

Preoperative Exercise Training to Prevent Postoperative Pulmonary Complications in Adults Undergoing Major Surgery: A Systematic Review and Meta-analysis with Trial Sequential Analysis

Benjamin Assouline¹, Evelien Cools¹, Raoul Schorer¹, Bengt Kayser², Nadia Elia^{1,3}, Marc Licker^{1,3}

¹Department of Anesthesiology, Pharmacology and Intensive Care, University Hospital of Geneva, CH-1211 Geneva, Switzerland

²Institute of Sport Sciences, Synathlon, Uni-Centre, CH-1015 Lausanne, Switzerland

³Faculty of Medicine, University of Geneva, CH-1211 Geneva, Switzerland

Correspondence: Marc Licker, Department of Anesthesiology, Pharmacology and Intensive Care, University Hospital Geneva & Faculty of Medicine, CH-1206 Geneva.

E-mail: marc-joseph.licker@hcuge.ch

Role of the funding source: There was no external funding source for this project. The corresponding author had full access to all the data and carried responsibility for the decision to submit for publication.

Author Contributions: ML, BK, EC, BA and NE designed the study. EC, BA and ML searched the literature and extracted the data. RS contributed to data verification. BA, NE and ML analyzed the data. ML, BA, EC, NE, RS, NE and BK interpreted the data. ML drafted the manuscript, and BK, RS, BA, NE and EC critically reviewed the manuscript. The corresponding author had full access to all the data and carried responsibility for the decision to submit for publication.

Conflict of interest: Marc Licker and Bengt Kayser are authors of one of the trials included in this review. The other authors have no conflict of interest to disclose.

Key words: Exercise training, postoperative pulmonary complications, major surgery

Word Count: 3844

Subject Category: 8.26 Respiratory Muscles: Disease/Rehabilitation

Abstract

Rationale: Preoperative poor physical fitness and respiratory muscle weakness are associated with postoperative pulmonary complications that result in prolonged hospital length of stay and increased mortality.

Objectives: Examine the effect of preoperative exercise training on the risk of postoperative pulmonary complications across different surgical settings.

Methods: We searched MEDLINE, Web of Science, Embase, Pedro, and the Cochrane Central Register, without language restrictions, for studies from inception to July, 2020. We included randomized controlled trials that compared patients receiving exercise training with those receiving usual care or sham training before cardiac, lung, esophageal, or abdominal surgery. Postoperative pulmonary complications were the main outcome; secondary outcomes were preoperative functional changes, postoperative mortality, cardiovascular complications and hospital length of stay. The study was registered with PROSPERO (N° CRD42018096956).

Results: From 29 studies, 2'070 patients were pooled for meta-analysis. Compared to the control group, preoperative exercise training was associated with a lower incidence of postoperative pulmonary complications (23 studies, 1'864 patients, [RR] 0.52; 95% CI 0.41-0.66, grading of evidence: moderate); Trial Sequential Analysis confirmed effectiveness and there was no evidence of difference of effect across surgeries, type of training (respiratory muscles, endurance or combined) and preoperative duration of training. At the end of the preoperative period, exercise training resulted in increased peak oxygen uptake (weighted mean difference [WMD] +2 ml/kg/min, 99%CI 0.3 to 3.7) and higher maximal inspiratory pressure (WMD +12.2

cmH₂O, 99%CI 6.3 to 18.2). Hospital length of stay was shortened (WMD -2.3 days 99%CI -3.82 to -0.75) in the intervention group whereas no difference was found in postoperative mortality.

Conclusion: Preoperative exercise training improves physical fitness and reduces the risk to develop postoperative pulmonary complications while minimizing hospital resources utilization regardless of the type of intervention and surgery performed.

Abstract Word Count: 290

Over 230 million surgical procedures are performed worldwide each year. This number will continue to grow, in rich countries to cater an aging population and in emerging countries to match a growing need for invasive procedures with increasing health care capacities.^{1,2}

Complications arising from surgery represent major healthcare challenges. They prolong the hospital length of stay, increase medical costs and may decrease patients' quality of life and survival.³ Nowadays, postoperative pulmonary complications (PPCs) outnumber cardiac complications and their incidence ranges from 4% to 80%, depending on patient comorbidities, the type of surgery and the criteria used to define PPCs.^{4,5}

Besides advanced age and preexisting cardiopulmonary disease, low levels of physical fitness and respiratory muscle weakness are associated with poor overall outcomes following major surgery.^{6,7} In the early postoperative period, the contractile performance of respiratory muscles is impaired due to the residual effects of anesthetics and muscular relaxant drugs, to surgery-induced inflammation, ventilator-associated respiratory muscle disuse, and incisional pain causing afferent-mediated reflex inhibition of the phrenic nerve.⁸ Consequent to the patient's inability to fully expand the lungs and to clear airway secretions, atelectasis often develops in the early hours after tracheal extubation, paving the way to bacterial translocation with later onset of pneumonia.^{9,10}

Hence, there is a physiological rationale for training-induced improvement in physical fitness to enhance a patient's ability to sustain surgical stress. Various forms of physical rehabilitation strategies such as endurance training (ET) and respiratory muscle training (RMT) have demonstrated their effectiveness to enhance physical fitness and induce morphological and functional changes in the diaphragm while improving clinical conditions in patients

suffering from chronic obstructive pulmonary disease, neurological disorders and heart failure.¹¹⁻¹³ These training modalities have also been applied within the short waiting time period before surgery to enhance patient's physiological reserve and facilitate postoperative recovery.

Numerous systematic reviews have investigated the impact of preoperative exercise training on different clinical and functional outcomes. Most of them either focused on specific population groups (i.e. lung cancer¹⁴⁻¹⁹, colorectal cancer²⁰, oesophago-gastric cancer²¹, abdominal cancer^{22,23}, or any cancer²⁴), or specific procedures (cardiac surgery²⁵, vascular surgery²⁶, colorectal surgery²⁷ or major abdominal surgery²⁸⁻³⁰). Besides randomized controlled trials, some of these systematic reviews included non-randomized trials^{17,22,24,25,31}, observational cohort studies^{19,20,29}, single group trials^{17,31} or even case series.¹⁹ These specific analyses resulted in small numbers of trials being included and pooled, and since none of the previous meta-analyses performed with no trial sequential analysis (TSA). Therefore, it remained difficult to differentiate between negative and underpowered results and to catch the impact of pre-operative exercise interventions across different surgical settings.

Given recent additional publications in this active clinical field, an updated systematic review and meta-analysis, including TSA was warranted to assess the evidence for effectiveness of physical training within a limited preoperative time frame in preventing PPCs, while controlling for the risk of type I and II errors of conventional meta-analysis methods, and enabling to assess its clinical and functional impact across different surgical settings.

Methods

Protocol and Registration

This review is reported according to the PRISMA statement³² and the protocol was registered with the International Prospective Register of Systematic Reviews (CRD42018096956). The following minor changes were made to the registered protocol: RevMan 5.3, STATA 14 and the Cochrane Risk of Bias tool were used instead of the JBI-MASARI instrument and unpublished trials were not searched; grade assessment of the quality of evidence and TSA were performed; relative risks (RR) were reported instead of odds ratios for the primary outcome.

Information Sources and Search

MEDLINE, Web of Science, EMBASE, Pedro and the Cochrane Library were searched from inception to 14/07/2020, without language restriction, using free-text and MeSH terms related to surgery (lung, cardiac, oesophageal, abdominal), preoperative physical training (inspiratory or respiratory muscle training, prehabilitation, physical or exercise training) and randomized controlled trial [RCT]. Abdominal surgery entailed vascular or visceral interventions via laparotomy or laparoscopy; oesophageal surgery was considered separately given the thoracic, abdominal or combined surgical approaches. References from retrieved articles were reviewed for additional studies.

Eligibility Criteria

We included RCTs in adults undergoing elective surgery that examined the effects of preoperative physical exercise compared with usual care (control group) on postoperative outcome or hospital resource utilization. Trials were excluded if they were published as abstract only, if the exercise intervention was of low intensity or combined with a non-exercise based therapy (i.e., cognitive or nutritional intervention), was applied postoperatively (exclusively, or pre- and postoperatively), and if two different interventions were compared.

Study Selection

Two authors screened the titles and abstracts of potentially relevant records; two authors independently selected the trials based on full-text review. Disagreements were resolved by consensus.

Data Collection Process

For each included study, we extracted patient's characteristics and comorbidities, study site, surgery performed and information on the intervention (exercise modality, number of sessions, cumulated duration and timing before surgery).

Data Items

The primary endpoint was the incidence of PPCs. Secondary study endpoints entailed: preoperative changes in peak oxygen consumption (peakVO₂), maximal inspiratory pressure (MIP), six-minute walking test (6MWT), forced expiratory volume in the first second [FEV₁],

forced vital capacity [FVC], as well as in-hospital and thirty-day mortality, the occurrence of postoperative atelectasis, pneumonia and cardiovascular complications, the need for prolonged mechanical ventilation and the length of stay in ICU and hospital.

Corresponding authors were contacted for missing data (Table S1).

Risk of Bias in Individual Studies

The risk of bias of all studies was assessed using the Cochrane risk of bias tool and GRADEpro GDT (GRADEpro Guideline Development Tool [Software], McMaster University, 2015).-The assessment of the risk of bias was made on studies reporting on the primary outcome (PPC), by three investigators independently. Disagreements were resolved by discussion. Included trials were rated as low risk of bias when 5 domains were judged as low risk of bias.³³

Summary measures and synthesis of results. Meta-analyses were performed if data from at least 3 trials or 100 patients could be combined. For the main outcome, RRs with 95% confidence interval (CIs) were computed to compare intervention and control groups at the study level.

For secondary outcomes, we lowered the alpha-level to 0.01 due to multiple analyses and report RRs with 99% CIs. The effect estimates of individual studies were combined into a pooled weighted estimate using Mantel–Haenszel weights. In case of zero events, a constant continuity correction was applied by adding 0.5 to each cell.

For continuous outcomes, the mean differences in effects between intervention and control groups were computed at the study level, and pooled into weighted mean differences (WMDs) using the inverse variances method. For peakVO₂, MIP and 6MWT, we calculated

preoperative changes (between baseline and after training/usual care) in the two treatment arms separately.

We *a priori* expected that the included RCTs would be heterogeneous and used a random effects model throughout. Heterogeneity was estimated using I^2 statistic ($I^2 > 50\%$ considered relevant).

Prespecified subgroup analyses included stratification by surgeries, exercise training modality and duration of preoperative training for our primary outcome.

Publication bias was assessed graphically using funnel plots.³⁴

We performed TSA with O'Brien-Fleming alpha-spending boundaries for the primary outcome and for all stratified analyses to identify the minimum information size required to verify our hypotheses of a 30% risk reduction of PPCs' incidence (alpha-error 5%, power of 80%, 2-sided test). The incidence of PPC's in the control arm was estimated to be 30%.

All analyses were performed using RevMan 5.3 (Cochrane Collaboration, Oxford, UK), STATA 14 (StataCorp 2015. College Station TX: StataCorp LP) and TSA software (version 0.9 beta software, Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen, Denmark (<http://www.ctu.dk/>)).³⁵

Results

Selection of Studies

After removing 1'672 double hits, the search identified 1'405 unique records of which 1'351 did not fulfil the inclusion criteria (Figure 1). From a total of 54 selected articles, 25 were excluded

(Table S2). Hence, 29 studies involving 2'070 patients were included in the quantitative analyses.³⁶⁻⁶⁴

Risk of Bias within Studies

A summarized risk of bias assessment for studies reporting on PPCs is presented in Figure S1 and S2. Ten of 23 studies were rated as having low risk of bias for assessment of the primary outcome.^{38,40,42,45-47,49,52,59,63} Participants were not blinded to the intervention in all but one study.³⁸ High risk of bias was rated in two studies regarding blinding of outcome assessors,^{55,60} in two studies for incomplete outcome data,^{39,61} and in one study for selective outcome reporting.⁶¹ There was no trend regarding risk of bias over time (2014 to 2020: 6 of 16 trials [38%] were rated low risk of bias, compared to 4 of 13 trials [31%] before 2014).

