Title: Proactive physical activity programs in lung cancer surgical patients at short and mid-term: A Systematic Review and Meta-Analysis

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Abstract

Objective: To assess the effects of proactive physical activity (PA) programs on lung cancer patients undergoing lung resection at short and mid-term.

Methods: We conducted a literature search through MEDLINE, Science Direct, Web of Science, and the Cochrane Library (last search October 2023). The GRADE System and the Cochrane tool were applied to quality assessment. The included studies focused on the application of proactive PA interventions among lung cancer surgical patients compared to usual or standard care. We performed a meta-analysis addressing hospital stay, cancer-related symptoms, quality of life, and exercise capacity at short and mid-term.

Results: We selected 9 studies, which included 798 lung cancer patients. Proactive interventions were applied in combination with respiratory training and exercise in most of the studies. The treatment status was heterogeneous. Significant results in favour of proactive interventions were observed for hospital stay, cancer-related symptoms, quality of life, and short and mid-term exercise capacity.

Conclusions: Proactive PA interventions showed positive effects for reducing length stay, enhancing exercise capacity at short and mid-term, alleviating cancer-related symptoms, and improving the quality of life for lung cancer surgical patients.

Practice Implications: Proactive interventions can optimize the timing and setting of PA results around lung surgical treatment.

Keywords. Lung Cancer, Lung Resection, Proactivity, Hospital Stay, Quality of Life, Exercise capacity, cancer-related symptoms.

1. 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]. Complete surgical tumour resection remains a prerequisite for a cure and extended survival, even beyond 5 years in patients with early-stage by up to 75% [3,4]. For this reason, lung resection serves as the primary treatment for these patients [5].

Despite this improvement in survival, overwhelmingly patients experience significant disease- and treatment-related reductions in the overall state [6,7]. This health condition exhibits a complex interaction with preoperative physical functioning, deconditioning because of hospitalization, and the appearance of surgical stress. All of these deleteriously disturbed outcomes can induce physical, psychological, and social difficulties, which exert a negative effect on health-related quality of life [8] in short and long-term [9].

For these reasons, there is a critical need for strategies before and after lung resection, where a growing interest has arisen regarding the use of nonpharmacological interventions. Physical activity (PA) has been shown to improve management and recovery from cancer [10] and be safe and feasible for cancer survivors [11], improving physical and mental functioning during treatment [12,13], combating treatment side effects [14], reducing healthcare costs [15,16], recurrence, mortality [14], and improving quality of life at short and mid-term [17,18].

However, lung cancer survivors may have added difficulty being active as a result of symptoms associated with treatment, adopting an inactive lifestyle [19]. Individualized programming is required so participants can take advantage of the benefits of physical activity. When reaching the WHO recommendations is not appropriate for an individual, high importance should be placed on avoiding inactivity and reducing sedentary behaviours [20], and there is a need to tailor interventions based on these aspects to patient's personal goals and levels of physical and pulmonary function [21].

The patient's role in their recovery is also considered an important aspect of care [22,23] because an active role can improve patient outcomes and satisfaction with the surgical experience [24,25]. A recent review identified self-efficacy as the strongest predictor of intentions to perform more physical activity sustained over time [26]. Nonetheless, there is still a scarcity of concrete evidence regarding the most effective approach to deliver rehabilitation in this particular context.

In this line, proactive PA interventions have been proposed as a healthcare´s concept which may present opportunities to improve PA results sustained over time [27-29]. The application is supported by a growing body of literature since proactive interventions have shown to be effective behavioural change strategies [30,31], including for promoting physical activity [32,33]. Positive effects on PA behaviour have been shown in similar populations such as inactive adults [34] and patients with chronic diseases [35] at short and mid-term. Therefore, proactive PA interventions may be an effective strategy for improving short and mid-term PA levels for cancer survivors.

To our knowledge, no systematic review has synthesized the literature on proactive PA interventions in lung cancer surgical patients. So, the purpose of this systematic review and meta-analysis was to summarize existing proactive interventions promoting PA in lung cancer surgical patients to provide an up-to-date overview of intervention studies. Specific objectives include (1) describing the characteristics of these interventions (e.g., organizations, support, supportive material) and (2) determining the short and mid-term effects of these interventions in lung cancer patients underwent lung resection.

2. Methods

2.1. Study registration

This systematic review is adhered to the guidelines outlined in the Cochrane Handbook for Systematic Reviews [36] and follows the checklist provided by the Preferred Reporting Items for Systematic Reviews (PRISMA) statement [37]. The protocol for this study is registered under the International Prospective Register of Systematic Reviews (PROSPERO) with the number CRD42024497518.

2.2. Search strategy

We systematically searched the following databases—MEDLINE (via PubMed), Science Direct, Web of Science and Cochrane Library—for published studies from their inception up to October 2023. Our search strategy in MEDLINE involved several steps: (1) a comprehensive exploration of the MeSH Database, (2) the formulation of keywords through the examination of key terms used in existing systematic reviews, and (3) expert guidance and review by a specialist.

The effectiveness of this search strategy was rigorously tested and refined specifically for this review. Following this, the strategy was adjusted for indexing across each database. In addition to our systematic search, we conducted a manual screening of the reference lists in the included studies and relevant review articles to identify any additional studies that may not have been captured initially but could be potentially included in this review.

To formulate the research question, we applied the PICOS model (Participants, Interventions, Comparisons, Outcome, and Study Design) [38].

(P) Population: Adult patients underwent or candidate to lung resection surgery for lung cancer without restrictions on cancer type or state.

(I) Interventions: Proactive PA interventions.

(C) Comparison: A control intervention in which lung cancer patients received either a placebo, no treatment, usual care, or standardized conventional care with no active role in the intervention.

(O) Outcome: Hospital stay, cancer-related symptoms, quality of life and/or exercise capacity at short and/or mid-term.

(S) Study Design: Randomized clinical trials and pilot randomized clinical trials were included.

Detailed information about the search strategy is provided in the Appendix A.

Proactive physical activity interventions were considered as interventions that uses proactive outreach, a systems-level model of patient engagement that systematically identifies and reaches out to patients to connect them with treatment. Some of the reported key intervention components have been proactive outreach, healthcare delivery, supportive coach, and motivational interviewing and psychoeducation [27]. These approaches use action planning and motivational interviewing to promote PA:

· *Action planning*. Making a specific plan that specifies how the behavior will be performed. It is especially well-suited for enabling individuals to overcome environmental and psychological barriers [31].

· *Motivational interviewing*. A patient-centered approach for facilitating behavior change. It can foster high quality communication and empower participants to overcome barriers to exercise [30].

Following the collection of records from the databases, the study selection process involved eliminating duplicates and screening titles, abstracts, and eligible full texts. To mitigate potential selection bias, two investigators (A.H.; C.V.) conducted the literature search. Any disagreements were resolved by a third reviewer (J.M.). After the selection of studies, data extraction and a quality assessment were carried out.

Data extraction was conducted following the data extraction checklist outlined in the Cochrane Handbook for Systematic Reviews [36]. The extracted data encompassed authors, year of publication, study design and setting, cancer subtype, cancer stage, treatment status, surgical information, number of patients, sex distribution, mean age, intervention description, study frequency and duration, and reported outcomes.

The risk of bias of each study was assessed using the Cochrane Risk-of-Bias tool version 2.0 (RoB-2) [39]. The tool evaluates five domains: randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and the selection of the reported result. Studies are categorized based on their risk of bias as high, unclear, or low. The assessment results are generated using the Microsoft Excel spreadsheet template provided with the ROB2 tool.

The assessment of outcome quality was carried out using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system [40]. This tool considers five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The certainty level for the overall body of evidence is categorized as having a quality: “high”, “moderate”, “low”, or “very low”.

2.3. Meta-analysis

Quantitative analysis was conducted using The Review Manager 5 (Rev-Man version 5.1, updated March 2011) software for all studies presenting post-intervention means and standard deviations of length of stay, exercise capacity, exercise capacity at follow-up and cancer-related symptoms. The mean difference value was used to assess the quality of life. Data, including final mean values, standard deviations, and the number of patients assessed at different endpoints for each treatment arm, were extracted to estimate overall mean differences between treatment arms.

For articles with insufficient data to calculate effect size (e.g., no provided means or standard deviation), authors were contacted to obtain the required information. When p-values or 95% confidence intervals were available, and standard deviations were missing, calculations were performed following the guidelines outlined in the Review Manager manual [41]. These measures were implemented to maximize the reliability and validity of the findings. When the same group was included more than once in a figure, the sample was divided by the number of times included [36].

