 • Pneumonectomy: 1 • Wedge resection: 2	• HRQoL • Fatigue
Sebio Garcia [22], 2017	• IG: 10, UC: 12 • RCT • Aerobic exercises, resistance exercises, breathing exercises	• NR	IG: 69.4 ± 9.4 UC: 70.9 ± 6.1	• Respiratory disease: IG: 7 (70%), UC: 4 (33%), p = NR • Cardiovascular disease: IG: 8 (80%), UC: 9 (75%), p = NR • DM II: IG: (10%), UC: 1 (8%), p = NR	• VATS	• HRQoL
Tenconi [33], 2021	• IG: 70, UC: 70 • RCT • Aerobic exercises, resistance exercises, breathing exercises, therapeutic education	• I and II: NR	IG: 66.0 ± 10.6 UC: 67.7 ± 10.8 p = NR	• NR	• VATS • RATS	• HRQoL
Exercise rehabilitation						
Jastrzebski [26], 2018	• IG: 22, UC: 21 • RCT • Aerobic exercises, resistance exercises, breathing exercises	• NR	IG: 69.8 ± 6.0 UC: 69.0 (±9.6) p = NR	• NR	• Lobectomy	• HRQoL
Lu [31], 2020	• 16 • Prospective cohort • Aerobic exercises, resistance exercises, Tai-Chi	• I, II, and IIIa: NR	59 (44−63) p = NR	• NR	• Lobectomy: 8 • Wedge resection: 3 • Segmentectomy: 2 • Lobectomy and wedge resection: 3 • Segmentectomy and wedge resection: 1	• HRQoL • Fatigue
Messagi-Sartor [32], 2019	• IG: 16, UC: 21 • RCT • Aerobic exercises, breathing exercises	• I and II: NR	IG: 64.2 ± 8.1 UC: 64.8 ± 8.9 p > 0.05	• COPD (27%): IG: NR, UC: NR	• VATS: IG: 2, UC: 1 • Thoracotomy: IG: 14 UC: 20	• HRQoL • Fatigue
Combination of exercise prehabilitation and exercise rehabilitation						
Granger [24], 2018	• 37 • Prospective cohort • Aerobic exercises, resistance exercises	• I: 22 II: 5 III: 2 IV: 3 Unknown: 5	62.7 ± 10.5 P=NR	• NR	• Lobectomy: 20 • Wedge resection: 10 • Segmentectomy: 3	• HRQoL • Fatigue

Table 2 (*continued*)

First author, year	Number of participants, n Study design Intervention	Stage of disease, n	Mean age, year, ±SD (range)	Comorbidity, n	Type of surgery, n	Outcome measures
					• Pneumonectomy: 2 • Other: 2	
Kadiri [27], 2019	• 31 • Prospective cohort • Aerobic exercises, resistance exercises	• NSCLC: 17 Stage IV NSCLC: 1 Other lung cancer type: 7 Benign: 6	64 ± 12	• Ischemic heart disease: 2 (6%) • COPD: 9 (29%)	• NR	• HRQoL • Fatigue

Abbreviations: ASA = American Society of Anesthesiologists; DM = diabetes mellitus; COPD = chronic obstructive pulmonary disease; CT = chemotherapy; HRQoL = health-related quality of life; IG = intervention group; NR = not reported; NSCLC = non-small cell lung cancer; RATS = robot assisted thoracic surgery; RCT = randomized clinical trial; RT = radiotherapy; SD = standard deviation; UC = usual care group; VATS = video-assisted thoracic surgery.

3.1.2. Exercise prehabilitation and rehabilitation

Patients followed exercise prehabilitation in eight studies [21–23,25,28–30,33], exercise rehabilitation in three studies [26,31,32], and a combination of exercise prehabilitation and rehabilitation in two studies [24,27]. The postoperative follow-up time differed between 21 days [26], 30 days [21,22,25,27–30,33], two months [21,24,32], three months [22,31], and six months [32], whereas one study did not describe the length of postoperative follow-up [23]. Physical exercise training interventions included aerobic exercise training [21–33], resistance exercise training [21–24,26,27,31,33], and breathing exercises [22,25,26,28–30,32,33]. The intervention period for exercise prehabilitation lasted one week [25,28–30], two weeks [33], or four weeks [23], whereas this was two weeks [26] or eight to twelve weeks [31,32] for exercise rehabilitation and nine weeks for a combination of exercise prehabilitation and rehabilitation [24]. The number of sessions varied from two or three times a day for breathing exercises [25,31–33], three to five times a week for aerobic, resistance, and breathing exercises [21–24,26], and six or seven times a week for aerobic and breathing exercises [27–30], with a training session duration between 30 and 90 min. All physical exercise training interventions were prescribed at a moderate or high training intensity. Supervision of the intervention was applied by physical therapists [21,22,24,30,31,33], trained nurses [25,29,30], or a consult by phone [23]. The content of exercise prehabilitation and/or rehabilitation programs is reported in Table 3.