Study Characteristics

The main characteristics of the study population are summarized in table 1. The RCTs were published between 1998 and 2020 and conducted in 13 different countries (5 in China,^{40,45,49-51} and in the Netherlands,^{41,42,46,47,59} 4 in Brazil^{37,44,56,63} and in the UK,^{36,43,48,58} 3 in Spain,^{38,53,62} 1 each in Canada,⁵⁵ Italy,⁵⁷ Japan,⁶¹ Israel,⁶⁰ Switzerland,⁵² Turkey,⁵⁴ France⁶⁴ and USA)³⁹. All studies were single centre, except two.^{52,59} The median number of patients per study was 44 (range 15 to 276). Ten studies focused on abdominal surgery [N=535],^{36-38,41-43,48,53,56,58} 11 on lung surgery [N=606],^{39,45,49-52,54,57,62,63},⁶⁴ six on cardiac surgery [N=628],^{40,44,46,47,55,60} and two on esophageal surgery [N=301].^{59,61} Eight trials included procedures performed under a minimally invasive approach, laparoscopy, robotic-or video-assisted surgery.^{36,45,49,50,52,53,59,62} The median

of the reported mean ages of the participants across studies was 64 years (range of reported means from 36 to 75 years), the median reported proportion of women per trial was 34% (range of reported proportions from 6 to 100%). From 17 studies where this information was reported, the median of prevalence of COPD was 30% (range from 7% to 100%).

The exercise training interventions were conducted in specialized centers (hospital in 17 studies, fitness centre in one study), at home (7 studies) or combining home and hospital settings (4 studies); they consisted in ET (8 studies),^{36,38,43,52,54,55,57,58} RMT (12 studies)^{37,40,41,44-48,53,59,60,64} or combined ET-RMT (9 studies).^{39,42,49-51,56,61-63} Each exercise training session lasted from 15 to 180 minutes, was performed 2 to 21 times per week, over 1 to 8 weeks before surgery with a median reported cumulated time of training of 460 min (interquartile range [IQR] 385 – 600 min) (Supplemental data, table S3).

The impact of preoperative exercise training on the incidence of PPCs was reported in 23 trials, on early postoperative mortality in 11, on the incidence of cardiovascular complications in 10, on the need for postoperative ventilation in 7 and on the hospital length of stay in 12 studies (Table 3 and S4). VO_2 peak, MIP, 6MWT, FEV₁ and FVC were reported in 5, 10, 7, 6 and 4 studies, respectively (Tables 2 and S4).

The PPCs were defined using the Clavien-Dindo Classification Score or the Thoracic Morbidity Mortality system,^{38,45,49,52,61,64} Kroenke's grading system,^{40,46} the Melbourne Group scale⁶² or other specific criteria.^{36,37,39,41,42,47,48,50,51,54,60,63} In two studies,^{44,60} the definition criteria for PPCs were not mentioned (Table S5).

The adherence to the training intervention was reported in 10 trials with a median of the reported adherence to the prescribed training sessions of 87% (range from 67% to 100%)

(Table S6).^{36,39,42,43,48,52,58,59,62,64} Adverse events were not reported in 13 RCTs and declared absent in 15 RCTs; Tew et al⁵⁸ reported two (out of 27) patients who interrupted their training program, one due to dizziness and the other to angina pectoris.

Synthesis of Results

Primary outcome. The incidences of PPCs in the control and intervention groups were 31.1% and 17.7%, respectively (in studies classified as low risk of bias, 32.4% vs 19.7%). Hence, preoperative exercise training was associated with a reduced risk of PPCs compared with the control group (RR 0.52; 95% CI 0.41 to 0.66; $I^2=36\%$; number needed to treat computed from risk ratio [NNT] of 8; Figure 2). The funnel plot for the primary outcome suggested no publication bias (Figure S3).

The TSA estimated that, based on our preset criteria, a sample size of 1'354 was required to reach a definite conclusion (Figure S4). The studies included 1'864 patients, the cumulative Z curve crossed the alpha spending boundary in 2011, reached the required information size in 2017 and remained above the 5% threshold since. Therefore, the evidence of an effect of at least a 30% reduction in PPCs was confirmed. The meta-analysis of the 10 low risk of bias RCTs (1'239 patients) suggested a reduced risk of PPCs (RR 0.57; 95% CI 0.40 to 0.80; $I^2=55\%$). In TSA, the cumulative Z curve crossed the alpha spending boundary but the required information size was not reached (Figure S5). Due to an increased heterogeneity, the required information size was higher in the low risk of bias studies.

Subgroup analyses of the primary endpoint did not show differences in the impact of physical exercise training on PPCs according to type of surgeries ($p=0.71$, figures 3 and S6), to

modalities of physical training ($p=0.46$, fig S7), or time of exercise administration ($p=0.30$, figure S8). Overall, the quality of evidence was considered moderate since 10 of the 23 analysed RCTs with the primary outcome were judged low risk of bias (figure S9).

Secondary endpoints. Patients in the two treatment arms presented similar baseline peak VO_2 (mean values of 17.4 ml.kg^{-1} and 17.2 ml.kg^{-1} in the control and intervention groups, respectively), MIP (mean values of $77 \text{ cmH}_2\text{O}$ and $81 \text{ cmH}_2\text{O}$, in control and intervention groups, respectively) and 6MWT (mean values of 419 m and 431 m in the control and intervention groups, respectively). During the preoperative waiting period, the control group presented non-significant changes and, exercise training led to increase in peak VO_2 (WMD $+1.72 \text{ ml.kg}^{-1}.\text{min}^{-1}$, 99%CI 0.33 to 3.11) and in MIP (WMD $+15.5 \text{ cmH}_2\text{O}$, 99%CI 12.5 to 18.4) with no significant change at the 6MWT (WMD $+30.7 \text{ m}$, 99%CI -2.3 to 63.6) (Table 2). Preoperative peak VO_2 and MIP were greater in patients who underwent exercise training compared with controls (Table 2). The 6MWT, FEV1 and FVC did not differ significantly between the two groups.

The early postoperative mortality rate was 2.3% and the incidence of cardiovascular complications was 11.0%, with no difference between the two groups (Table 3). Preoperative exercise training was associated with lower risks of pneumonia (RR 0.72 99%CI 0.52 to 0.98 , $I^2=2\%$) and atelectasis (RR 0.48 , 99%CI 0.29 to 0.81 , $I^2=0\%$), along with shorter in-hospital length of stay (WMD -2.3 days 99%CI -3.82 to -0.76 , $I^2=50\%$).

Discussion

Summary of Evidence

This systematic review and meta-analysis examined various exercise training programs prescribed during the generally short preoperative waiting period and summarizes their efficacy in terms of preoperative meaningful functional changes and postoperative clinically relevant outcomes. The results indicate that short-term exercise training enhances patient physical fitness before major surgery and provides protective effects against PPCs confirmed by TSA, regardless of the type, duration and timing of intervention, patient's population or type of surgery. Our findings further suggest that, preoperative exercise training is probably safe, and may spare health care resources by shortening ICU and hospital lengths of stay.

Previous meta-analysis,¹⁴⁻³¹ have explored the impact of uni- or multimodal training modalities applied during the pre- and/or postoperative periods mostly in groups of patients with specific pathologies (e.g., cancer, aortic aneurysm, coronary artery disease, obesity). The evidence supporting any beneficial effects of pre- and/or postoperative physical training was weakened by the limited number of RCTs available per pathology or procedure, leading to small numbers of analysed patients, and did not allow to compare the impact of these intervention across various surgical settings.

In this meta-analysis, the study population encompassed patients undergoing the most common major surgical procedures performed worldwide, namely valve or coronary artery bypass surgery, aortic aneurysm repair, bariatric surgery as well as lung and digestive cancer resection.

Physical training varied in terms of exercise modalities (ET, RMT or combined), training time window before surgery (one to eight weeks), cumulated training duration, workload intensity (moderate or high), and logistic aspects (hospital and/or home-based training settings). It has been suggested that training-induced physiological improvements are inversely related to baseline fitness level and directly to the training load as expressed by the cumulative sum of the product of exercise intensity and duration of each training session.⁶⁵ Compared to a healthy population, our surgical patients presented substantial impairments in aerobic capacity (~60% predicted peak VO₂),⁶⁶ in walking capacity (~60% predicted SMWT)⁶⁷ and in inspiratory muscle strength (~70% of predicted MIP).⁶⁸ This could explain that, training-induced protective pulmonary effects were achieved regardless of the preoperative time delay. Patients who trained over one week likely engaged in more intense, frequent and longer exercise sessions than those who trained >1 week, triggering favourable phenotypical changes, as reported in patients with COPD.⁶⁹

Preoperative RMT using resistive threshold loading devices, volume incentive spirometry and/or breathing exercises resulted in inspiratory muscle strengthening as reflected by a 20% gain in MIP (mean increase of 15 cmH₂O, compared with baseline). Experimental and clinical studies have demonstrated that 1-8 weeks of RMT resulted in improved neural control of respiratory muscles and increased thickness of the diaphragm due to hypertrophic changes of fast-twitch fibres and a higher proportion of slow oxidative fibres with enhanced aerobic mechanical performances.^{70,71} Such reinforcement and resistance to fatigue of the respiratory muscles would enable patients to better sustain the higher ventilatory workload in the early postoperative period while preventing atelectasis formation and improving gas exchange. Due

to the enhanced metabolic capacity and more efficient contraction-relaxation of the respiratory muscles, there is less muscle fatigue, which in turn would alleviate the sympathetic mediated vasoconstriction and promote blood flow redistribution from the respiratory muscles towards the limb muscles (metaboreflex), improving therefore the walking capacity.⁷²

We also observed that preoperative moderate-to-high intensity ET using cycle-ergometer or treadmill exercise increased peakVO₂ during CPET (11% gain in peakVO₂, compared with baseline). In agreement with previous analyses, such training failed to produce any gain in functional lung capacity and FEV₁ since airflow limitation is associated with irreversible damage in lung parenchyma and airways.⁷³ In contrast, a strong body of scientific evidence supports the contention that an ET-induced improvement in aerobic capacity results from a rapid increase in mitochondrial oxidative capacity and biogenesis within all working skeletal muscle through up-regulation of peroxisome proliferative activated receptor- α coactivator-1 and key enzymes in the tricarboxylic acid cycle.^{74,75} Short-term ET has also been shown to induce early cardiovascular adaptive changes as reflected by greater muscular capillary density and increased cardiac output owing to an expanded blood volume with improved ventricular relaxation, reduced sympathetic neural drive and enhanced vasodilatory response, all factors that facilitate the oxygen delivery and uptake to match the energy demand within working skeletal muscle.^{76,77} Finally, given the higher ventilatory load imposed by moderate-to-high ET, structural and functional adaptive changes have also been reported within the respiratory muscles conferring higher strength and resistance to fatiguing contractions while reducing the metaboreflex.⁷⁸

Altogether, our findings indicate that, by reversing respiratory muscle weakness and low aerobic capacity, preoperative exercise training is an effective and protective strategy against PPCs following cardiac, lung and abdominal surgery. In patients undergoing oesogastric surgery, Valkenet et al⁵⁹ found no favourable clinical effect of preoperative RMT whereas Yamana et al⁶¹ reported a lower incidence of PPCs in patients receiving combined ET-RMT. Severe sarcopenia, depressed immunity and a frail physical status are more frequent among these patients making them more vulnerable to pneumonia and sepsis. Therefore, in these patients, multimodal reconditioning approaches using combined physical training modalities in addition to nutritional and psychological support, may be necessary over longer periods of time.