Continuous outcomes were analyzed using weighted mean differences when all studies measured outcomes on the same scale. Standardized mean differences were employed when different scales were assumed to measure the same underlying symptom or condition. The 95% confidence intervals were computed for all outcomes. Overall mean effect sizes were estimated using random effect models or fixed effect models based on I^2 tests for statistical heterogeneity. $I^2 < 50\%$ is considered to be a meta-analysis

with low heterogeneity, and a fixed-effects model was used [36]. A visual inspection of the forest plots for outlier studies was also undertaken.

3. RESULTS

3.1. Study selection

A total of 5692 records were initially identified through database searching, streamlining to 5146 titles after duplicates were removed. The screening of titles and abstracts resulted in 80 full-text articles for comprehensive review. 71 articles were excluded for not meeting the inclusion criteria, leaving 9 studies eligible for inclusion. No additional studies were found through alternative methods. A total of 9 studies were included in the qualitative and quantitative syntheses [42-50]. The PRISMA flow chart is illustrated in Figure 1.

Please, Insert Figure 1

3.2. Study characteristic

Table 1 presents the characteristics of the sample studies and the methodological evaluation of the included studies.

Respect to design of the included articles, 7 randomized controlled trials [42-44,46,48-50] and 2 pilot randomized control trials were presented [45,47]. 5 studies included patients in an early cancer stage [42-44,46,47], and 3 studies includes lung cancer patients in any cancer stage [45,48,50]. One study didn´t report the stage of the patient [49]. Concerning treatment status, three studies included lung cancer candidates for a lung resection [42-44], and five studies recruited patients underwent surgery [45-49]. Half of the sample was assigned to the intervention group and the other half to the control group.

A total of 798 lung cancer patients have been included in this review, who presented an homogeneous sex distribution (50% men vs 50% women), and a mean age ranging from 56 to 71 years old. 371 patients received an open surgery and 278 a Video-Assisted surgery (VATS). Most patients underwent a lobectomy (65.26%), 27.34% underwent a segmentomy, and 1.5% underwent a total lung resection. Only 29 wide resections were reported.

When the Cochrane Risk of Bias Assessment was applied, three studies exhibited a high risk of bias [43,45,47], while four studies raised some concerns [42,44,48,50]. The studies conducted by Lui JF, et al. [46] and Reeve J, et al. [49] demonstrated a low risk of bias. The domains primarily contributing to a higher risk of bias were associated with "deviations from the intended interventions". Figure 2 presents the detailed information about the risk of bias assessments.

After assessing the certainty level for the body of evidence, we have concluded that further research was very unlikely to change our confidence in the estimate of effects on hospital stay, quality of life, exercise capacity and exercise capacity at follow-up. Only the assessment of the outcome cancer-related symptoms

showed a very low quality when GRADE system was applied. The assessment of the quality of the evidence using GRADE is fully described in Figure 3.

Please, Insert Figure 2

Please, Insert Figure 3

Table 1. Characteristics of the included studies

Study (year)	Study Design	Etiology And Stage	Surgical Status	Surgery type VATS / Thoracotomy	Extent of resection Lung/Lobectomy/ Segmentomy/ Wedge resection	Sample N (Male/Female)	Age Years ± SD	Risk of Bias
Patel YS, et al. (2023) [42]	RCT	I-IIIA NSCLC	Before	**IG:** 41/4 **CG**: 41/9	**IG**: 0/17/28/0 **CG**: 0/28/17/5	**IG**: 45 (14/31) **CG**: 50 (26/24)	**IG:** 65.53 ± 8.66 **CG:** 68.78 ± 8.79	Some Concerns
Tenconi S, et al. (2021) [43]	RCT	I-II NSCLC	Before	**IG:** 16/52 **CG:** 16/53	**IG:** 0/36/32/- **CG:** 0/38/31/-	**IG**: 70 (38/32) **CG**: 70 (48/22)	**IG:** 66.0 ± 10.61 **CG:** 67.74 ± 10.84	High
Liu Z, et al. (2020) [44]	RCT	I-III NSCLC	Before	- -	**IG:** 0/37/0/0 **CG:** 0/35/0/0	**IG**: 37 (12/25) **CG**: 36 (11/25)	**IG:** 56.2 ± 10.3 **CG:** 56.2 ± 8.7	Some Concerns
Sunahara M, et al. (2023) [45]	PILOT	I-IV	After	**IG:** 14/8 **CG:** 17/7	**IG:** 1/13/5/3 **CG:** 0/14/4/6	**IG**: 22 (15/7) **CG**: 24 (13/11)	**IG:** 71.5 ± 59.8-79.3 **CG:** 71.0 ± 65.5-77.0	High
Liu JF, et al. (2021) [46]	RCT	I-IIIA	After	**IG:** 26/0 **CG:** 28/0	**IG:** 1/17/3/5 **CG:** 1/14/3/10	**IG**: 26 (12/14) **CG**: 28 (10/18)	**IG:** 64.2 ± 5.9 **CG:** 66.3 ± 7.9	Low
Hoffman AJ, et al (2014) [47]	PILOT	I-IIIA NSCLC	After	**IG:** 0/37 **CG:** 0/35	**IG:** 0/37/0/0 **CG:** 0/35/0/0	**IG**: 37 (17/20) **CG**: 35 (15/20)	**IG:** 67.4 ± 9.7 **CG:** 65.6 ± 10.1	High

Arbane G, et al. (2014) [48]	RCT	I-IV NSCLC	After	**IG:** 19/45 **CG:** 19/45	- -	**IG**: 64 (29/35) **CG**: 67 (43/24)	**IG:** 67 ± 11 **CG:** 68 ± 11	Some Concerns
Reeve J, et al. (2010) [49]	RCT	-	After	**IG:** 0/42 **CG:** 0/34	**IG:** 6/27/7/- **CG:** 3/22/7/-	**IG**: 42 (26/16) **CG**: 34 (21/13)	**IG:** 63 ± 13 **CG:** 65 ± 11	Low
Hui-Mei C, et al (2015) [50]	RCT	I-IV	Any status	- -	- -	**IG**: 56 (24/32) **CG**: 55 (25/30)	**IG:** 64.64 ± 11.54 **CG:** 62.51 ± 9.64	Some Concerns

VATS: Video-Assisted Thoracic Surgery; SD: Standard Deviation; RCT: Randomized Controlled Trial; NSCLC: Non-Small cell lung cancer; IG: Intervention Group; CG: Control Group

Table 2 presents the details about applied interventions and obtained results of the included studies.

The studies were conducted in a hospital environment during the hospital surgical stay, except the study of Hui-Mei C, et al. [50] that was carried out in a medical care center. Two studies were conducted in a Tertiary-care hospital [42,46,49] and three in a teaching hospital [46-48].

Respect to proactive PA interventions, most of the studies applied an action planning based on home-based walking, that was self-monitored according to heart rate, rating of perceived exertion, or number of steps per day. Other performed physical activities were jogging, cycling [44], and exergame-based physical activity [48]. The main target goal parameter among studies was the time spent, which ranged from 20 to 60 minutes per day.

The motivational interviews were mostly given by phone calls and face-to-face. The objective of these encounters was encouragement, counselling, and promoting compliance with the intervention. The main components of the psychoeducation were self-efficacy, goal-setting, and counselling PA. Other included components were relaxation skills [44] and symptom management [47].

The application of proactive PA interventions was heterogeneous. Three studies [45,47,50] applied the proactive PA interventions isolated or combined with usual care, and 6 studies applied it in combination with other therapies [41-43,45,47,48]. The main added therapies were respiratory [42-44,46,48,49], aerobic [43,48,49] and resistance training [43,44,48,49].

The intervention support presented a wide range of possibilities. Five interventions were provided by scientific researchers [42,44,46,48,50], three by physiotherapists [43,45,49], and one by nurses [47]. Motivational interviewing was provided face-to-face and by phone calls. Only one study [42] used daily SMS. Most of the studies applied one-initial or daily face-to-face encounters during the hospital stay, added to weekly telephone encounters at discharge. The most provided supporting materials were PA diaries and the Borg RPE scale. Other supporting materials were activity trackers, pedometers, HR monitors and booklets.

The duration of the interventions was different for pre and post-surgery interventions. The duration of the pre-surgical interventions was 2 weeks, while the duration of the post-surgical interventions ranged from 1 to 3 months. The duration of the sessions ranged between 20 and 60 minutes, and the weekly frequency between 2 and 5 days a week. Only the studies of Reeve J, et al [49] and Liu JF, et al [46] provided daily sessions, 7 days per week.