3.1.3. Methodological quality

Results addressing the methodological quality of the included studies are depicted in Table 4. Of the included RCTs, three studies [25,29,32] scored a low risk of bias, four studies [22,28,30,33] were classified as having some risk of bias, and one study [26] as having a high risk of bias. Often, studies showed an unclear description of the randomization process (n = 5), unclear assignment to intended interventions (n = 4), and poor adherence to the intended interventions (n = 6). Of the five included observational studies, four [23,24,27,31] showed a moderate risk of bias and one [21] a serious risk of bias. The latter was mainly caused by a high risk on the items confounding (n = 5), patient selection (n = 3), and a poor description of the intervention classification (n = 1).

3.1.4. Therapeutic quality

Results of the therapeutic quality assessment of the physical exercise training programs are depicted in Table 4. Four studies [25,29,32,33] (38%) scored some risk of ineffectiveness and nine studies [21–24,26–28,30,31] (62%) a high risk of ineffectiveness. Often, physical exercise training programs scored a high risk of ineffectiveness on the items patient selection (n = 9), description of the dosage of the physical exercise training program (n = 10), type and timing of the outcome assessment (n = 6), and low adherence to the program (n = 5).

3.2. Health-related quality of life and fatigue

Effects of exercise prehabilitation and/or rehabilitation on HRQoL and fatigue are shown in Table 5. HRQoL was the primary outcome in four studies [21–23,32] and a secondary outcome in nine studies [24–31,33]. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ- C30) questionnaire for HRQoL was used in nine studies [23–25,27–32], whereas the short form 36 questionnaire (SF-36) was used in two studies [22,26], and both the functional assessment of cancer therapy-lung (FACT-L) [21] and short-form 12 questionnaire (SF-12) in one study [33]. Fatigue was measured with the EORTC QLQ- C30 subscale for fatigue in five studies [23,24,27,31,32], the fatigue index in two studies [25,30], and the FACT-L subscale for fatigue in one study [21].

3.2.1. Exercise prehabilitation

Six RCT's [22,25,28–30,33] and two prospective cohort studies [21,23] investigated the effect of exercise prehabilitation on HRQoL. One study [21] showed that exercise prehabilitation significantly improved HRQoL on the EORTC-QLQ-C30 lung cancer subscale. Other studies found a significantly higher overall HRQoL measured with the EORTC-QLQ-C30 [25], emotional function on the EORTC-QLQ-C30 [30], and a significant improvement in the physical component summary on the SF-36 [22] after exercise prehabilitation as compared to the usual care group. Fatigue was measured in four studies [21,23,25,30] with the subscale fatigue on the EORTC QLQ-C30, the fatigue index in two studies [25,30], and with the FACT-L subscale for fatigue in one study [21], in which there was no statistically significant effect of exercise prehabilitation on fatigue.

3.2.2. Exercise rehabilitation

Two RCTs [26,32] and one prospective cohort study [31] investigated the effect of exercise rehabilitation on HRQoL. The subscales 'global quality of life' and 'emotional functioning' of the EORTC-QLQ-C30 significantly improved during exercise rehabilitation [31]. These subscales improved in the exercise rehabilitation group compared to usual care in one study [26]. Fatigue was measured in two studies by the EORTC QLQ-C30 [31,32], in which there was no statistically significant effect of exercise rehabilitation on fatigue.

3.2.3. Combination of exercise prehabilitation and rehabilitation

In two prospective cohort studies [24,27], HRQoL was measured with the EORTC-QLQ-C30. One of these studies [27] showed an

Table 3
Content of exercise prehabilitation and rehabilitation according to the items of therapeutic quality.