Preoperative exercise training was not associated with relevant changes in the occurrence of cardiovascular complications among the included trials. Supra-ventricular arrhythmias - the most frequent postoperative cardiac events in cardiothoracic procedures- are mainly related to surgery-induced inflammation and autonomic nerve injuries, which are therefore poorly responsive to any physical training intervention. In contrast, myocardial ischemia/infarct and worsening/new heart failure are rare events that could benefit from the enhanced endothelial function, myocardial capillarization and ventricular relaxation associated with short-term exercise training.⁷⁹ From the 16 trials reporting adverse events during the training period, one trial reported a single patient who experienced short-lasting angina pectoris (one in 657 participants). Therefore, in patients in whom severe or unstable ischemic heart disease can be ruled out based on preoperative work up, ET with/without RMT can be safely conducted at home or in medicalized settings, as far as the first session is supervised by a physiotherapist with immediate access to rescue facilities and resources.

Strengths and Limitations

The strengths of our systematic review include its comprehensive and up-to-date search, the broad eligibility criteria for all major surgeries that enhance generalizability and subgroups comparisons, and methodological rigor to examine the different training modalities (type, duration, intensity, frequency). Our analyses of functional and clinical outcomes included more than 2'000 participants, yielded robust secondary analyses results, and were supported by conservative TSA.

Several limitations need to be acknowledged. First, 23 of the 29 included studies had a sample size less than 100 patients and are therefore subjected to small study effect bias.⁷⁹ There were also deficiencies in reporting information regarding procedural aspects such as dropout rate and adherence to the intervention.

Second, the diagnosis of PPCs was based on variable clinical criteria with the risk of under- or over estimating the true incidence of PPCs. However, this factor should have equally affected the two groups, and secondary analysis on the occurrence of atelectasis and pneumonia has confirmed the favourable effects of exercise training. Since double-blinding was not achieved in most studies, this could potentially have biased the assessment of PPC.

Third, the exercise programs were highly heterogeneous in terms of their practical modalities, their physiological targets and the role of supervision. Although protection against PPCs could be achieved by providing exercise training over just one week, our data did not allow identification of a minimum exercise training volume/load associated with a favourable clinical outcome.

Fourth, we were unable to assess the risk-benefit and cost-benefit ratios related to the intervention. Although the risk related to moderate/intense training appears minimal, adverse events were not reported in 13 trials, and it remains unclear whether none occurred or were underreported while the costs related to health care were not at all considered in most of the included studies. Nevertheless, the observed reduction in hospital length of stay (-2 to 3 days) would obviously largely offset the costs related to 10 to 30 supervised training sessions.⁸⁰

Conclusion

In conclusion, this systematic review supports the generalization of preoperative exercise training to reduce the risk of PPCs, with firm evidence from TSA in patients undergoing thoracic, abdominal cardiac or lung procedures, and when ET or combined ET-RMT are used.

Further large high-quality studies using clinical endpoints defined by standardized criteria are required to explore the essential components of exercise training (e.g., optimal duration, intensity and frequency of training sessions), but also to quantify the cost-effectiveness which remains a largely unanswered question despite numerous published trials, and to question the potential benefits of bundles of interventions including resistance exercises, nutritional support and stress-relaxation techniques.

The future of preoperative exercise training may yet lie with protocols that permit a more individualized approach based on a greater understanding of the complex interplay between a genetic background, pathophysiological features and social environments of patients scheduled to undergo major surgical procedures.

References

1. Weiser TG, Haynes AB, Molina G, et al. Estimate of the global volume of surgery in 2012: an assessment supporting improved health outcomes. *Lancet*. 2015;385 Suppl 2:S11.
2. Gupta S, Groen RS, Kyamanywa P, et al. Surgical care needs of low-resource populations: an estimate of the prevalence of surgically treatable conditions and avoidable deaths in 48 countries. *Lancet*. 2015;385 Suppl 2:S1.
3. Khuri SF, Henderson WG, DePalma RG, et al. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. *Ann Surg*. 2005;242(3):326-341; discussion 341-323.
4. Fernandez-Bustamante A, Frenzl G, Sprung J, et al. Postoperative Pulmonary Complications, Early Mortality, and Hospital Stay Following Noncardiothoracic Surgery: A Multicenter Study by the Perioperative Research Network Investigators. *JAMA Surg*. 2017;152(2):157-166.
5. Miskovic A, Lumb AB. Postoperative pulmonary complications. *Br J Anaesth*. 2017;118(3):317-334.
6. Hall DE, Arya S, Schmid KK, et al. Association of a Frailty Screening Initiative With Postoperative Survival at 30, 180, and 365 Days. *JAMA Surg*. 2017;152(3):233-240.
7. Lee CHA, Kong JC, Ismail H, Riedel B, Heriot A. Systematic Review and Meta-analysis of Objective Assessment of Physical Fitness in Patients Undergoing Colorectal Cancer Surgery. *Dis Colon Rectum*. 2018;61(3):400-409.
8. Welvaart WN, Paul MA, Stienen GJ, et al. Selective diaphragm muscle weakness after contractile inactivity during thoracic surgery. *Ann Surg*. 2011;254(6):1044-1049.
9. van Kaam AH, Lachmann RA, Herting E, et al. Reducing atelectasis attenuates bacterial growth and translocation in experimental pneumonia. *Am J Respir Crit Care Med*. 2004;169(9):1046-1053.
10. Sieck GC, Ferreira LF, Reid MB, Mantilla CB. Mechanical properties of respiratory muscles. *Compr Physiol*. 2013;3(4):1553-1567.
11. Booth FW, Roberts CK, Thyfault JP, Rueggsegger GN, Toedebusch RG. Role of Inactivity in Chronic Diseases: Evolutionary Insight and Pathophysiological Mechanisms. *Physiol Rev*. 2017;97(4):1351-1402.
12. Wuytack F, Devane D, Stovold E, et al. Comparison of outpatient and home-based exercise training programmes for COPD: A systematic review and meta-analysis. *Respirology*. 2018;23(3):272-283.
13. Long L, Mordi IR, Bridges C, et al. Exercise-based cardiac rehabilitation for adults with heart failure. *Cochrane Database Syst Rev*. 2019;1:CD003331.
14. Cavalheri V, Granger C. Preoperative exercise training for patients with non-small cell lung cancer. *Cochrane Database Syst Rev*. 2017;6:CD012020.
15. Crandall K, Maguire R, Campbell A, Kearney N. Exercise intervention for patients surgically treated for Non-Small Cell Lung Cancer (NSCLC): a systematic review. *Surg Oncol*. 2014;23(1):17-30.
16. Mainini C, Rebelo PF, Bardelli R, et al. Perioperative physical exercise interventions for patients undergoing lung cancer surgery: What is the evidence? *SAGE Open Med*. 2016;4:2050312116673855.

17. Pouwels S, Fiddelaers J, Teijink JA, Woorst JF, Siebenga J, Smeenk FW. Preoperative exercise therapy in lung surgery patients: A systematic review. *Respir Med*. 2015;109(12):1495-1504.
18. Rodriguez-Larrad A, Lascurain-Aguirrebena I, Abecia-Inchaurregui LC, Seco J. Perioperative physiotherapy in patients undergoing lung cancer resection. *Interact Cardiovasc Thorac Surg*. 2014;19(2):269-281.
19. Sebio Garcia R, Yanez Brage MI, Gimenez Moolhuyzen E, Granger CL, Denehy L. Functional and postoperative outcomes after preoperative exercise training in patients with lung cancer: a systematic review and meta-analysis. *Interact Cardiovasc Thorac Surg*. 2016;23(3):486-497.
20. Boereboom C, Doleman B, Lund JN, Williams JP. Systematic review of pre-operative exercise in colorectal cancer patients. *Tech Coloproctol*. 2016;20(2):81-89.
21. Bolger JC, Loughney L, Tully R, et al. Perioperative prehabilitation and rehabilitation in esophagogastric malignancies: a systematic review. *Dis Esophagus*. 2019.
22. Hijazi Y, Gondal U, Aziz O. A systematic review of prehabilitation programs in abdominal cancer surgery. *Int J Surg*. 2017;39:156-162.
23. Thomas G, Tahir MR, Bongers BC, Kallen VL, Slooter GD, van Meeteren NL. Prehabilitation before major intra-abdominal cancer surgery: A systematic review of randomised controlled trials. *Eur J Anaesthesiol*. 2019;36(12):933-945.
24. Steffens D, Beckenkamp PR, Hancock M, Solomon M, Young J. Preoperative exercise halves the postoperative complication rate in patients with lung cancer: a systematic review of the effect of exercise on complications, length of stay and quality of life in patients with cancer. *Br J Sports Med*. 2018;52(5):344.
25. Snowdon D, Haines TP, Skinner EH. Preoperative intervention reduces postoperative pulmonary complications but not length of stay in cardiac surgical patients: a systematic review. *J Physiother*. 2014;60(2):66-77.
26. Pouwels S, Willigendael EM, van Sambeek MR, Nienhuijs SW, Cuypers PW, Teijink JA. Beneficial Effects of Pre-operative Exercise Therapy in Patients with an Abdominal Aortic Aneurysm: A Systematic Review. *Eur J Vasc Endovasc Surg*. 2015;49(1):66-76.
27. Gillis C, Buhler K, Bresee L, et al. Effects of Nutritional Prehabilitation, With and Without Exercise, on Outcomes of Patients Who Undergo Colorectal Surgery: A Systematic Review and Meta-analysis. *Gastroenterology*. 2018;155(2):391-410 e394.
28. Heger P, Probst P, Wiskemann J, Steindorf K, Diener MK, Mihaljevic AL. A Systematic Review and Meta-analysis of Physical Exercise Prehabilitation in Major Abdominal Surgery (PROSPERO 2017 CRD42017080366). *J Gastrointest Surg*. 2020;24(6):1375-1385.
29. Luther A, Gabriel J, Watson RP, Francis NK. The Impact of Total Body Prehabilitation on Post-Operative Outcomes After Major Abdominal Surgery: A Systematic Review. *World J Surg*. 2018;42(9):2781-2791.
30. Pouwels S, Stokmans RA, Willigendael EM, et al. Preoperative exercise therapy for elective major abdominal surgery: a systematic review. *Int J Surg*. 2014;12(2):134-140.
31. Singh F, Newton RU, Galvao DA, Spry N, Baker MK. A systematic review of pre-surgical exercise intervention studies with cancer patients. *Surg Oncol*. 2013;22(2):92-104.

32. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ*. 2015;350:g7647.
33. Savovic J, Turner RM, Mawdsley D, et al. Association Between Risk-of-Bias Assessments and Results of Randomized Trials in Cochrane Reviews: The ROBES Meta-Epidemiologic Study. *Am J Epidemiol*. 2018;187(5):1113-1122.
34. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560.
35. Wetterslev J, Jakobsen JC, Gluud C. Trial Sequential Analysis in systematic reviews with meta-analysis. *BMC Med Res Methodol*. 2017;17(1):39.
36. Barakat HM, Shahin Y, Khan JA, McCollum PT, Chetter IC. Preoperative Supervised Exercise Improves Outcomes After Elective Abdominal Aortic Aneurysm Repair: A Randomized Controlled Trial. *Ann Surg*. 2016;264(1):47-53.
37. Barbalho-Moulim MC, Miguel GP, Forti EM, Campos Fdo A, Costa D. Effects of preoperative inspiratory muscle training in obese women undergoing open bariatric surgery: respiratory muscle strength, lung volumes, and diaphragmatic excursion. *Clinics (Sao Paulo)*. 2011;66(10):1721-1727.
38. Barberan-Garcia A, Ubre M, Roca J, et al. Personalised Prehabilitation in High-risk Patients Undergoing Elective Major Abdominal Surgery: A Randomized Blinded Controlled Trial. *Ann Surg*. 2018;267(1):50-56.
39. Benzo R, Wigle D, Novotny P, et al. Preoperative pulmonary rehabilitation before lung cancer resection: results from two randomized studies. *Lung Cancer*. 2011;74(3):441-445.
40. Chen X, Hou L, Zhang Y, et al. The effects of five days of intensive preoperative inspiratory muscle training on postoperative complications and outcome in patients having cardiac surgery: a randomized controlled trial. *Clin Rehabil*. 2019;33(5):913-922.
41. Dronkers J, Veldman A, Hoberg E, van der Waal C, van Meeteren N. Prevention of pulmonary complications after upper abdominal surgery by preoperative intensive inspiratory muscle training: a randomized controlled pilot study. *Clin Rehabil*. 2008;22(2):134-142.
42. Dronkers JJ, Lamberts H, Reutelingsperger IM, et al. Preoperative therapeutic programme for elderly patients scheduled for elective abdominal oncological surgery: a randomized controlled pilot study. *Clin Rehabil*. 2010;24(7):614-622.
43. Dunne DF, Jack S, Jones RP, et al. Randomized clinical trial of prehabilitation before planned liver resection. *Br J Surg*. 2016;103(5):504-512.
44. Ferreira PE, Rodrigues AJ, Evora PR. Effects of an inspiratory muscle rehabilitation program in the postoperative period of cardiac surgery. *Arq Bras Cardiol*. 2009;92(4):275-282.
45. Huang J, Lai Y, Zhou X, et al. Short-term high-intensity rehabilitation in radically treated lung cancer: a three-armed randomized controlled trial. *J Thorac Dis*. 2017;9(7):1919-1929.
46. Hulzebos EH, Helders PJ, Favie NJ, De Bie RA, Brutel de la Riviere A, Van Meeteren NL. Preoperative intensive inspiratory muscle training to prevent postoperative pulmonary

- complications in high-risk patients undergoing CABG surgery: a randomized clinical trial. *JAMA*. 2006;296(15):1851-1857.
47. Hulzebos EH, van Meeteren NL, van den Buijs BJ, de Bie RA, Brutel de la Riviere A, Helders PJ. Feasibility of preoperative inspiratory muscle training in patients undergoing coronary artery bypass surgery with a high risk of postoperative pulmonary complications: a randomized controlled pilot study. *Clin Rehabil*. 2006;20(11):949-959.
 48. Kulkarni SR, Fletcher E, McConnell AK, Poskitt KR, Whyman MR. Pre-operative inspiratory muscle training preserves postoperative inspiratory muscle strength following major abdominal surgery - a randomised pilot study. *Ann R Coll Surg Engl*. 2010;92(8):700-707.
 49. Lai Y, Huang J, Yang M, Su J, Liu J, Che G. Seven-day intensive preoperative rehabilitation for elderly patients with lung cancer: a randomized controlled trial. *J Surg Res*. 2017;209:30-36.
 50. Lai Y, Su J, Qiu P, et al. Systematic short-term pulmonary rehabilitation before lung cancer lobectomy: a randomized trial. *Interact Cardiovasc Thorac Surg*. 2017;25(3):476-483.
 51. Lai Y, Su J, Yang M, Zhou K, Che G. [Impact and Effect of Preoperative Short-term Pulmonary Rehabilitation Training on Lung Cancer Patients with Mild to Moderate Chronic Obstructive Pulmonary Disease: A Randomized Trial]. *Zhongguo Fei Ai Za Zhi*. 2016;19(11):746-753.
 52. Licker M, Karenovics W, Diaper J, et al. Short-Term Preoperative High-Intensity Interval Training in Patients Awaiting Lung Cancer Surgery: A Randomized Controlled Trial. *J Thorac Oncol*. 2017;12(2):323-333.
 53. Llorens J, Rovira L, Ballester M, et al. Preoperative inspiratory muscular training to prevent postoperative hypoxemia in morbidly obese patients undergoing laparoscopic bariatric surgery. A randomized clinical trial. *Obes Surg*. 2015;25(6):1003-1009.
 54. Pehlivan E, Turna A, Gurses A, Gurses HN. The effects of preoperative short-term intense physical therapy in lung cancer patients: a randomized controlled trial. *Ann Thorac Cardiovasc Surg*. 2011;17(5):461-468.
 55. Sawatzky JA, Kehler DS, Ready AE, et al. Prehabilitation program for elective coronary artery bypass graft surgery patients: a pilot randomized controlled study. *Clin Rehabil*. 2014;28(7):648-657.
 56. Soares SM, Nucci LB, da Silva MM, Campacci TC. Pulmonary function and physical performance outcomes with preoperative physical therapy in upper abdominal surgery: a randomized controlled trial. *Clin Rehabil*. 2013;27(7):616-627.
 57. Stefanelli F, Meoli I, Cobuccio R, et al. High-intensity training and cardiopulmonary exercise testing in patients with chronic obstructive pulmonary disease and non-small-cell lung cancer undergoing lobectomy. *Eur J Cardiothorac Surg*. 2013;44(4):e260-265.
 58. Tew GA, Batterham AM, Colling K, et al. Randomized feasibility trial of high-intensity interval training before elective abdominal aortic aneurysm repair. *Br J Surg*. 2017;104(13):1791-1801.
 59. Valkenet K, Trappenburg JCA, Ruurda JP, et al. Multicentre randomized clinical trial of inspiratory muscle training versus usual care before surgery for oesophageal cancer. *Br J Surg*. 2018;105(5):502-511.

60. Weiner P, Zeidan F, Zamir D, et al. Prophylactic inspiratory muscle training in patients undergoing coronary artery bypass graft. *World J Surg.* 1998;22(5):427-431.
61. Yamana I, Takeno S, Hashimoto T, et al. Randomized Controlled Study to Evaluate the Efficacy of a Preoperative Respiratory Rehabilitation Program to Prevent Postoperative Pulmonary Complications after Esophagectomy. *Dig Surg.* 2015;32(5):331-337.
62. Sebio Garcia R, Yanez-Brage MI, Gimenez Moolhuyzen E, Salorio Riobo M, Lista Paz A, Borro Mate JM. Preoperative exercise training prevents functional decline after lung resection surgery: a randomized, single-blind controlled trial. *Clin Rehabil.* 2017;31(8):1057-1067.
63. Morano MT, Araujo AS, Nascimento FB, et al. Preoperative pulmonary rehabilitation versus chest physical therapy in patients undergoing lung cancer resection: a pilot randomized controlled trial. *Arch Phys Med Rehabil.* 2013;94(1):53-58.
64. Laurent H, Aubreton S, Galvaing G, et al. Preoperative respiratory muscle endurance training improves ventilatory capacity and prevents pulmonary postoperative complications after lung surgery. *Eur J Phys Rehabil Med.* 2020;56(1):73-81.
65. Storen O, Helgerud J, Saebo M, et al. The Effect of Age on the V O₂max Response to High-Intensity Interval Training. *Med Sci Sports Exerc.* 2017;49(1):78-85.
66. Rapp D, Scharhag J, Wagenpfeil S, Scholl J. Reference values for peak oxygen uptake: cross-sectional analysis of cycle ergometry-based cardiopulmonary exercise tests of 10 090 adult German volunteers from the Prevention First Registry. *BMJ Open.* 2018;8(3):e018697.
67. Camarri B, Eastwood PR, Cecins NM, Thompson PJ, Jenkins S. Six minute walk distance in healthy subjects aged 55-75 years. *Respir Med.* 2006;100(4):658-665.
68. Sclauser Pessoa IM, Franco Parreira V, Fregonezi GA, Sheel AW, Chung F, Reid WD. Reference values for maximal inspiratory pressure: a systematic review. *Can Respir J.* 2014;21(1):43-50.
69. Zeng Y, Jiang F, Chen Y, Chen P, Cai S. Exercise assessments and trainings of pulmonary rehabilitation in COPD: a literature review. *Int J Chron Obstruct Pulmon Dis.* 2018;13:2013-2023.
70. Downey AE, Chenoweth LM, Townsend DK, Ranum JD, Ferguson CS, Harms CA. Effects of inspiratory muscle training on exercise responses in normoxia and hypoxia. *Respir Physiol Neurobiol.* 2007;156(2):137-146.
71. Jaenisch RB, Bertagnolli M, Borghi-Silva A, Arena R, Lago PD. Respiratory Muscle Training Improves Diaphragm Citrate Synthase Activity and Hemodynamic Function in Rats with Heart Failure. *Braz J Cardiovasc Surg.* 2017;32(2):104-110.
72. Dempsey JA, Romer L, Rodman J, Miller J, Smith C. Consequences of exercise-induced respiratory muscle work. *Respir Physiol Neurobiol.* 2006;151(2-3):242-250.
73. McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2015(2):CD003793.
74. Gidlund EK, Ydfors M, Appel S, Rundqvist H, Sundberg CJ, Norrbom J. Rapidly elevated levels of PGC-1 α -b protein in human skeletal muscle after exercise: exploring regulatory factors in a randomized controlled trial. *J Appl Physiol (1985).* 2015;119(4):374-384.

75. Granata C, Jamnick NA, Bishop DJ. Principles of Exercise Prescription, and How They Influence Exercise-Induced Changes of Transcription Factors and Other Regulators of Mitochondrial Biogenesis. *Sports Med.* 2018;48(7):1541-1559.
76. Murias JM, Kowalchuk JM, Paterson DH. Time course and mechanisms of adaptations in cardiorespiratory fitness with endurance training in older and young men. *J Appl Physiol (1985).* 2010;108(3):621-627.
77. Roman MA, Rossiter HB, Casaburi R. Exercise, ageing and the lung. *Eur Respir J.* 2016;48(5):1471-1486.
78. Sollanek KJ, Burniston JG, Kavazis AN, et al. Global Proteome Changes in the Rat Diaphragm Induced by Endurance Exercise Training. *PLoS One.* 2017;12(1):e0171007.
79. Bernardo BC, Ooi JYY, Weeks KL, Patterson NL, McMullen JR. Understanding Key Mechanisms of Exercise-Induced Cardiac Protection to Mitigate Disease: Current Knowledge and Emerging Concepts. *Physiol Rev.* 2018;98(1):419-475.
80. Barberan-Garcia A, Ubre M, Pascual-Argente N, et al. Post-discharge impact and cost-consequence analysis of prehabilitation in high-risk patients undergoing major abdominal surgery: secondary results from a randomised controlled trial. *Br J Anaesth.* 2019;123(4):450-456.