The most repeated outcomes were hospital stay [42,43-45,48], cancer-related symptoms [42,43,45,47,49,50], exercise capacity [43-48], and quality of life [42,43,45,47,48,50]. No studies reported significant differences in length of stay when the intervention groups were compared to control groups [42,43-46,48]. Concerning cancer-related symptoms, five studies reported significant differences

between groups [42,45,47,49,50], one study [47] reported in-groups significant improvements for the intervention group, and two studies [49, 50] showed significant results between groups at follow-up.

Five studies [43-47] also reported significant improvements in exercise capacity when the intervention group was compared to the control group. Two studies [42,47] reported significant improvements in the intervention group from baseline. Two studies [43,46] showed significant results between groups at follow-up.

Finally, the quality of life was measured by 6 studies [42,43,46,47,48,50]. Two studies [42,45] reported significant differences between groups and other two [43,48] didn´t show significant results. Only one study [42] reported significant in-group improvement in the intervention group, and another study showed significant differences between groups at follow-up [49]

Other outcomes including PA levels [42,48,50], muscle strength [48,49], pulmonary function [43,44], or mood of the patients [43,44,50], were assessed in the included studies with heterogenous between-groups and in-group results.

Table 2. Characteristics of interventions.

Study (year)	Setting	Intervention Groups	Intervention Support	Supporting Material	Intervention duration and frequency	Outcomes	Main Results
Patel YS, et al. (2023) [42]	Tertiary-care Hospital	**Intervention Group** Action Planning: Walking with a self-monitoring count, >10% weekly Steps/d up to 10000 steps/d Motivational interviewing: Automatic SMS personized to motivate and encourage Psychoeducation: Self-efficacy; Goal-Setting + Respiratory Training + Standard Care **Control Group** Standard Care: Concerning smoking cessation	**Professional**: Scientific Researcher **Via**: SMS **Sessions**: 1 initial Face-to-Face; Daily SMS reminders	Activity tracker Booklet	4 weeks	Hospitality Stay Quality of Life: Eq-5D-5L Symptoms: Eq-5D pain Other variables: PA Levels, sleep levels, complications, side effects, chest tube duration	**Hospital Stay:** No significant differences between groups. **Quality of Life:** Intervention group improve significantly after intervention. Significant Differences between groups in favors to intervention group. **Symptoms:** Significant differences Between groups in favors to intervention group.

Tenconi S, et al. (2021) [43]	Hospital	**Intervention Group** *Domiciliary* Action Planning: home-based walking with a self-monitoring count steps/d, at 60-80%MHR up to 30min/d Motivational interviewing: NR Psychoeducation: Self-efficacy; Counseling PA *Ambulatory* + Psychoeducation + Aerobic Training + Resistance Training + Respiratory Training + Scar massage + Functional Exercise + Standard care **Control Group** Standard Care: · 1 Presurgical Educative Session (counselling and self-care management) · Postsurgical Respiratory training	**Professional**: Physician & Physiotherapist **Via**: Face-to-Face **Sessions**: ambulatory and domiciliary	Pedometer Diary HR monitor	**Presurgical** 2week 14 season: 6 ambulatory 2-3 d/w 2 h/d 8 domiciliary 3-4 d/w 1 h/d **Postsurgical** 8 week 39 season: 15ambulatory 2 d/w 2h 15min /d 24Domiciliary 3 d/w 1 h/d	Hospitality Stay Exercise capacity: 6MWT Quality of Life: SF-12 Symptoms: NRS Other variables: pulmonary function, mood, complications, adherence	**Hospitality Stay**: No significant differences between groups. **Exercise capacity**: Significant Differences between groups in favors to intervention group 1 and 3 months after surgery. **Quality of Life**: No significant results. **Symptoms**: No significant results.

Liu Z, et al. (2020) [44]	Hospital	**Intervention Group** Action Planning: Walking, jogging or cycling at self-monitoring moderate to high intensity. Working on 13-15RPE and 70%THR. 3d/w 30min/d Motivational interviewing: Phone Calls for checking the compliance of the intervention Psychoeducation: Self-efficacy; Goal setting; Relation skills with relaxion music + Resistance Exercise + Respiratory Training + Nutrition Counseling and Supplementation + Usual Care **Control Group** Usual Care: perioperative medical care, smoking cessation, abstinence	**Professional**: Scientific Researcher **Via**: Face-To-Face & TLFN **Sessions**: 1 initial Face-to-Face; Weekly TLFN	Diary Booklet HR monitor RPE Scale	2 week 5 d/w	Hospitality Stay Exercise capacity: 6MWT Other variables: pulmonary function, disability, mood, short-term recovery, chest tube duration, side effects, deaths	**Hospital Stay:** No significant differences between groups. **Exercise capacity**: Significant Differences between groups in favors to intervention group.

Sunahara M, et al. (2023) [45]	Hospital	**Intervention Group** Action Planning: Walking with a self-monitoring count Motivational interviewing: Face-to-Face physical activity goal in hospital stay; Phone Calls for exercise encouragement and setting a higher physical activity goal at discharge Psychoeducation: Self-efficacy; Goal setting; PA benefices + Postoperative exercise program **Control Group** Postoperative exercise program: Early mobilizations, Premature ambulation, Resistance exercise, Treadmill or Cycloergometer Aerobic exercise	**Professional**: Physiotherapist **Via**: Face-to-Face & TLFN **Sessions**: 2x20min Hospital Face-to-Face; Weekly TLFN at discharge	Activity tracker	**Hospital** 5 d/w 20 min/d	Hospitality Stay Exercise capacity: 6MWT Quality of Life: SF-36 Symptoms: CFS;CDS Other variables: PA Levels, mood	**Hospitality Stay**: No significant differences between groups. **Exercise capacity**: Significant Differences between groups in favors to intervention group. **Quality of Life**: Significant Differences between groups in favors to intervention group. **Symptoms**: Significant Differences between groups in favors to intervention group.

Liu JF, et al. (2021) [46]	Teaching Hospital	**Intervention Group** Action Planning: Home-based HIIT walking and limbs´ exercises with a self-monitoring count steps/d, achieving 60min/d at 11-13RPE Motivational interviewing: Only Face-to-Face and Phone Calls for checking the compliance of the intervention Psychoeducation: None + Inspiratory Muscle Training + Standard care **Control Group** Standard care: Smoking cessation, upper and lower limb exercise, respiratory physiotherapy	**Professional**: Scientific Researcher **Via**: Face-to-Face & TLFN **Sessions**: 1 each 2days TLFN; 1 each 2 weeks Face-to-Face	Activity tracker Diary RPE Scale	6 week 7 d/w	Exercise capacity: 6MWT Other variables: respiratory muscle function, lung expansion volume, complications	**Exercise Capacity:** Significant Differences between groups in favors to intervention group 2 week, postintervention and 3 months after surgery.

Hoffman AJ, et al (2014) [47]	Teaching Hospital	**Intervention Group** Action Planning: Exergame-based walking and balance at self-monitoring light intensity (<3METs). Starting at 5min/d 5d/w, >5 min weekly up to 30 min if patient achieved 70/100 confidence. Working on <3RPE and <60%HRR Motivational interviewing: Home visits and Phone Calls for exercise counseling and motivating to continue with the intervention Psychoeducation: Self-efficacy, Goal setting; Symptom management **Control Group** Usual Care: Not specified	**Professional**: Nurse **Via**: Face-To-Face & TLFN **Sessions**: 2 initial Face-to-Face; 5 TLFN	Pedometer Diary HR monitor RPE Scale	6 weeks 5 d/w 5-30 min/d	Exercise capacity: 6MWT Quality of Life: SF-36; QLI Symptoms: MDASI; BFI Other variables: self-management, PSE, balance, adherence, side effects, acceptability	**Exercise capacity**: Intervention group improve significantly after intervention. Significant Differences between groups in favors to intervention group. **Quality of Life**: Differences between groups in favors to intervention group but not report significance. **Symptoms**: Intervention group improve significantly after intervention. Significant Differences between groups in favors to intervention group.