First author, year	Patient selection	Type and dosage of the preoperative exercise program (F: Frequency, I: intensity, T: Time, T: Type)	Qualified supervisor	Primary outcome of the study Type and timing of outcome assessment	Safety
Exercise prehabilitation					
Coats [23], 2013	45−80 years, SpO_2 <80% during CPET, comorbidities	• Based on: NR • Program duration: 4 weeks **Aerobic exercises**: **F**: 3−5/week, **I**: 60−80% of CPET WR_{peak}, with reduction of intensity in case of a 1−10 Borg dyspnea scores ≥6, **T**: 30 min, **T**: Cycle ergometer **Resistance exercises**: **F**: 3−5/week, **I**: 2−3 kg, progressively increasing, **T**: 2 × 10−15 repetitions, **T**: gravity-resisted exercises	Consult by phone by the researchers	• HRQoL • HRQoL and fatigue: at baseline and after four weeks (before surgery)	No adverse events
Huang [25], 2017	>70 years, BMI >30, COPD with heavy smoking history, FEV_1/FVC ratio ≤70%	• Based on: NR • Program duration: 1 week **Aerobic exercises**: **F**: 7/week, **I**: Own speed and power, progressively increased the resistance range, **T**: 20 min, **T**: cross-trainer **Breathing exercises**: **F**: 2−3/day, **I**: NR, **T**: 15−20, **T**: threshold inspiratory muscle trainer	Trained nurses	• Postoperative pulmonary complications • HRQoL and fatigue: at baseline and after one week (before surgery)	NR
Lai [28], 2016	≥70 years	• Based on: NR • Program duration: 1 week **Aerobic exercises**: **F**: 1/day, **I**: self-preferred speed and power, **T**: 30 min, **T**: cross-trainer	Aerobic exercises supervised by a physical therapist	• Change in 6MWD • HRQoL: at baseline and after one week (before surgery)	NR
Lai [29] 2017	>75 years, >20 pack-year smoking history, BMI >30 kg/m^2, ppoFEV_1 <60%, ppoDLCO <60%, COPD	• Based on: NR • Program duration: 1 week **Aerobic exercises**: **F**: 1/day, **I**: not clearly reported, **T**: 30 min, **T**: cross-trainer Breathing exercises: **F**: 2−3/day, **I**: NR, **T**: 15−20 min, **T**: threshold inspiratory muscle trainer and manual deep breathing exercises	Physical therapist dedicated to thoracic surgery patients	• Postoperative pulmonary complications • HRQoL: at baseline and after one week (before surgery)	No adverse events
Lai [30] 2019	45−80 years and ppoFEV_1 <60%	• Based on: NR • Program duration: 1 week **Aerobic exercises**: **F**: 7/week, **I**: NR, **T**: 30 min, **T**: cross-trainer **Breathing exercises:** **F**: 3/day, **I**: NR, **T**: 20 breaths/session, **T**: threshold inspiratory muscle trainer	Aerobic exercises supervised by a physical therapist, respiratory exercises supervised by a trained nurse	• Postoperative pulmonary complications • HRQoL and fatigue: at baseline and after one week (before surgery)	No adverse events
Peddle [21], 2009	≥18 years	• Based on: NR • Program duration: NR **Aerobic exercises**: **F**: 5/week, **I-T**: week 1: increasing duration and intensity from 20 min at 60% of CPET VO_{2peak} to 30 min at 65% of CPET VO_{2peak}, weeks 2 and 3: 4 sessions of 25−30 min at 60−65% of CPET VO_{2peak} and 1 session of 20 min at the ventilatory anaerobic threshold. After week 3: 3 sessions of 60−65% of CPET VO_{2peak} for 30 −35 min, 1 threshold workout, and 1 interval workout per week, **T**: cycle ergometer	Exercise physiologist	• HRQoL and fatigue • HRQoL and fatigue: at baseline and after prehabilitation (before surgery)	No adverse events
Sebio Garcia [22], 2017	≥18 years, at least one of the following: (a) FEV_1 ≤80% of predicted value or BMI ≥30 or age ≥75 years or two or more co-morbidities identified in the Colinet Comorbidity Score	• Based on [40] • Program duration: NR **Aerobic exercises**: **F**: 3−5/week, **I**: interval training (1 min at high intensity (80% of CPET WR_{peak}) plus 4 min of active rest (performed at 50% of CPET WR_{peak}), **T**: 30 min, **T**: cycling **Resistance exercises:** **F**: 3−5/week, **I**: 25 repetition maximum test, **T**: 3 × 15 repetitions,	Physical therapist	• HRQoL • HRQoL: at baseline and after prehabilitation (before surgery)	No adverse events

Table 3 (*continued*)