Figure Legends:

Figure 1. PRISMA flow diagram for the systematic review and meta-analysis

Figure 2. Forrest plot of the effect of preoperative exercise training on postoperative pulmonary complications, including all randomized controlled trials

Figure 3: Analysis of postoperative pulmonary complications according to type of surgery, type of exercise training and duration of training

Table 1: Main characteristics of included studies

Study year	Sample N	Patient characteristics				Surgery	Training				
		Age (yr) mean	Women %	COPD %	Main Pathology	Type	Type	Site	Preop (week)	Cumulated time (min)	Intensity*
Laurent 2020	26	63.0	30.7	-	Cancer	Lung	RMT ^{1,2}	Home	3	360	Moderate
Chen 2019	197	61.7	28.4	-	CAD / VD	Cardiac	RMT ¹	Hospital	1	200	High
Valkenet 2018	241	63.2	22.8	13.7	Cancer	Oesophageal (61% MIA)	RMT ^{1,2}	Home	2	160	High
Sebio Garcia 2017	22	70.2	9.0	-	Cancer	Lung (100% MIA)	Comb ¹	Hospital	at least 2	660	Moderate
Huang 2017	60	63.9	30	16.7	Cancer	Lung (73% MIA)	RMT ¹	Hospital	1	840	Moderate
Lai 2017	101	64.2	44.5	43.5	Cancer	Lung (65% MIA)	Comb ¹	Hospital	1	385	Moderate
Lai 2017	60	72.1	43.5	15	Cancer	Lung (68% MIA)	Comb ¹	Hospital	1	385	Moderate
Licker 2017	151	64.0	36.3	38.3	Cancer	Lung (17% MIA)	ET ¹	Hospital	3 to 4	460	High
Tew 2017	53	74.8	6.0	24.5	Aneurysm	Abdominal	ET ¹	Hospital	4	360	High
Barberan-Garcia 2017	125	71.0	26.0	-	Cancer (75%)	Abdominal	ET ^{1,2}	Home	4	560	High

Barakat 2016	124	73.4	10.5	33.1	Aneurysm	Abdominal (63% MIA)	ET ¹	Hospital	6	1080	Moderate	
Dunne 2016	38	61.5	28.5	18.5	Cancer	Abdominal (100% MIA)	ET ¹	Hospital	4	420	High	
Lai 2016	48	63.5	42.0	71.0	Cancer	Lung	Comb ¹	Hospital	1	385	Moderate	
Yamana 2015	60	67.1	22.0	-	Cancer	Oesophageal	Comb ¹	Hospital	at least 1	420	Moderate	
Llorens 2015	44	73.4	47.0	-	Obesity	Abdominal	RMT ^{1,2}	Home	4	600	Moderate	
Sawatzky 2014	15	63.5	19.5	-	CAD	Cardiac	ET ¹	Fitness centre	8	980	High	
Soares 2013	28	56.5	47.0	-	Cancer (78%)	Abdominal	Comb ^{1,2}	Home, Hospital	2 to 3	550	Moderate	
Stefannelli 2013	40	-	-	-	100	Cancer	Lung	ET ¹	Hospital	3	1700	High
Morano 2013	21	66.5	62.5	79.0	Cancer	Lung	Comb ¹	Hospital	4	600	High	
Benzo 2011	17	71.1	53.0	100	Cancer	Lung	Comb ¹	Hospital	1	420	Moderate	
Pehlivan 2011	60	54.4	-	-	Cancer	Lung	ET ¹	Hospital	1	N.R.	High	
Barbalho- Moulim 2011	32	35.5	100	-	Obesity	Abdominal	RMT ^{1,2}	Hospital	2 to 4	270	Moderate	
Kulkarni 2010	34	62.5	42.5	-	N.R.	Abdominal	RMT ²	Home	2	420	Moderate	
Dronkers	41	70.0	25.9	90.3	Cancer	Abdominal	Comb ^{1,2}	Home,	2 to 4	1035	High	

2010								Hospital			
Ferreira 2009	30	62.7	26.7	6.7	CAD / VD	Cardiac	RMT ²	Home	2 to 4	N.R.	Moderate
Dronkers 2008	16	64.5	75.0	10.0	Aneurysm	Abdominal	RMT ^{1,2}	Hospital	2 to 3	225	Moderate
Hulzebos 2006	276	66.9	22.1	20.7	CAD	Cardiac	RMT ^{1,2}	Home	2 to 4	490	High
Hulzebos 2006	26	70.3	50.0	30.0	CAD	Cardiac	RMT ^{1,2}	Home	2 to 4	490	High
Weiner 1998	84	61.5	-	-	CAD	Cardiac	RMT ¹	Hospital	2 to 4	540	Moderate

CAD, coronary artery disease; Comb, combined training; ET, endurance training; MIA, minimally invasive approach; NR, not reported; RMT, respiratory muscle training; VD, valvular disease.

¹ supervised training; ² unsupervised training

* Moderate intensity: achieve <75% of maximal heart rate for endurance training; achieve $\geq 30\%$ of maximal inspiratory pressure or $\geq 30\%$ of maximal voluntary ventilation or use volumetric/incentive spirometry for respiratory muscle training; or no physiological marker used as a target for endurance training/respiratory muscle training.

* High intensity: achieve $\geq 75\%$ maximal heart rate, 100% peak workrate, or >5 rate perceived exercise for endurance training; achieve $\geq 60\%$ maximal inspiratory pressure or guided to achieve rate perceived exercise >5 for respiratory muscle training.

Table 2: Functional study outcomes in adults enrolled in randomized controlled trials of exercise training versus usual care/sham before major surgery

	N RCTs (N patients)	WMD (99% CI)	I²	P value overall effect*
Peak VO₂ (ml/kg/min)				
Intra-group preop changes				
Exercise group	5 (150)	+ 1.72 (0.33, 3.11)	28	0.001
Control group	5 (151)	- 0.21 (-1.07, 0.64)	0	0.520
Inter-group Exercise vs Control	5 (301)	+2.03 (0.34, 3.72)	51	0.002
Maximal Inspiratory Pressure (cmH₂O)				
Intra-group preop changes				
Exercise group	10 (487)	+ 15.5 (12.5, 18.4)	0	< 0.00001
Control group	10 (483)	0.8 (-2.2, 3.7)	0	0.490
Inter-group Exercise vs Control	10 (970)	+12.2 (6.3, 18.2)	52	< 0.00001
Six Minute Walk Test (m)				
Intra-group preop changes				
Exercise group	7 (261)	+30.7 (-2.3, 63.6)	42	0.020
Control group	7 (262)	+ 1.1 (-20.1, 22.4)	0	0.089
Inter-group Exercise vs Control	7 (523)	+47.3 (-8.7, +103.4)	81	0.030
FEV₁ (% pred)				
Inter-group Exercise vs Control	6 (349)	+1.15 (-2.7, 5.0)	0	0.440
FVC (% pred)				
Inter-group Exercise vs Control	4 (285)	+1.19 (-2.9, 5.3)	0	0.450

PeakVO₂, peak oxygen consumption; FEV₁, forced expiratory volume at the first second; FVC, forced vital capacity, N: number of trials or patients; WMD: Weighted Mean Differences; CI: Confidence Interval.

*Only p-values < 0.01 are considered statistically significant at the 1% level

Table 3: Clinical study outcomes in adults enrolled in randomized controlled trials of exercise training versus usual care (control) before major surgery

Discrete data	N=RCTs (N patients)	RR (99% CI)	I² %	P value overall effect
In-hospital or 30-day mortality	11 (1176)	1.01 (0.37, 2.75)	0	0.980
Cardiovascular complications	10 (996)	0.71 (0.40, 1.26)	12	0.120
Prolonged mechanical ventilation*	7 (507)	0.50 (0.21, 1.17)	0	0.030
ICU stay (Hours)	4 (435)	-5.03(-10.32,0.26)	71	0.06
Hospital LOS (Days)	12 (927)	-2.28 (-3.82 -0.76)	50	0.0001
Pneumonia	21 (1681)	0.72 (0.52, 0.98)	2	0.006
Atelectasis	11 (592)	0.48 (0.29, 0.81)	0	0.0003

ICU, intensive care unit; LOS, length of stay

*More than 48 hours, more than 6 hours after surgery

Dichotomous outcomes express as risk ratio (RR) and 99% confidence interval (99%CI)

Continuous outcomes expressed as weighted mean difference (WMD) and 99%CI.; p-values are considered statistically significant if <0.01.