Arbane G, et al. (2014) [48]	Teaching Hospital	**Intervention Group** *Hospital Stay* + Aerobic and Resistance Exercise + Usual Hospital Care *Discharge* Action Planning: home-based Walking with a self-monitoring count up to 30min/d Motivational interviewing: Phone Calls for exercise counseling, encouragement, and motivating to continue with the intervention Psychoeducation: Goal setting **Control Group** Usual Hospital Care: rutinary physical therapy, airway clearance techniques, mobilization and upper limb activities	**Professional**: Scientific Researcher **Via**: Face-To-Face & TLFN **Sessions**: Face-to-Face hospital; Weekly TLFN at discharge	Pedometer	5 Hospital days 4 Weeks 30 min/d at discharge	Hospitality Stay Exercise capacity: ISWT Quality of Life: SF-36; QLQ-LC13 Other variables: PA Levels, sleep levels, muscle strength, side effects	**Hospital Stay:** No significant differences between groups. **Exercise Capacity:** No significant results. **Quality of Life:** No significant results.

Reeve J, et al. (2010) [49]	Tertiary-care Hospital	**Intervention Group** *Hospital Stay* + Respiratory training + Aerobic exercise Walking program + Resistance Exercise + Usual Medical and Nurse Care + Non-specific postoperative exercise advice *Discharge* Action Planning: home-based Walking self-monitoring at 5-7RPE. Achieving >20min/d up to 1-2km/d initially Motivational interviewing: Previous to discharge for stablishing goal setting Psychoeducation: Self-efficacy; Goal-Setting + Resistance Exercise **Control Group** Usual Medical and Nurse Care: including Early mobilizations, Premature ambulation Non-specific postoperative exercise advices	**Professional**: Physiotherapist **Via**: Face-to-Face **Sessions**: Daily hospital	Diary Booklet RPE Scale	3 Months 7 d/w	Quality of Life: SF-36 Symptoms: NSR (0-30) Other variables: upper limb function, muscle strength, ROM, adherence	**Quality of Life:** Significant Differences between groups in favors to intervention group at 3 months after surgery. **Symptoms:** Significant Differences between groups in favors to intervention group at discharge, 1 and 3 months after surgery.

Hui-Mei C, et al (2015) [50]	Medical Center	**Intervention Group** Action Planning: home-based Walking at self-monitoring moderate intensity at 60-80%THR & 13-15RPE Motivational interviewing: Phone calls for exercise counseling and motivating to continue with the intervention Psychoeducation: Self-efficacy; Goal-Setting + Usual medical Care **Control Group** Usual medical Care	**Professional**: Scientific Researcher **Via**: Face-To-Face & TLFN **Sessions**: Weekly TLFN-Counseling	Diary Booklet RPE Scale	12 weeks 3 day/w 40 min/session	Symptoms: MDASI-T; PSQI Other variables: PA Levels, sleep Variables, mood, adherence, side effects	**Symptoms:** Significant differences Between groups after intervention in favors to intervention group. Significant differences Between groups in PSQI after intervention and 6 Months after intervention in favors to intervention group.

M: Month; W: Week; D: Day; H: Hours; min: minutes; Reps: repetitions; TLFN: Telephone; HR: Heat Rate; HRR: Heart Rate Rest; MHR: Maximum Heart Rate; THR: Target Heart Rate; RPE: Borg's rating of perceived exertion; IMT: Inspiratory Muscle Training; PIM; Pressure Inspiratory maximum; MET: Metabolic Equivalent of task; RM: Repetition Maximum; HIIT: High Intensity Interval Training; Eq-5D: Euroqol-5Dimensions; PA Levels: Physical Activity Levels; 6MWT: 6 Minutes Walking Test; SF-12/36: Medical Outcomes Study Short Form-12/36; NRS: Numeric Rating Scale; CDS: Cancer Dyspnea Scale; CFS: Cancer Fatigue Scale; MDASI: MD Anderson Symptom Inventory; BFI: Brief Fatigue Inventory; ISWT: Incremental Shuttle Walk Distance; QLQ-L13: European Organization for Research and Treatment of Cancer-QOL- Lung subscale; ROM: Range of Movement; PSQI: Pittsburgh Sleep Quality Index; NR: Not Reported.

3.3. Results obtained in Meta-Analysis

The results obtained in the meta-analysis with respect to length of stay were analyzed as shown in Figure 4. The pooled mean difference (MD) showed a significant overall effect of proactive intervention compared to the control groups (MD=-0.50; 95% CI=-0.97,-0.02; p=0.04). The results showed a low heterogeneity, detecting a variability of $I^2 = 47\%$, not attributable to chance.

Please, Insert Figure 4

Results obtained in exercise capacity have been analyzed across 6MWD values as shown in Figure 5. The pooled mean difference (MD) showed significant overall effect of proactive intervention compared to the control group (MD = 67.33, 95% CI=15.05,119.62; p= 0.01). Heterogeneity was high (I2= 93%), not attributable to chance.

Please, Insert Figure 5

Figure 6 presents the results obtained in the meta-analysis for exercise capacity at follow-up. The pooled mean difference (MD) showed a significant overall effect of proactive intervention compared to the control groups (MD=65.83; 95% CI= 56.05,75.60; p< 0.00001). The results showed a low heterogeneity, detecting a variability of $I^2 = 28\%$, not attributable to chance.

Please, Insert Figure 6

Figure 7 shows the results obtained in the meta-analysis for cancer-related symptoms. The pooled standardized mean difference (SMD) showed a significant overall effect of proactive interventions: experimental group compared with control group (SMD =-0.76, 95% CI= -1.53,0.01; p=0.05). The results show a high heterogeneity, detecting significant variability of I2=91%, not attributable to chance.

Please, Insert Figure 7

The results obtained in the meta-analysis with respect to quality of life divided by subscales were analyzed as shown in Figure 8. For Global quality of life, the pooled standardized mean difference (SMD) showed a significant overall effect of proactive interventions when compared to control group (SMD = 0.44; 95%CI = 0.07; 0.82; p=0.02). However, for Physical, Role, and Mental quality of life, the pooled standardized mean difference (SMD) didn't show a significant overall effect of proactive interventions when compared to control group (SMD = 0.16; 95%CI=-0.37,0.69; p=0.55) ; (SMD = 0.16; 95%CI=-0.57,0.89; p=0.66) ; (SMD = 0.01; 95%CI=-0.52,0.53; p=0.97), respectively. But respect to total quality of life, the pooled standardized mean difference (SMD) showed a significant overall effect of proactive interventions when compared to control group (SMD = 0.25; 95%CI=0.00,0.50; p=0.05). The results don´t show heterogeneity, detecting variability of $I^2=0\%$.

Please, Insert Figure 8

4. Discussion and conclusion

4.1. Discussion

This systematic review and meta-analysis were conducted to evaluate the short and mid-term effects of proactive PA interventions on patients undergoing lung cancer resection. Our findings revealed positive outcomes associated with the implementation of proactive physical activity interventions in lung cancer surgical patients. These interventions demonstrated significant improvements in reduced length of stay, cancer-related symptoms, enhanced quality of life, and increased exercise capacity in the short and mid-term.

These results are in line with previous proactive intervention studies [42-50]. Grimmett C, et al. [51] performed a systematic review reporting similar benefits to ours, after applying physical activity behaviour change interventions to promote physical activity in the general population of cancer survivors. Additionally, patients who actively participated in exercise programs after undergoing surgery have shown improvements in physical performance, survival rates, and overall well-being at short [52,53], and mid-term [54-56].

The sample in our systematic review is similar those in other lung cancer reviews [54,57], exhibiting heterogeneity in clinical profiles and intervention timing. The treatment moment in the included studies was also heterogeneous, reflecting the broader uncertainty in cancer reviews about the optimal moment to engage with cancer patients. However, active interventions have proved to be beneficial independent of the time between surgery and the start of the intervention [58]. There exists sufficient evidence indicating that pre- or post-surgery exercise interventions, individually, improve the functional state in lung cancer patients undergoing surgery [21].

The studies presented different durations for pre and post-surgical interventions. It was around 2 weeks in the preoperative period and ranged from 1 to 3 months in the post-operative period. These results are in line with other perioperative interventions in patients undergoing lung cancer resection [59]. The differences in duration between both periods are conditioned by the situation in front of the surgery, however, 1-2 weeks before surgery have proven to be enough to find significant improvements in main outcomes including length of stay, surgery complications, and fastened recovery period [60,61].

Concerning the development of proactive physical activity interventions, the studies showed a homogeneous action planning and motivational interviewing, where the main physical activity developed was walking. In this line, previous studies have shown action planning [31] and motivational interviewing [30] to be effective behavioral change strategies, including for promoting physical activity [32,33]. Proactive management has been used to address utilization barriers in providing treatment for smoking [62,63], or chronic musculoskeletal pain [27].