First author, year	Patient selection	Type and dosage of the preoperative exercise program (F: Frequency, I: intensity, T: Time, T: Type)	Qualified supervisor	Primary outcome of the study Type and timing of outcome assessment	Safety
		T: six exercises using Thera bands and body mass for the large muscle groups **Breathing exercises:** **F**: 2/day, **I**: 80% of vital capacity, **T**: 6 cycles of 5 repetitions, **T**: incentive spirometry coach2			
Tenconi [33], 2021	All patients	• Based on [41] • Program duration: 2–3 weeks **Aerobic exercises**: **F**: 2–3/week, **I**: NR, **T**: 30–40 min, **T**: at the outpatient clinic: cycling; home-based: walking **Resistance exercises**: **F**: 2–3/week, **I**: maximal load (previously determined with the 10-repetition maximum test), **T**: 2–3 sets of 10 repetitions, **T**: lower limbs (extensor muscle group), upper limbs (biceps, triceps, deltoids, latissimus dorsi, pectoralis), and abdominal wall **Breathing exercises**: **F**: 1/day, **I**: ≥30% of maximal predicted inspiratory pressure and adapted to the patient's tolerance, **T**: 15–30 min, **T**: threshold inspiratory muscle trainer	Physical therapist	• Change in 6MWD • HRQoL: at baseline and 6 months after surgery	Adverse events: IG: 2 (7%): mild, 17 (55%): moderate, 11 (37%): severe, UC: 2 (4%): mild, 37 (69%): moderate, 15 (28%): severe
Exercise rehabilitation					
Jastrzebski [26], 2018	ECOG 0-1	• Based on: NR • Program duration: 2 weeks, 10 (±4) weeks after surgery **Aerobic exercises**: **F**: 5/week, **I**: 30–80% of HR_{peak}, **T**: 20–30 min, **T**: cycle ergometer or treadmill **Resistance exercises**: **F**: 5/week, **I**: 40–70% of 1RM, **T**: NR, **T**: Nordic walking **Breathing exercises**: **F**: 5/week, **I**: NR, **T**: 30, **T**: breathing, a prolonged exhalation exercise, and chest percussion	NR	• Change in 6MWD and HRQoL • HRQoL: at the first day of exercise rehabilitation and after exercise rehabilitation at day 21	Minor adverse events: arthritis: n = 1, knee pain: n = 2
Lu [31], 2020	18–75 years, ECOG 0-2	• Based on: NR • Program duration: 12 weeks, 6–12 weeks after surgery **Aerobic exercises**: **F**: 2/week, **I**: 15 min on 80% of baseline mean walk speed on the 6MWT and increased at moderate intensity (Borg-score 4–10, somewhat hard), **T**: 90 min, **T**: treadmill **Resistance exercises**: **F**: NR, **I**: Borg-score 4–10, somewhat hard, **T**: 3 sets of 8–15 repetitions, **T**: major limb movement	Specialized physical therapist	• Feasibility and safety of delivering rehabilitation • HRQoL and fatigue: at the start of exercise prehabilitation and after exercise rehabilitation at 12 weeks	No adverse events
Messagi-Sartor [32], 2019	<80 year	• Based on: NR • Program duration: 8 weeks, 6 weeks after surgery **Aerobic exercises**: **F**: 3/week, **I**: 60% of baseline WR_{peak} on the CPET, **T**: 30 min, **T**: cycle ergometer **Breathing exercises**: **F**: 3/**week**, 2/day, **I**: 50% of PI_{max} and PE_{max} and adjusted weekly by 10 cm cm H_2O, **T**: 5 sets of 10 repetitions, **T**: inspiratory and expiratory muscle trainer	Physical therapist	• HRQoL • HRQoL and fatigue: at the start of exercise rehabilitation and after exercise rehabilitation at 8 weeks	No adverse events

(*continued on next page*)

Table 3 (*continued*)

First author, year	Patient selection	Type and dosage of the preoperative exercise program (F: Frequency, I: intensity, T: Time, T: Type)	Qualified supervisor	Primary outcome of the study Type and timing of outcome assessment	Safety
Combination of exercise prehabilitation and rehabilitation					
Granger [24]	≥18 years	• Based on: NR • Program duration: 9 weeks: ≤7 days preoperative and until 8 weeks postoperative **Aerobic exercises**: **F**: 5/week, **I**: moderate, **T**: 30 min, **T**: walking **Resistance exercises**: **F**: 3/week, **I**: moderate (1–10 Borg dyspnea scale 4–6, somewhat hard), **T**: 2 sets of 10–15 repetitions, **T**: major muscle groups	Specialized physical therapist	• Feasibility and safety of delivering prehabilitation and rehabilitation • HRQoL and fatigue: at baseline before prehabilitation (before surgery) and at 8 weeks after rehabilitation (after surgery)	No adverse events
Kadiri [27], 2019	All patients	• Based on [42] • Program duration: NR **Aerobic exercises F**: 1/day, **I**: a target heart rate (>60% of maximum heart rate), **T**: at least 20 min, **T**: walking, swimming, exercise classes or cycling **Resistance exercises:** **F**: 1/day, **I**: a target heart rate (>60% of maximum heart rate), **T**: 10 × 3 min per exercise, **T**: upper and lower limb	Physical therapist	• Postoperative pulmonary complications and length of hospital stay • HRQoL and fatigue: at baseline (before surgery) and 6 weeks after rehabilitation (after surgery)	No adverse events