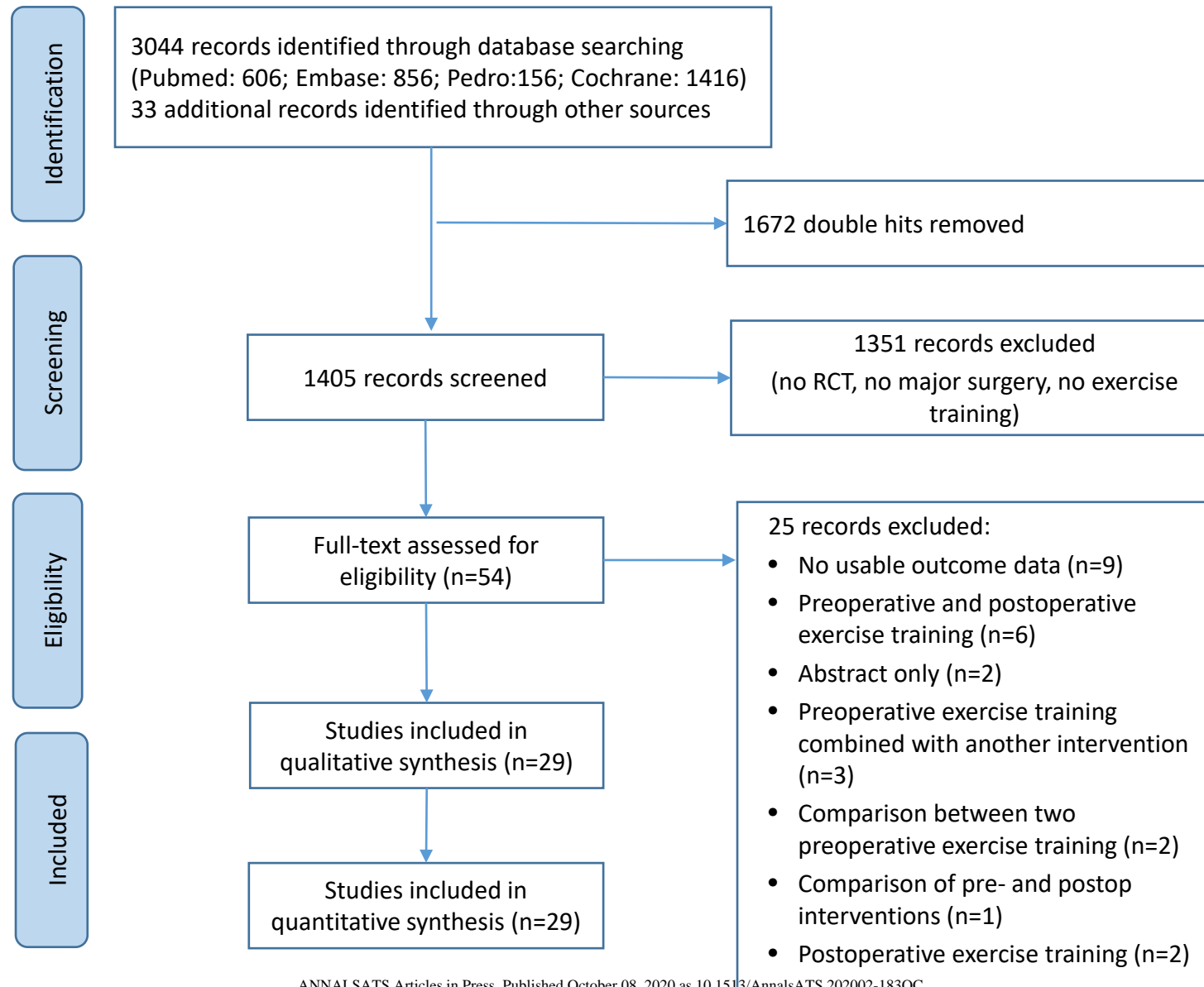
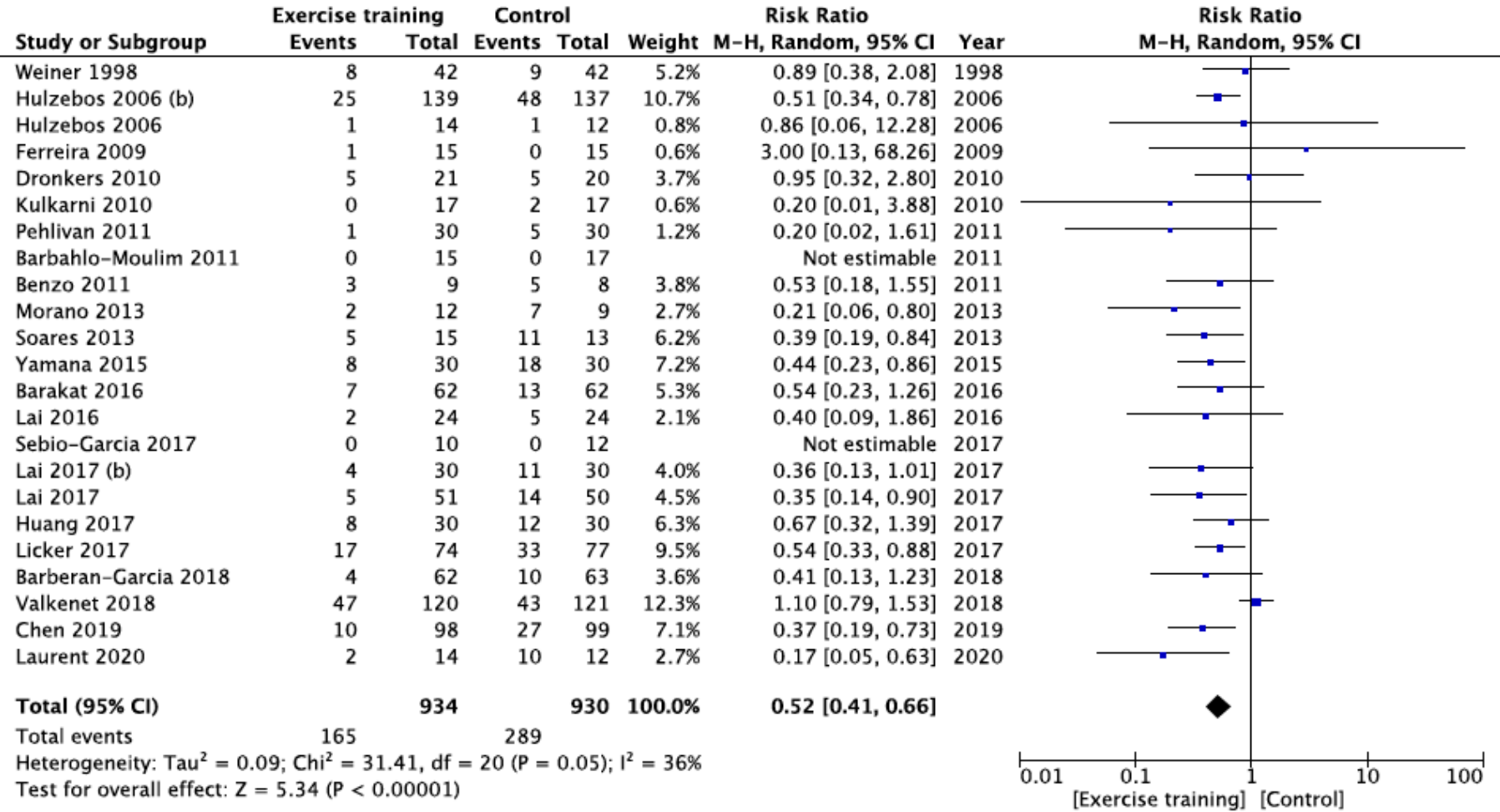
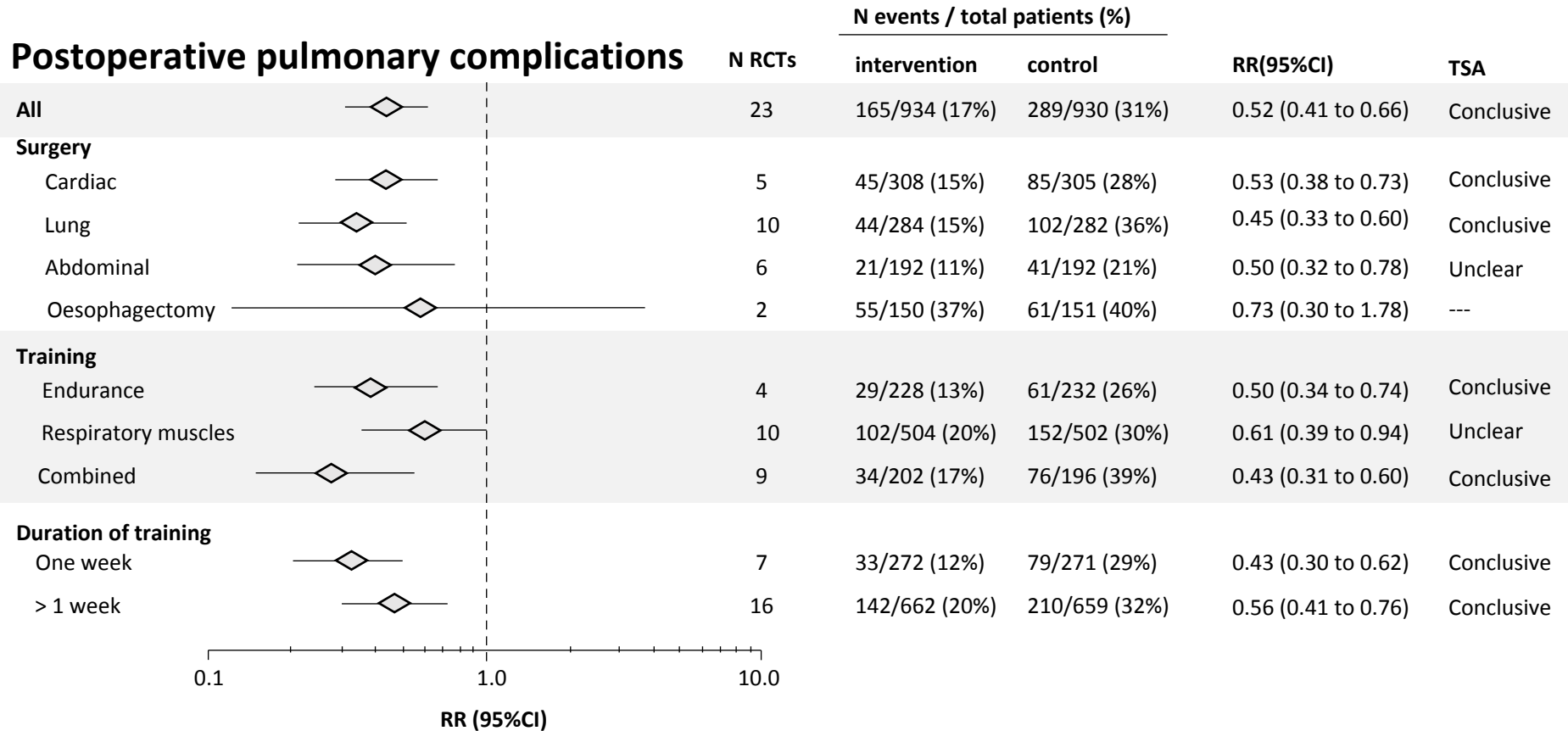
Figure 1 PRISMA flow diagram for the systematic review and meta-analysis.

Figure 2 . Forrest plot of the effect of preoperative exercise training on postoperative pulmonary complications, including all randomized controlled trials



Postoperative pulmonary complications



Online Data Supplement

Preoperative Exercise Training to Prevent Postoperative Pulmonary Complications in Adults Undergoing Major Surgery: A Systematic Review and Meta-analysis with Trial Sequential Analysis

Benjamin Assouline, Evelien Cools, Raoul Schorer, Bengt Kayser, Nadia Elia, Marc Licker

Fig S1: Overview of risk of bias across individual trials according to study characteristics. Each bias domain was evaluated carefully from every trial and decided whether the information provided reflected a low risk of bias (green), high risk of bias (red), or if insufficient information was provided and the risk of bias was therefore unclear (yellow).

Author, year	Sequence generation	Allocation Concealment	Blinding of participants and personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other bias
Laurent 2020	+	+	-	?	+	?	+
Chen 2019	+	+	-	+	+	?	+
Valkenet 2018	+	+	-	+	+	+	+
Barberan-Garcia 2018	+	+	?	+	+	+	?
Huang 2017	+	+	-	+	+	?	+
Tew 2017	+	+	-	+	+	?	?
Lai 2017	+	+	-	+	+	?	+
Lai 2017 *	?	?	-	+	+	?	+
Sebio-Garcia 2017	+	+	-	+	?	?	?
Licker 2017	+	+	-	+	+	?	+
Barakat 2016	+	+	-	+	?	?	+
Dunne 2016	+	+	-	+	+	?	?
Lai 2016	+	?	-	?	?	+	?
Yamana 2015	?	?	-	?	-	-	?
Llorens 2015	+	+	-	+	?	?	+
Sawatzky 2014	+	+	-	-	+	?	+
Morano 2013	+	+	-	+	+	?	+
Stefanelli 2013	?	?	-	?	+	+	?
Soares 2013	+	+	-	?	?	?	?
Barbalho-Moulim 2011	+	+	-	+	?	+	?
Benzo 2011	?	?	-	+	-	+	+
Pehlivan 2011	?	?	-	?	+	+	?
Kulkarni 2010	+	+	-	?	+	?	-
Dronkers 2010	+	+	-	+	+	?	+
Ferreira 2009	?	?	-	?	+	?	+
Dronkers 2008	+	+	-	+	+	?	?
Hulzebos 2006	+	+	-	+	+	+	+
Hulzebos 2006 (Pilot) [§]	+	+	-	+	+	?	+
Weiner 1998	?	?	-	-	?	+	?

Fig. S2. Summary of risk of bias of across the 23 trials reporting on the primary endpoint and included in the systematic review. Information for every study characteristic was pooled from every trial (green: low risk of bias; yellow: unclear risk of bias; red: high risk of bias), combined and overall results expressed in percentages.