Walking, as the main selected activity, is in line with the selection of previous studies, since walking represents an ideal form of aerobic activity, due to its ease of accessibility and relatively low impact. It

has a low risk of injury [64] and is considered safe to recommend for previously sedentary individuals [65]. The recommendation of the included studies was walking around 30min/day 2-5 times a week, achieving the general recommendations for cancer patients [66,67].

Providing supporting materials seems to be a key factor for success in proactive interventions. Materials such as activity trackers or pedometers which allow the self-monitoring of count day have proved to be effective at increasing walking [68,69], and tracking adherence sustained over time, ultimately, by encouraging motivation [70].

Upon meta-analyzing the results of comparing proactive PA interventions to other treatments, statistically significant differences were observed in favour of the intervention group. In this line, previous systematic reviews and meta-analyses have reported that perioperative exercise may shorten the length of hospital stay, decrease cancer-related symptoms, and increase the 6MWD and quality of life [71-73]. The use of the 6MWT as a measure of exercise capacity and cardiorespiratory fitness is commonly applied and particularly highlighted in lung cancer patients due to its importance as a post-surgical complications and survivor predictor [74].

It is important to note that in the qualitative results, no study has shown significant results on length of stay against our quantitative results which have reported significant differences between groups ($p=0.04$). This important finding could be explained by the sample side of the studies, which could disturb the significance of the study results.

Additionally, in the same line as our results, other studies have shown significant improvements at mid-term and long-term after the application of proactive interventions [27] or other walking-based interventions [29]. However, it is difficult to find long-term results in lung cancer studies due to the low survival rate of these patients [75].

There were some limitations to be considered when interpreting the results of this study. First, there were not enough randomized controlled trials providing sufficient data on cancer-related symptoms and quality of life at mid-term. Second, our analysis includes a small number of studies, precluding the feasibility of conducting subgroup analyses. Nonetheless, it is worth noting that previous reviews on the cancer population have been carried out with a similar number of studies [76]. The calculation of sample size has been thoroughly examined in the included studies, contributing to the robustness of the conclusions drawn in each of them. In addition, while conducting a meta-analysis with studies with small sample sizes presents challenges, such as increased uncertainty and potential bias, careful consideration of study quality, sensitivity analyses, and appropriate statistical techniques can help mitigate these limitations and yield meaningful insights [41]. Third, despite concerted efforts to minimize bias and heterogeneity, variations in the study sample and intervention approaches may have contributed to the observed variability in results.

The inclusion of patients at various clinical stages necessitates the adaptation and individualization of interventions, resulting in heterogeneity among them. As patients present with diverse medical histories,

levels of severity, and response to treatment, a one-size-fits-all approach is inadequate. Individualizing physical activity interventions in patients is crucial for optimizing health outcomes and ensuring adherence to exercise regimens. Tailoring exercise programs to suit the specific needs, preferences, and abilities of each patient can lead to greater engagement and motivation, ultimately enhancing the effectiveness of the intervention. This personalized approach ensures that patients receive the most appropriate care and support to optimize their outcomes [77]. Consequently, the observed heterogeneity in interventions reflects the nuanced nature of patient care, where flexibility and customization are paramount to achieving successful results across different clinical contexts. However, despite differences in the duration or frequency of interventions, they all share a common foundation. All of them included specific strategies to motivate and promote behavior change through clear goals, feedback, identification of barriers, and offering behavior maintenance strategies.

To improve generalizability, future studies should include larger, mid and long-term, multicenter randomized controlled proactive intervention trials if it could be possible.

4.2 Conclusion

In conclusion, this systematic review and meta-analysis suggest that proactive PA intervention may shorten length of hospital stay, decrease cancer-related symptoms, and increase the exercise capacity and quality of life in surgical lung cancer patients at short and mid-term.

However, caution is warranted in interpreting the results, given the heterogeneity among the included studies. The review did not yield conclusive findings regarding the better treatment moment for applying proactive PA interventions. Larger RCTs with follow-up are needed to confirm the effects of these interventions in such a patient population, and making possible to identify the subgroups of patients who may benefit most from these interventions.

4.3 Practice Implications

Our review holds significant clinical implications for rehabilitation practice which need to be reported. Proactive PA interventions emerge as valuable tools with the potential to enhance the short and mid-term recovery of lung cancer patients, with specific results in quality of life, exercise capacity, and cancer-related symptoms. For the first time, this study has shown significant effects of the application of proactive PA interventions on the reduction of hospital stay.

Incorporating pre- and post-surgery interventions into the clinical workflow can be seamlessly achieved, and the outcomes of such interventions can guide future strategies for optimizing the timing and setting of physical activity both before and after surgical treatment.

Declarations

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Legends

Figure 1. PRISMA flow chart of literature search and study selection [36]

Figure 2. Cochrane Risk-of-Bias tool version 2.0.

Figure 3. GRADE evidence.

Figure 4. Illustration of changes in hospital stay.

Figure 5. Illustration of changes in exercise capacity.

Figure 6. Illustration of changes in exercise capacity at mid-term.

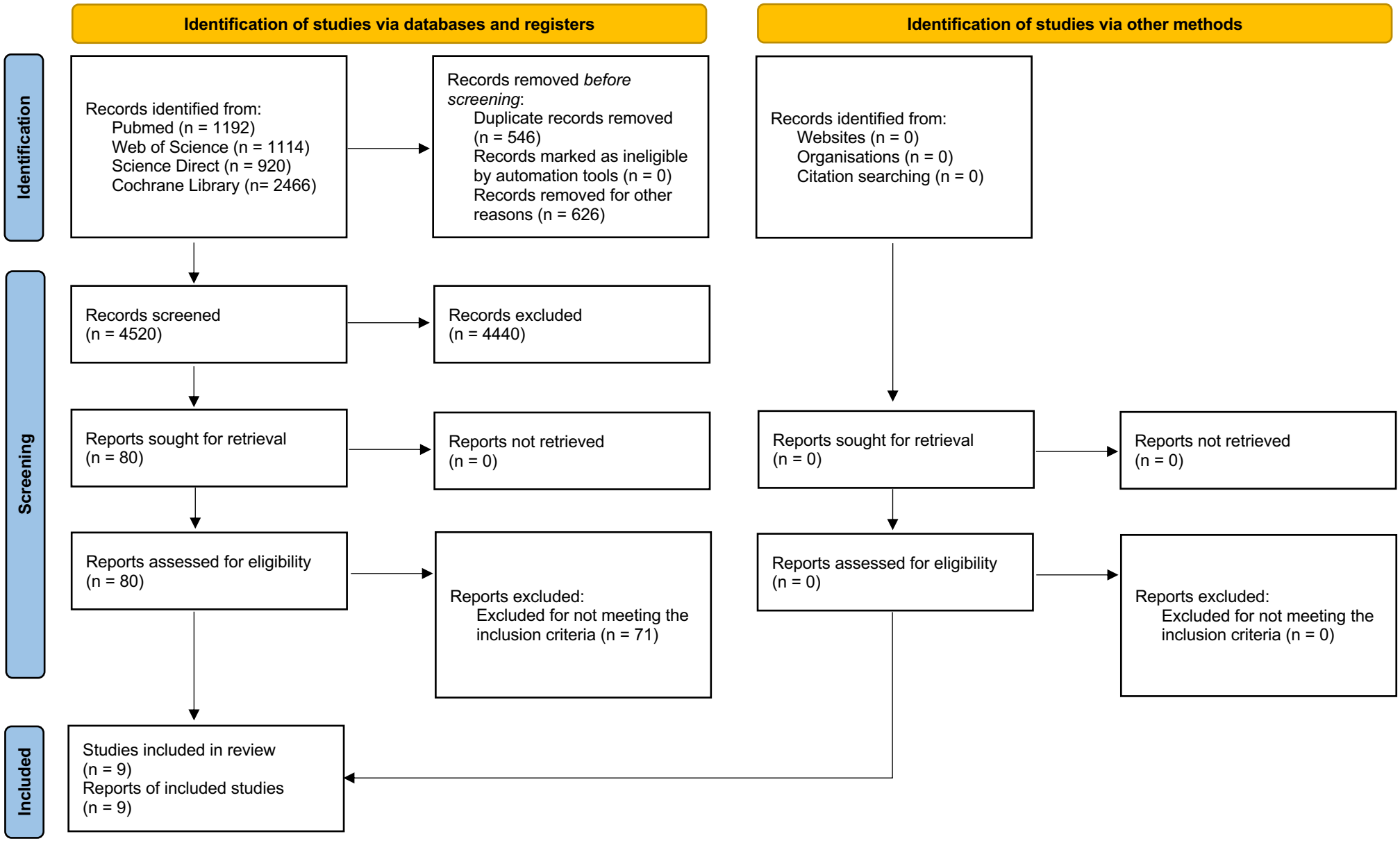
Figure 7. Illustration of changes in cancer-related symptoms.