Abbreviations: 1RM = one-repetition maximum; 6MWT = 6-min walk test; 6MWD = 6-min walk distance; BMI = body mass index; COPD = chronic obstructive pulmonary disease; CPET = cardiopulmonary exercise test; IG = intervention group; HR_{peak} = heart rate at peak exercise; HRQoL = health-related quality of life; ECOG = Eastern cooperative oncology group; FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; NR = not reported; PI_{max} = maximal inspiratory mouth pressure; PE_{max} = maximal expiratory mouth pressure; ppoDLCO = predicted postoperative diffusing capacity of the lung for carbon monoxide; $ppoFEV_1$ = predicted postoperative forced expiratory volume in 1 s; SpO_2 = peripheral oxygen saturation; UC = usual care; VO_{2peak} = oxygen uptake at peak exercise; WR_{peak} = work rate at peak exercise.

improvement in HRQoL five months after combined exercise prehabilitation and rehabilitation compared to preoperative HRQoL. Fatigue was measured in both studies by the EORTC QLQ-C30 [24,27] in which there was no statistically significant effect of exercise prehabilitation and rehabilitation on fatigue.

4. Discussion

The aim of this systematic review was to appraise current available evidence regarding the effects of exercise prehabilitation and rehabilitation on perceived HRQoL and fatigue in patients undergoing surgery for NSCLC. Half of studies that applied exercise prehabilitation or exercise rehabilitation reported small statistically significant improvements in HRQoL, but in most studies this only concerned different subscales of the used questionnaire which make the clinical usefulness of the changes unclear. None of the studies reported a statistically significant decrease in fatigue. Due to the large heterogeneity of physical exercise training programs, the short intervention duration in some studies, the generally high risk of bias concerning methodological quality, and the high risk of ineffectiveness regarding therapeutic quality in most studies, the results of this systematic review must be interpreted with caution.

This is the first systematic review that examined the effect of exercise prehabilitation and/or rehabilitation on postoperative HRQoL and fatigue thereby accounting for the quality of the exercise intervention (i-CONTENT tool). Regardless of the risk of ineffectiveness score for the applied prehabilitation and/or rehabilitation programs, there was an inconsistent effect of exercise prehabilitation and/or rehabilitation on HRQoL. Heterogeneity across the items of the i-CONTENT tool, along with the risk of bias regarding HRQoL and fatigue, influences the certainty ratings supporting the efficacy and effectiveness of exercise prehabilitation and/or rehabilitation. Previous systematic reviews also reported a minimal improvement in HRQoL after prehabilitation and/or rehabilitation in patients with NSCLC undergoing surgery [15–17], which is possibly caused by the limited number and the low quality of evidence of included trials. In addition, in this systematic review, the duration of the exercise program was only one week in four studies [25,28–30] and two weeks in two studies [26,33]. In a previous systematic review [34] in which exercise training was performed by patients with NSCLC undergoing surgery, a duration of an exercise program of at least four weeks was recommended to improve HRQoL. Thus, those programs with a duration of merely one or two weeks might not be expected to improve HRQoL. In a previous study [35], it was reported that regained muscle mass associated with aging improved a patient's performance of activities of daily living, reduced cancer-related fatigue, and improved HRQoL after sixteen-weeks whole-body resistance training. Moreover, in a qualitative study [36] among patients with NSCLC, benefits of exercise rehabilitation were reported by participants such as improvements in muscle strength, aerobic fitness, and motivation, making sense of a goal that prevented boredom, feeling more prepared for future challenges, and improved ability to manage surgery-related symptoms. Most participants reported the exercise program to be feasible and to appreciate the individualized prescription and monitoring support from experienced physical therapists, as well as partly supervised exercises in a home-based setting [36]. Furthermore, fatigue is one of the most frequently mentioned barriers to adherence to exercise interventions among patients with lung cancer [17,37]. Exercises or tools decreasing these symptoms are very important for both patients and clinicians to incorporate as goals in the exercise intervention [17,37].

4.1. Strengths and limitations

A strength of this study was the use of i-CONTENT tool, leading to a more appropriate evaluation of the quality of the interventions next to methodological quality applied despite the heterogeneity of

Table 4
Results of methodological quality according to the Cochrane risk of bias tool and the Robins-1 tool, and therapeutic quality according to the i- CONTENT tool.