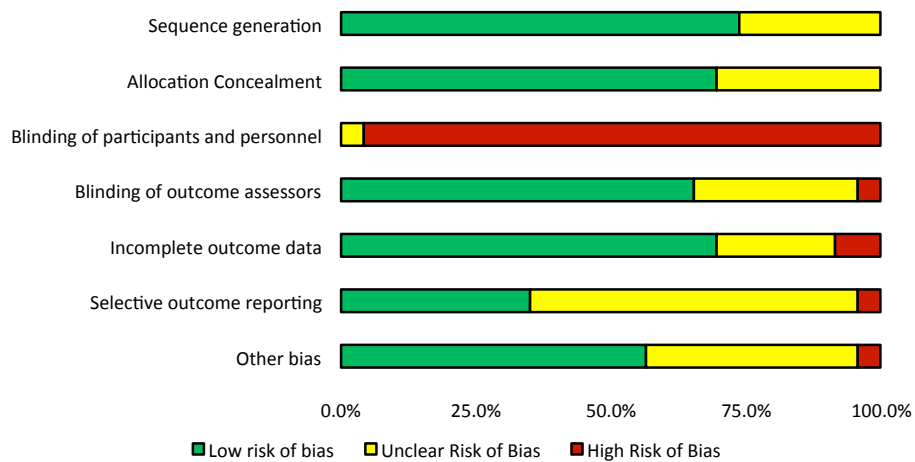


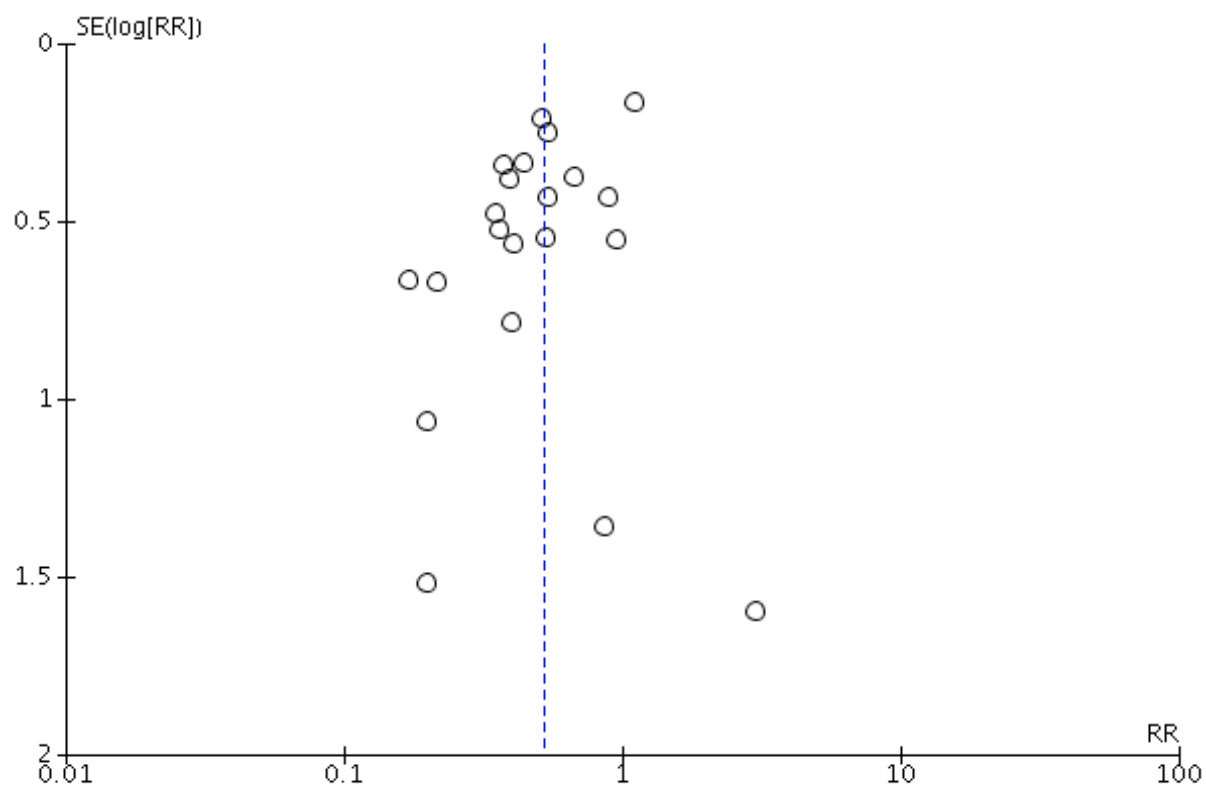
Fig S3: Funnel plot for postoperative pulmonary complications

Figure S4: Trial sequential analysis of 23 trials comparing intervention with control for postoperative pulmonary complications (scaled trial distance). This figure illustrates that the cumulative Z curve (blue line) crosses the conventional boundary for benefit and the trial sequential monitoring boundary for benefit. A diversity-adjusted required information size of 1'354 patients was calculated using $\alpha = 0.05$ (2-sided) and $\beta = 0.20$ (power of 80%) for an anticipated relative risk reduction of 30%.

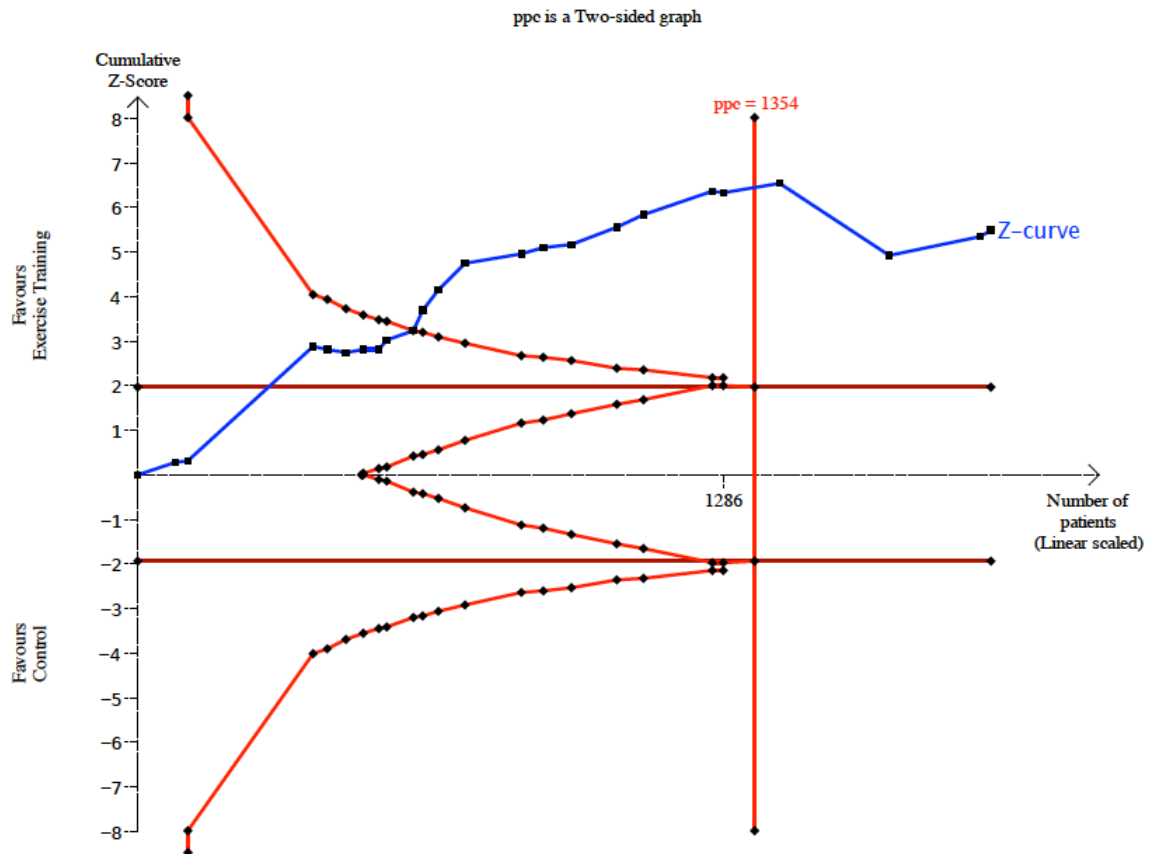


Fig S5: Forrest plot of the effect of preoperative exercise training on postoperative pulmonary complications, including randomized controlled trials with low risk of bias.

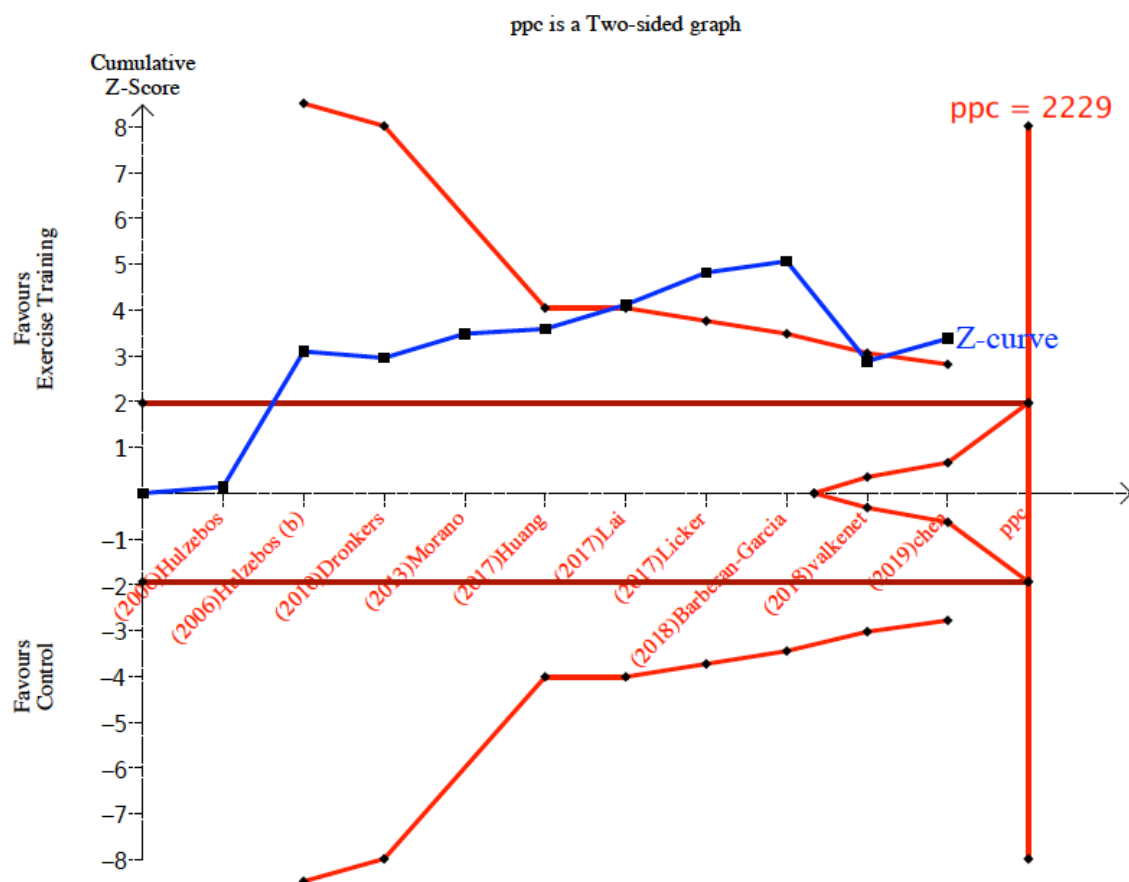
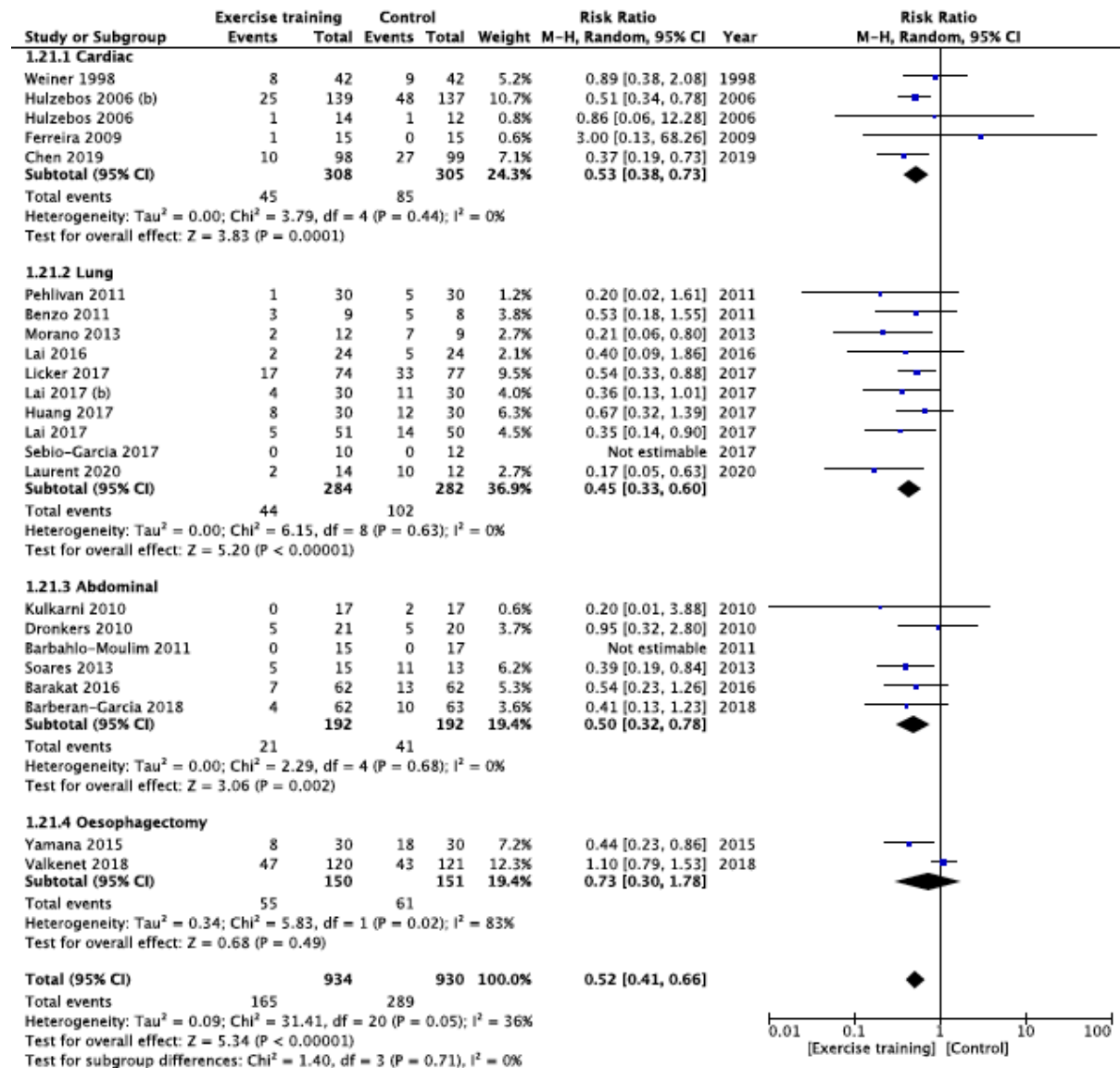