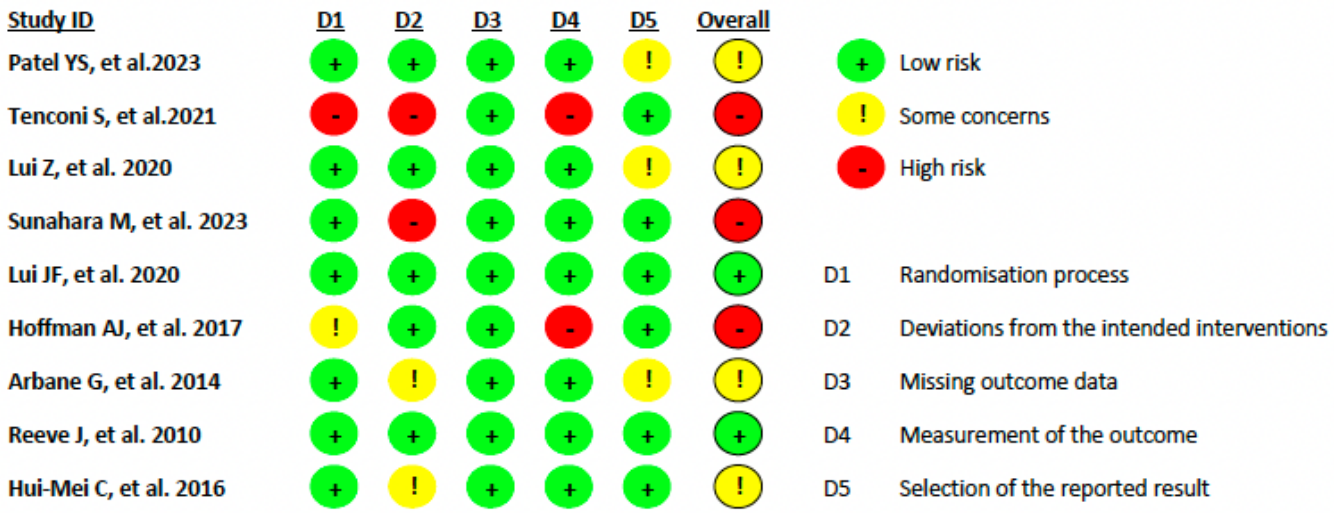
Figure 8. Illustration of changes in quality of life.

Appendix A. Search strategy.

Database	Search	Query	Items found
PubMed	#1	"lung cancer" OR "lung malignancy" OR "thoracic malignancy" OR lung tum* OR lung aden* OR "lung carcinoma" OR “thoracic cancer” OR “NSCLC” OR “lung neoplasms" OR "lung" OR lung* OR "lung neoplasm"	1.124.867
	#2	“General Surgery” OR “Pulmonary Surgical Procedures” OR “Respiratory Resection” OR “Pulmonary Resection” OR “Thoracic surgery” OR “Thoracic Surgical Procedures” OR “Surgical Procedures Operative” OR surg* OR operat* OR resect* OR “Lung resection surgery” OR lobectomy OR pneumonectomy OR "wedge resection” OR “preoperative care” OR “preoperative period” OR preoperat* OR pre-operat* OR pre-surgery OR presurg* OR pre-surg* OR “postoperative care” OR “postperative period” OR postoperat* OR post-operat* OR post-surgery OR postsurg* OR post-surg*	85.910
	#3	Proactive OR “Proactive intervention” OR “Proactive coaching” OR “Proactive Physical Activity” OR " Physical activity" OR “Physical activity coach” OR Coach* OR Coaching OR ”Coaching Programs” OR "Health Coach" OR "Health Coaching" OR “motor activity” OR physical activit* OR "Activity levels" OR walk OR walking OR “exercise movement techniques” OR “step count” OR accelerometer OR pedometer OR behav* OR “community based” OR “health promotion” OR “lifestyle change” OR exercise OR education OR “physical education” OR “physical exercise” OR “exercise therapy” OR “exercise movement techniques” OR “motor activity” OR “physical fitness” OR “lifestyle program” OR training OR rehabilitation OR fitness	93.554
	#4	[filters: Randomized Control Trial]	-
	#5	#1 AND #2 #3 AND #3	**1192**
Web of Science	#1	"lung cancer" OR "lung malignancy" OR "thoracic malignancy" OR lung tum* OR lung aden* OR "lung carcinoma" OR “thoracic cancer” OR “NSCLC” OR “lung neoplasms" OR "lung" OR lung* OR "lung neoplasm"	1.956.063
	#2	“General Surgery” OR “Pulmonary Surgical Procedures” OR “Respiratory Resection” OR “Pulmonary Resection” OR “Thoracic surgery” OR “Thoracic Surgical Procedures” OR “Surgical Procedures Operative” OR surg* OR operat* OR resect* OR “Lung resection surgery” OR lobectomy OR pneumonectomy OR "wedge resection” OR “preoperative care” OR “preoperative period” OR preoperat* OR pre-operat* OR pre-surgery OR presurg* OR pre-surg* OR “postoperative care” OR “postperative period” OR postoperat* OR post-operat* OR post-surgery OR postsurg* OR post-surg*	21.491.993
	#3	Proactive OR “Proactive intervention” OR “Proactive coaching” OR “Proactive Physical Activity” OR " Physical activity" OR “Physical activity coach” OR Coach* OR Coaching OR ”Coaching Programs” OR "Health Coach" OR "Health Coaching" OR “motor activity” OR physical activit* OR "Activity levels" OR walk OR walking OR “exercise movement techniques” OR “step count” OR accelerometer OR pedometer OR behav* OR “community based” OR “health promotion” OR “lifestyle change” OR exercise OR education OR “physical education” OR “physical exercise” OR “exercise therapy” OR “exercise movement techniques” OR “motor activity” OR “physical fitness” OR “lifestyle program” OR training OR rehabilitation OR fitness	17.405.555
	#4	[Document Types: Clinical Trial]	-
	#5	#1 AND #2 #3 AND #3	**1.114**
Science Direct	#1	"lung cancer" OR "lung malignancy" OR "thoracic malignancy" OR lung tum* OR lung aden* OR "lung carcinoma" OR “thoracic cancer” OR “NSCLC” OR “lung neoplasms" OR "lung" OR lung* OR "lung neoplasm"	2.121.358
	#2	“General Surgery” OR “Pulmonary Surgical Procedures” OR “Respiratory Resection” OR “Pulmonary Resection” OR “Thoracic surgery” OR “Thoracic Surgical Procedures” OR “Surgical Procedures Operative” OR surg* OR operat* OR resect* OR “Lung resection surgery” OR lobectomy OR pneumonectomy OR "wedge resection” OR “preoperative care” OR “preoperative period” OR preoperat* OR pre-operat* OR pre-surgery OR presurg* OR pre-surg* OR “postoperative care” OR “postperative period” OR postoperat* OR post-operat* OR post-surgery OR postsurg* OR post-surg*	495.426
	#3	Proactive OR “Proactive intervention” OR “Proactive coaching” OR “Proactive	745.964

		Physical Activity” OR " Physical activity" OR “Physical activity coach” OR Coach* OR Coaching OR ”Coaching Programs” OR "Health Coach" OR "Health Coaching" OR “motor activity” OR physical activit* OR "Activity levels" OR walk OR walking OR “exercise movement techniques” OR “step count” OR accelerometer OR pedometer OR behav* OR “community based” OR “health promotion” OR “lifestyle change” OR exercise OR education OR “physical education” OR “physical exercise” OR “exercise therapy” OR “exercise movement techniques” OR “motor activity” OR “physical fitness” OR “lifestyle program” OR training OR rehabilitation OR fitness	
	#4	#1 AND #2 AND #3	**920**
Cochrane	#1	"lung cancer" OR "lung malignancy" OR "thoracic malignancy" OR lung tum* OR lung aden* OR "lung carcinoma" OR “thoracic cancer” OR “NSCLC” OR “lung neoplasms" OR "lung" OR lung* OR "lung neoplasm"	88.297
	#2	“General Surgery” OR “Pulmonary Surgical Procedures” OR “Respiratory Resection” OR “Pulmonary Resection” OR “Thoracic surgery” OR “Thoracic Surgical Procedures” OR “Surgical Procedures Operative” OR surg* OR operat* OR resect* OR “Lung resection surgery” OR lobectomy OR pneumonectomy OR "wedge resection” OR “preoperative care” OR “preoperative period” OR preoperat* OR pre-operat* OR pre-surgery OR presurg* OR pre-surg* OR “postoperative care” OR “postperative period” OR postoperat* OR post-operat* OR post-surgery OR postsurg* OR post-surg*	389.313
	#3	Proactive OR “Proactive intervention” OR “Proactive coaching” OR “Proactive Physical Activity” OR " Physical activity" OR “Physical activity coach” OR Coach* OR Coaching OR ”Coaching Programs” OR "Health Coach" OR "Health Coaching" OR “motor activity” OR physical activit* OR "Activity levels" OR walk OR walking OR “exercise movement techniques” OR “step count” OR accelerometer OR pedometer OR behav* OR “community based” OR “health promotion” OR “lifestyle change” OR exercise OR education OR “physical education” OR “physical exercise” OR “exercise therapy” OR “exercise movement techniques” OR “motor activity” OR “physical fitness” OR “lifestyle program” OR training OR rehabilitation OR fitness	376.009
	#4	#1 AND #2 AND #3	**2466**