Methodological quality (Cochrane risk of bias tool)

First author	Randomization process	Assignment to intended interventions	Adherence to intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall risk of bias
Exercise prehabilitation							
Huang [25]	Low	Low	Low	Low	Low	Low	Low
Lai [28]	Some	Low	High	Low	Low	Low	Some
Lai [29]	Low	High	High	Low	Low	Low	Low
Lai [30]	Some	Some	High	Low	Low	Low	Some
Sebio Garcia [22]	Some	High	Low	High	Low	Low	Some
Tenconi [33]	Some	Some	Some	Low	Low	Some	Some
Exercise rehabilitation							
Jastrzebski [26]	High	Low	High	high	High	High	High
Messagi-Sartor [32]	Low	Low	High	Low	Low	Low	Low

Methodological quality (Robins-1 tool)

First author	Confounding	Selection	Intervention classification	Deviation from interventions	Missing outcome data	Measurement of outcome	Selection of reported results	Overall risk of bias
Exercise prehabilitation								
Coats [23]	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
Peddle [21]	Moderate	Moderate	Moderate	Low	Low	Low	Moderate	Serious
Exercise rehabilitation								
Lu [31]	Moderate	Moderate	Moderate	Low	Low	Low	Low	Moderate
Combination of exercise prehabilitation and rehabilitation								
Granger [24]	Moderate	Moderate	Moderate	Low	Low	Low	Low	Moderate
Kadiri [27]	Moderate	No information	Moderate	Low	Low	Low	Low	Moderate

Therapeutic quality (i-CONTENT scale)[a]

First author	1. Patient selection	2. Dosage of the exercise program	3. Type of the exercise program	4. Qualified supervisor (if applicable)	5. Type and timing of outcome assessment	6. Safety of the exercise program	7. Adherence to the exercise program	Overall risk of ineffectiveness
Exercise prehabilitation								
Coats [23]	High	High	High	Low	High	High	High	High
Huang [25]	Low	High	Low	Low	Low	Low	Low	Some
Lai [28]	High	High	Low	Low	High	Low	Low	High
Lai [29]	Low	High	Low	Low	High	Low	Low	Some
Lai [30]	High	High	Low	Low	High	Low	Low	High
Peddle [21]	High	High	High	High	Low	High	High	High
Sebio Garcia [22]	High	High	High	High	High	High	Low	High
Tenconi [33]	High	Low	Low	Low	Low	Low	Low	Some
Exercise rehabilitation								
Jastrzebski [26]	High	High	High	Low	High	Low	Low	High
Lu [31]	High	High	Low	Low	High	Low	Low	High
Messagi-Sartor [32]	Low	Low	Low	Low	Low	Low	High	Some
Combination of exercise prehabilitation and exercise rehabilitation								
Granger [24]	High	High	High	High	High	High	High	High
Kadiri [27]	Low	High	High	High	High	Low	High	High

Methodological quality: low=low risk of bias, some= some concerns; high=high risk of bias, moderate=moderate risk of bias, serious=serious risk of bias.
Therapeutic quality: low=low risk of ineffectiveness; high=high risk of ineffectiveness.
[a]: Overall risk of ineffectiveness:
•Low risk of ineffectiveness: items 1, 2, 3, AND 7 scored a "low risk of ineffectiveness" AND ≥1 of the items 4, 5, 7 scored a "low risk of ineffectiveness".
•Some risk of ineffectiveness: items 1, 2, 3, AND 7 scored a "low risk of ineffectiveness" AND 1 of the items 4, 5, 7 scored a "low risk of ineffectiveness" OR 3 items with a score of "low risk of ineffectiveness" on item 1, 2, 3, and 7 AND ≥1 of the items 4, 5, 7 scored a "low risk of ineffectiveness".
•High risk of ineffectiveness: ≤2 items with a score of "low risk of ineffectiveness" on item 1, 2, 3, and 7.

the used exercise programs [38,39]. Regarding study limitations, there was a large heterogeneity of physical exercise training programs and measures used to assess HRQoL (domains). Furthermore, there was a high risk of ineffectiveness of the exercise interventions (e.g., inadequate description or lack of supervision, personalization, objective monitoring of training intensity, monitoring of adherence) and a high risk of bias in many studies. The generally poor methodological and therapeutic quality of the included studies was

Table 5
Effects of exercise prehabilitation and rehabilitation on health-related quality of life and fatigue.