Identification of studies via databases and registers
Identification of studies via other methods
Identification
Screening
Included
Records identified from:
Pubmed (n = 1192)
Web of Science (n = 1114)
Science Direct (n = 920)
Cochrane Library (n= 2466)
Records removed *before screening*:
Duplicate records removed (n = 546)
Records marked as ineligible by automation tools (n = 0)
Records removed for other reasons (n = 626)
Records identified from:
Websites (n = 0)
Organisations (n = 0)
Citation searching (n = 0)
Records screened (n = 4520)
Records excluded (n = 4440)
Reports sought for retrieval (n = 80)
Reports not retrieved (n = 0)
Reports sought for retrieval (n = 0)
Reports not retrieved (n = 0)
Reports assessed for eligibility (n = 80)
Reports excluded:
Excluded for not meeting the inclusion criteria (n = 71)
Reports assessed for eligibility (n = 0)
Reports excluded:
Excluded for not meeting the inclusion criteria (n = 0)
Studies included in review (n = 9)
Reports of included studies (n = 9)


Study ID
D1
D2
D3
D4
D5
Overall
Patel YS, et al.2023
Tenconi S, et al.2021
Lui Z, et al. 2020
Sunahara M, et al. 2023
Lui JF, et al. 2020
Hoffman AJ, et al. 2017
Arbane G, et al. 2014
Reeve J, et al. 2010
Hui-Mei C, et al. 2016
Low risk
Some concerns
High risk
D1 Randomisation process
D2 Deviations from the intended interventions
D3 Missing outcome data
D4 Measurement of the outcome
D5 Selection of the reported result

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Proactive PA Intervention	Standard Care	Relative (95% CI)	Absolute (95% CI)		
Symptoms												
5	randomised trials	serious[a]	very serious[b]	not serious	very serious[c]	strong association dose response gradient	175	180	-	SMD **0.76 SD lower** (1.53 lower to 0.01 higher)	⨁◯◯◯ Very low	CRITICAL
Quality of Life												
4	randomised trials	not serious	not serious	not serious	serious[d]	strong association	130	128	-	SMD **0.25 higher** (0 to 0.5 higher)	⨁⨁⨁⨁ High	CRITICAL
Exercise Capacity												
5	randomised trials	serious[a]	very serious[b]	not serious	not serious	strong association dose response gradient	168	170	-	MD **67.33 higher** (15.05 higher to 119.62 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Length of Stay												
5	randomised trials	serious[a]	not serious	not serious	not serious	strong association dose response gradient	233	241	-	MD **0.5 lower** (0.97 lower to 0.02 lower)	⨁⨁⨁⨁ High	CRITICAL
FU Exercise Capacity												
3	randomised trials	serious[a]	not serious	not serious	serious[d]	very strong association dose response gradient	107	103	-	MD **65.83 higher** (56.05 higher to 75.6 higher)	⨁⨁⨁⨁ High	IMPORTANT

CI: confidence interval; **MD:** mean difference; **SMD:** standardised mean difference

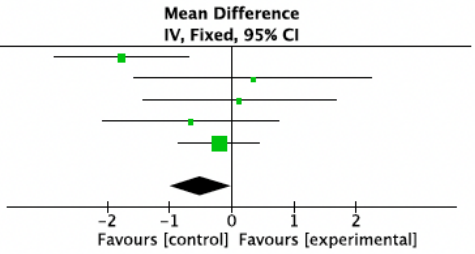
Explanations

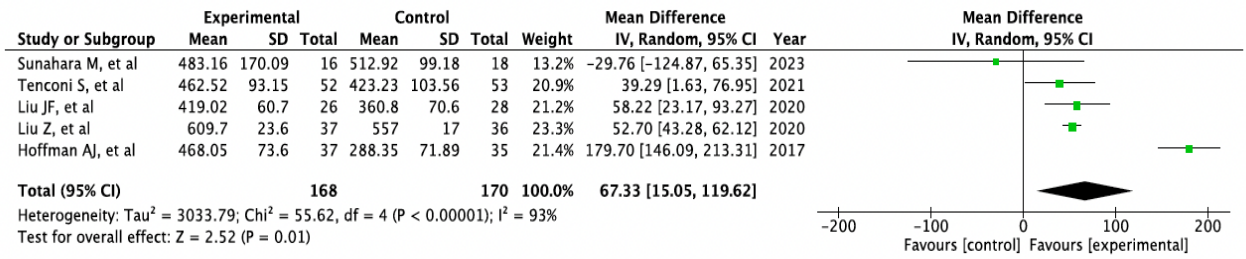
a. More studies present high than low risk of bias
b. High heterogeneity
c. Few studies and wide confidence intervals of the diamond shapes in the Forest plot
d. Few studies

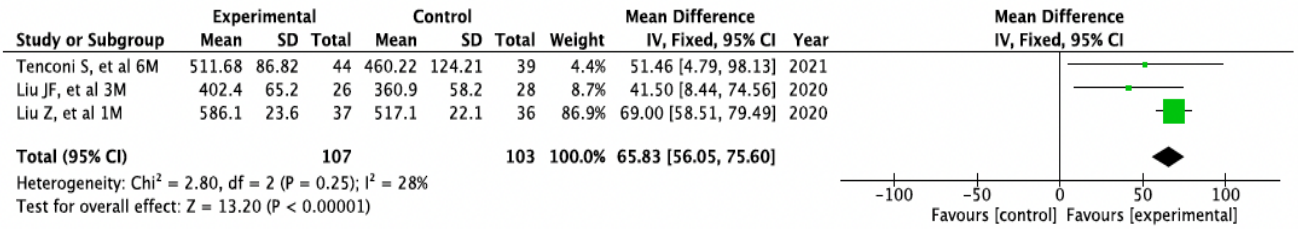
Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Patel YS, et al	2.67	1.61	45	4.44	3.48	50	19.7%	−1.77 [−2.84, −0.70]	2023
Sunahara M, et al	10.5	2.43	16	10.16	3.21	18	6.3%	0.34 [−1.56, 2.24]	2023
Tenconi S, et al	6.6	2.69	68	6.48	6	69	9.4%	0.12 [−1.43, 1.67]	2021
Liu Z, et al	8	3.08	37	8.66	3.08	36	11.3%	−0.66 [−2.07, 0.75]	2020
Arbane G, et al	6.83	2.27	67	7.03	1.51	68	53.4%	−0.20 [−0.85, 0.45]	2014
Total (95% CI)			**233**			**241**	**100.0%**	**−0.50 [−0.97, −0.02]**	

Heterogeneity: $Chi^2 = 7.61$, df = 4 (P = 0.11); $I^2 = 47\%$

Test for overall effect: Z = 2.05 (P = 0.04)



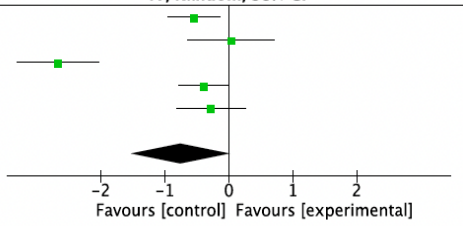

Experimental
Control
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI Year
IV, Random, 95% CI
Sunahara M, et al 483.16 170.09 16 512.92 99.18 18 13.2% -29.76 [-124.87, 65.35] 2023
Tenconi S, et al 462.52 93.15 52 423.23 103.56 53 20.9% 39.29 [1.63, 76.95] 2021
Liu JF, et al 419.02 60.7 26 360.8 70.6 28 21.2% 58.22 [23.17, 93.27] 2020
Liu Z, et al 609.7 23.6 37 557 17 36 23.3% 52.70 [43.28, 62.12] 2020
Hoffman AJ, et al 468.05 73.6 37 288.35 71.89 35 21.4% 179.70 [146.09, 213.31] 2017
Total (95% CI) 168 170 100.0% 67.33 [15.05, 119.62]
Heterogeneity: Tau² = 3033.79; Chi² = 55.62, df = 4 (P < 0.00001); I² = 93%
Test for overall effect: Z = 2.52 (P = 0.01)
-200
-100
0
100
200
Favours [control]
Favours [experimental]

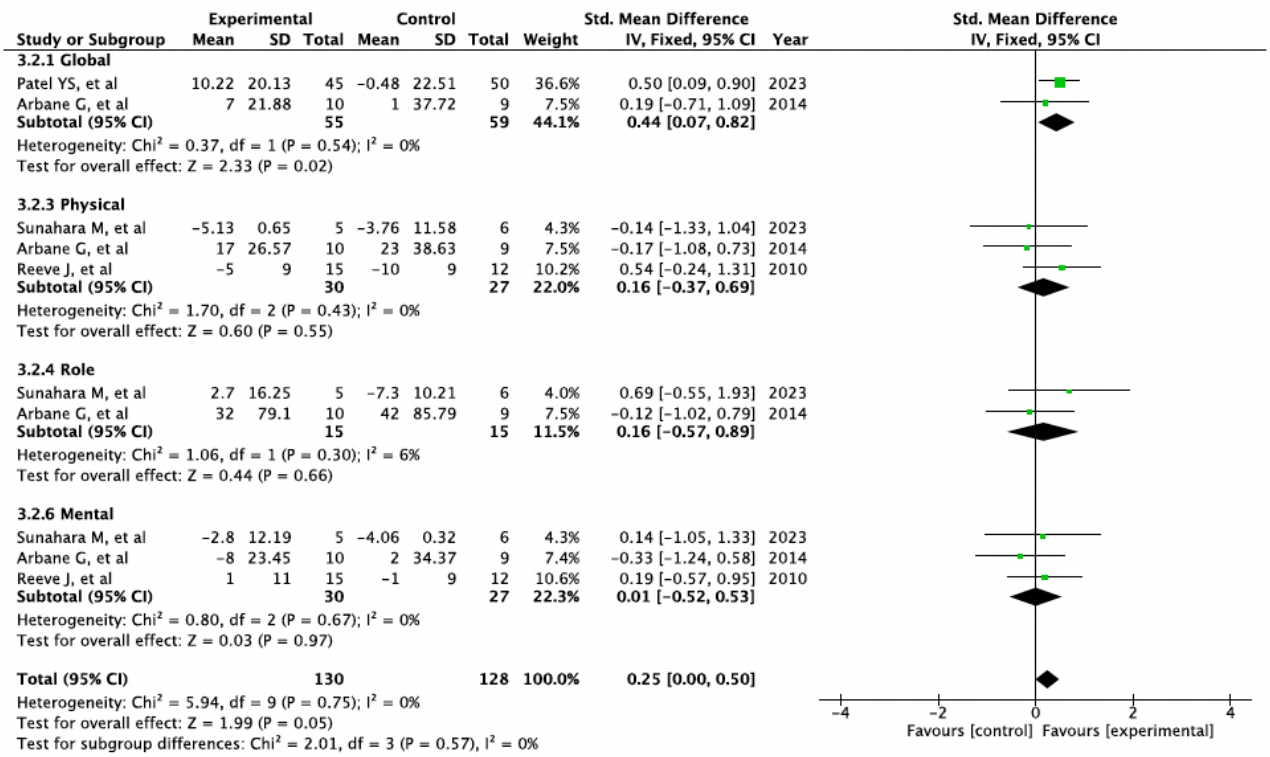

Experimental
Control
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI Year
IV, Fixed, 95% CI
Tenconi S, et al 6M 511.68 86.82 44 460.22 124.21 39 4.4% 51.46 [4.79, 98.13] 2021
Liu JF, et al 3M 402.4 65.2 26 360.9 58.2 28 8.7% 41.50 [8.44, 74.56] 2020
Liu Z, et al 1M 586.1 23.6 37 517.1 22.1 36 86.9% 69.00 [58.51, 79.49] 2020
Total (95% CI) 107 103 100.0% 65.83 [56.05, 75.60]
Heterogeneity: Chi² = 2.80, df = 2 (P = 0.25); I² = 28%
Test for overall effect: Z = 13.20 (P < 0.00001)
−100
−50
0
50
100
Favours [control]
Favours [experimental]

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Patel YS, et al	2.33	0.76	45	3	1.52	50	20.9%	−0.54 [−0.95, −0.13]	2023
Sunahara M, et al	18.87	12.07	16	17.7	43.3	18	19.0%	0.04 [−0.64, 0.71]	2023
Hoffman AJ, et al	0	0.7	37	4	2	35	19.2%	−2.67 [−3.32, −2.03]	2017
Hui-Mei C, et al	1.5	1.27	50	2.08	1.65	51	21.0%	−0.39 [−0.78, 0.00]	2016
Reeve J, et al	2	3	27	3	4	26	20.0%	−0.28 [−0.82, 0.26]	2010
Total (95% CI)			**175**			**180**	**100.0%**	**−0.76 [−1.53, 0.01]**	

Heterogeneity: $Tau^2 = 0.69$; $Chi^2 = 45.50$, df = 4 ($P < 0.00001$); $I^2 = 91\%$

Test for overall effect: Z = 1.93 (P = 0.05)




Experimental
Control
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI Year
IV, Fixed, 95% CI
3.2.1 Global
Patel YS, et al 10.22 20.13 45 -0.48 22.51 50 36.6% 0.50 [0.09, 0.90] 2023
Arbane G, et al 7 21.88 10 1 37.72 9 7.5% 0.19 [-0.71, 1.09] 2014
Subtotal (95% CI) 55 59 44.1% 0.44 [0.07, 0.82]
Heterogeneity: Chi² = 0.37, df = 1 (P = 0.54); I² = 0%
Test for overall effect: Z = 2.33 (P = 0.02)
3.2.3 Physical
Sunahara M, et al -5.13 0.65 5 -3.76 11.58 6 4.3% -0.14 [-1.33, 1.04] 2023
Arbane G, et al 17 26.57 10 23 38.63 9 7.5% -0.17 [-1.08, 0.73] 2014
Reeve J, et al -5 9 15 -10 9 12 10.2% 0.54 [-0.24, 1.31] 2010
Subtotal (95% CI) 30 27 22.0% 0.16 [-0.37, 0.69]
Heterogeneity: Chi² = 1.70, df = 2 (P = 0.43); I² = 0%
Test for overall effect: Z = 0.60 (P = 0.55)
3.2.4 Role
Sunahara M, et al 2.7 16.25 5 -7.3 10.21 6 4.0% 0.69 [-0.55, 1.93] 2023
Arbane G, et al 32 79.1 10 42 85.79 9 7.5% -0.12 [-1.02, 0.79] 2014
Subtotal (95% CI) 15 15 11.5% 0.16 [-0.57, 0.89]
Heterogeneity: Chi² = 1.06, df = 1 (P = 0.30); I² = 6%
Test for overall effect: Z = 0.44 (P = 0.66)
3.2.6 Mental
Sunahara M, et al -2.8 12.19 5 -4.06 0.32 6 4.3% 0.14 [-1.05, 1.33] 2023
Arbane G, et al -8 23.45 10 2 34.37 9 7.4% -0.33 [-1.24, 0.58] 2014
Reeve J, et al 1 11 15 -1 9 12 10.6% 0.19 [-0.57, 0.95] 2010
Subtotal (95% CI) 30 27 22.3% 0.01 [-0.52, 0.53]
Heterogeneity: Chi² = 0.80, df = 2 (P = 0.67); I² = 0%
Test for overall effect: Z = 0.03 (P = 0.97)
Total (95% CI) 130 128 100.0% 0.25 [0.00, 0.50]
Heterogeneity: Chi² = 5.94, df = 9 (P = 0.75); I² = 0%
Test for overall effect: Z = 1.99 (P = 0.05)
Test for subgroup differences: Chi² = 2.01, df = 3 (P = 0.57), I² = 0%
-4
-2
0
2
4
Favours [control]
Favours [experimental]