Author, year	Risk of bias Risk of ineffectiveness	Exercise intervention			Outcomes on quality of life and/or fatigue	Non-participation in the study Drop-outs Training adherence
		Aerobic exercises	Resistance exercises	Breathing exercises		
Exercise prehabilitation						
Coats [23], 2013, Prospective cohort	• Low • High	•	•		**HRQoL: EORTC-QLQ-C30** No statistically significant improvement **Fatigue: EORTC-QLQ-C30 fatigue subscale** No statistically but a clinically significant reduction	• n = 20 (35%) (n = 6 lack of time, n = 6 not specified, n = 5 lack of interest about engaging in a research project, n = 3 high level of anxiety, n = 3 scheduled surgery within one week of consent, n = 1 clinical deterioration) • n = 3 (n = 2 clinical deteriorations, n = 1 psychological distress) • 125% for aerobic and 83% for resistance exercise
Huang [25], 2017, RCT	• Low • Some	•		•	**HRQoL: EORTC-QLQ-C30** A statistically significant improvement in the IG compared to UC, **p=0.04** **Fatigue: fatigue index** No statistically significant reduction in the IG compared to UC	• NR • IG: n = 3, (n = 1 acute COPD exacerbation, n = 2 worsening knee pain, n = 2 loss of motivation), UC: n = 0 • 90%
Lai [28], 2016, RCT	• Some • High	•			**HRQoL: EORTC-QLQ-C30** No statistically significant increase was observed in the IG compared to UC	• n = 22 (refuse to participate) • IG: n = 4 (n = 1 lack of perceived benefit, n = 1 knee pain, n = 2 unknown) • NR
Lai [29] 2017, RCT	• Low • Some	•		•	**HRQoL: EORTC QLQ-C30** No statistically significant increase was observed in the IG compared to UC	• n = 24 (refuse to participate) • IG: n = 6 (n = 6 did not complete the follow-up assessment) • NR
Lai [30] 2019, RCT	• Some • High	•		•	**HRQoL: EORTC QLQ-C30** A statistically significant improvement in emotional function in the IG compared to UC, **p<0.01** **Fatigue: fatigue index** No statistically significant reduction in the IG compared to UC	• n = 22 (refuse to participate) • IG: n = 2 (n = 2 exercise intensity too high) • NR
Peddle [21], 2009, prospective observational	• Some • High	•			**HRQoL: FACT-L** A statistically significant improvement in the lung cancer subscale after prehabilitation compared with baseline, **p<0.01** **Fatigue: FACT subscale for fatigue** No statistically significant reduction after prehabilitation compared with baseline	• n = 13 (n = 6 lack of interest, n = 2 already exercising, n = 2 work, n = 2 no transportation, n = 1 = languages) • n = 3 (n = 1 surgical complication, n = 2 death) • Mean 88%
Sebio Garcia [22], 2017, RCT	• Some • High	•			**HRQoL: SF-36** A statistically significant improvement in the physical component summary in the IG compared to the UC, **p<0.01**	• n = 30 (n = 14 surgery in 1 week, n = 16 declined to participate), n = 2 after randomization in UC (referred to physical therapy) • IG: n = 1 (n = 1 clinical deterioration), UC: n = 2 (n = 2 lost to follow-up) • Median of 16 sessions (range 8–25): mean 50%
Tenconi [33], 2021, RCT	• Some • Some	•	•		**HRQoL: SF-12** No statistically significant improvement in the IG compared to UC	• NR • IG: n = 25 (n = 6 adjuvant treatment, n = 5 disease progression, n = 5 non primary lung neoplasm, n = 8 lost to follow-up, n = 1 other). UC: n = 30 (n = 15 adjuvant treatment, n = 2 disease progression, n = 3 non primary lung neoplasm, n = 9 lost to follow-up, n = 1 other) • 90% of the patients had accomplished 80% session adherence
Exercise rehabilitation						
Jastrzebski [26], 2018, RCT	• High • High	•	•	•	**HRQoL: SF-36** A statistically significant improvement within the IG and/or UC on the subscales: Pain: IG: **p=0.04**, UC: **p<0.01** Physical functioning: IG: **p=0.02** Physical health: IG: p = **0.05** General health: IG: **p<0.01** Vitality: UC: **p=0.02** Mental health: UC: **p<0.01**	• NR • No dropouts • NR
Lu [31], 2020 prospective cohort	• High • High	•	•		**HRQoL: EORTC QLQ-C30** A statistically significant improvement on emotional function compared with before	• n = 61 (n = 23 travel to far, n = 22 busy with personal affairs, n = 9 still hospital inpatient, n = 3 busy with work, n = 3 incorrect phone number, n = 1 do not want to participate) • n = 1 (unable to contact)

					rehabilitation, **p<0.01** **Fatigue: EORTC-QLQ-C30 fatigue subscale** No statistically significant reduction compared with before rehabilitation	• 47% of the participants attended at least 70% of the scheduled supervised exercise sessions, total attendance rate was 53% (181/340 possible supervised sessions).
Messagi-Sartor [32], 2019, RCT	• Low • Some	•	•	**HRQoL: EORTC-QLQ-30** No statistically significant difference between the IG and UC A clinically significant improvement within the IG and UC **Fatigue: EORTC-QLQ-C30 fatigue subscale** No statistically significant reduction between the IG and UC	• n = 19 (n = 2 postoperative complications, n = 4 no preoperative assessment, n = 6 declined to participate, n = 7 other reasons) • IG: n = 5 (n = 3 declined participations, n = 2 chemotherapy), UC: n = 8 (n = 5 declined participations, n = 2 chemotherapy, n = 1 postoperative complications) • >80% completion	
Combination of exercise prehabilitation and exercise rehabilitation							
Granger [24], 2018, prospective cohort	• Some • High	•	•	**HRQoL: EORTC-QLQ-30** No statistically significance improvement **Fatigue: EORTC-QLQ-C30 fatigue subscale** No statistically significant reduction	• n = 4 • n = 10 (n = 10 did not complete the follow-up assessment) • Median of 4 sessions		
Kadiri [27], 2019, prospective cohort	• Low • High	•	•	**HRQoL: EORTC-QLQ-30** A statistically significant improvement at 5 months postoperative compared with preoperative **Fatigue: EORTC-QLQ-C30 fatigue subscale** No statistically significant reduction	• NR • Before surgery 32%, after surgery 79% (pain, lack of motivation and generally feeling unwell) • Median of 4 (range 1–7) sessions a week. 32% did not use the app postoperative		

Abbreviations: EORTC-QLQ-30 = European for and of QLQ-C30; FACT = functional assessment of cancer therapy; FACT-L = functional assessment of cancer therapy of the lung; HRQoL = health-related quality of life; IG = intervention group; NR = not reported; NS = not significant; UC = usual care group.

mainly due to the non-description or incomplete description of the population, as well as the representativeness of the exercise intervention (e.g., frequency, intensity, type, time). There was considerable variation between studies concerning the type of surgery and the used outcome variables of HRQoL and fatigue questionnaires. This variation may have influenced the effects of exercise prehabilitation and/or rehabilitation on HRQoL and fatigue. Moreover, it should be mentioned that three studies took place at the same hospital in China [25,28,29]. This could have influenced expectations of researchers, physical therapists, (part of the) patients, methods, collection, and data analyses. As these three studies did not mention this potential overlap, it is important to raise awareness regarding both publication and reporting bias across these studies.

As mentioned earlier, the results of this systematic review must be interpreted with caution because of the heterogeneity of exercise programs and measures used to assess HRQoL and HRQoL domains, the high risk of ineffectiveness of the exercise interventions (e.g., caused by not describing or inserting of supervision, personalization, objective monitoring of exercise intervention and exercise intensity, training adherence), and the high risk of bias in many studies. Further research is required to investigate how to sustain positive effects of exercise over time and to determine essential attributes of exercise (mode, intensity, frequency, duration, timing) in patients with NSCLC, for an optimal effect on HRQoL and its subdomains.

5. Conclusion

There was an inconsistent effect of exercise prehabilitation and exercise rehabilitation on HRQoL in patients with NSCLC undergoing surgery, and no effect on fatigue. Due to the high risk of ineffectiveness of the exercise interventions, especially in case of a short duration of an exercise intervention, this systematic review cannot provide a definitive conclusion regarding the best form of exercises to improve HRQoL and reduce fatigue. It is recommended to investigate the impact of an exercise prehabilitation and/or rehabilitation program with high methodological and therapeutic quality (e.g., a duration of at least four weeks and a moderate- or high-exercise intensity) on HRQoL and fatigue in patients with NSCLC undergoing surgery in larger studies.

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Author contribution statement

Elisabeth J.M. Driessen: Study concepts, Data acquisition, Quality control of data and algorithms, Data analysis and interpretation, Manuscript preparation, Manuscript editing, Manuscript review, Robin J.E.F. Reinders: Study concepts, Data acquisition, Quality control of data and algorithms, Data analysis and interpretation, Manuscript preparation, Manuscript editing, Bart C. Bongers: Study concepts, Data analysis and interpretation, Manuscript preparation, Manuscript editing, Manuscript review, Maryska L.G. Janssen-Heijnen: Study concepts, Manuscript preparation, Janssen-Heijnen: Data analysis and interpretation, Manuscript editing, Manuscript review, Manuscript preparation, Melissa J.J. Voorn: Data acquisition, Quality control of data and algorithms, Data analysis and interpretation, Manuscript preparation, Manuscript editing, Manuscript review, V.E.M. van Kampen – van den

Boogaart: Manuscript review

Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Declaration of competing interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2023.04.008.

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