Fig S6: Postoperative pulmonary complications in patients receiving intervention training or usual care. (A) Forrest plot with subgroup analysis according to type of surgery (cardiac, lung, abdominal, esophageal). (B) Trial sequential analysis for surgical subgroups (A=Cardiac; B=Lung; C= Abdominal)

S6-A.



S6-B.

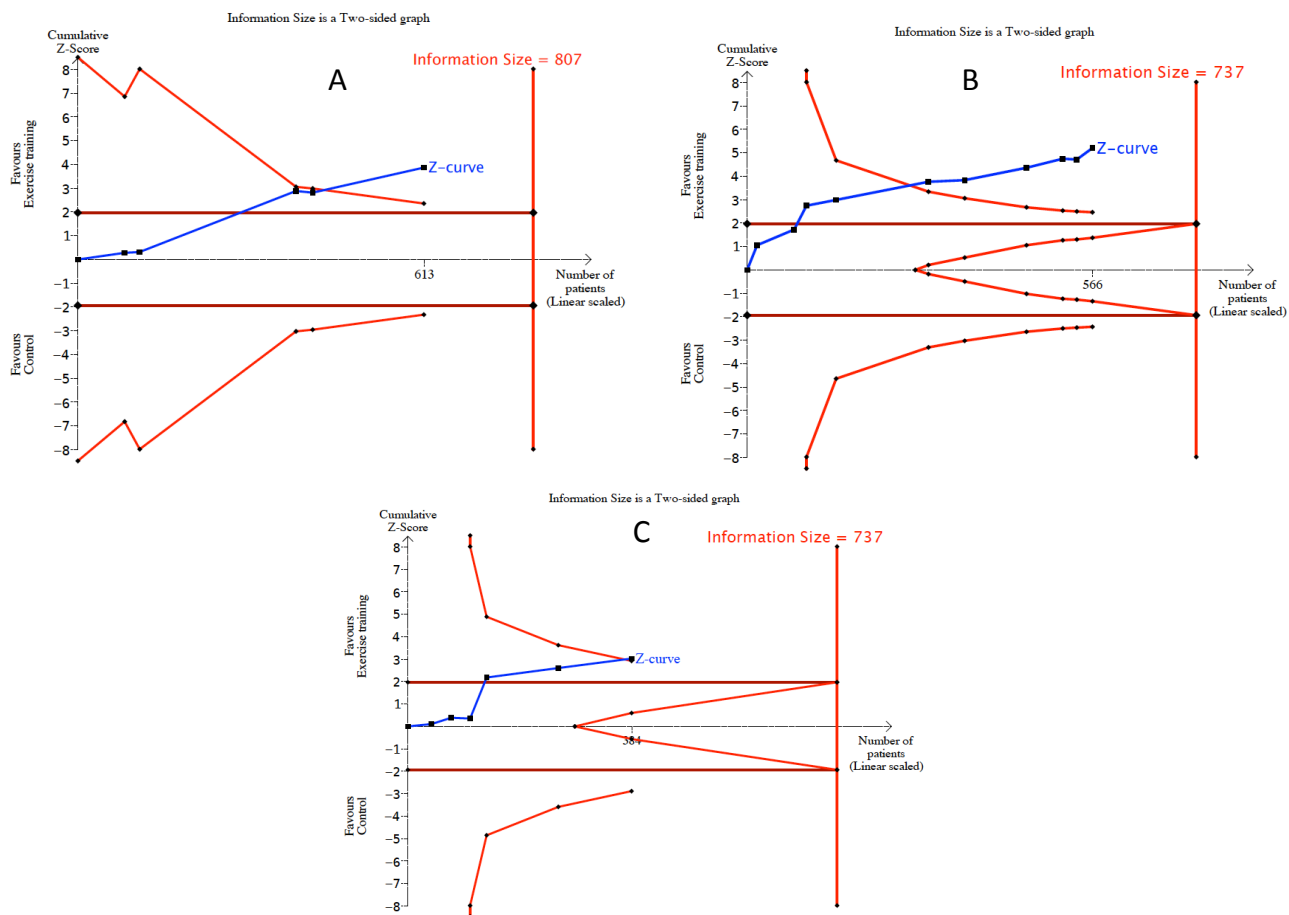
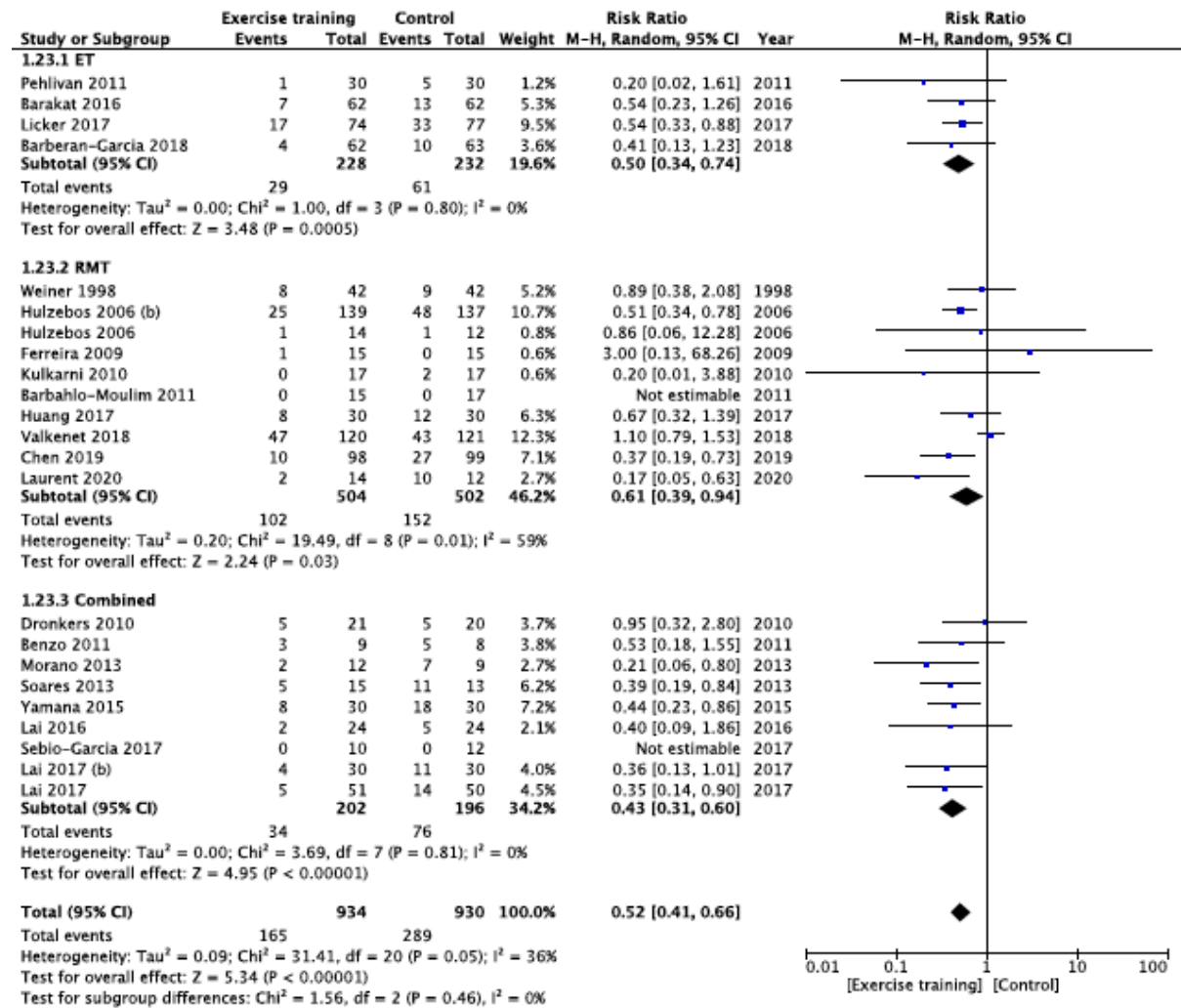


Fig S7: Postoperative pulmonary complications in patients receiving preoperative exercise training or usual care. (A) Forrest plot with subgroup analysis according to type of training (ET, endurance training; RMT, inspiratory muscle training; Combined). (B) Trial sequential analysis according to the type of training (A=ET; B=RMT; C= Combined)

S 7A



S7B

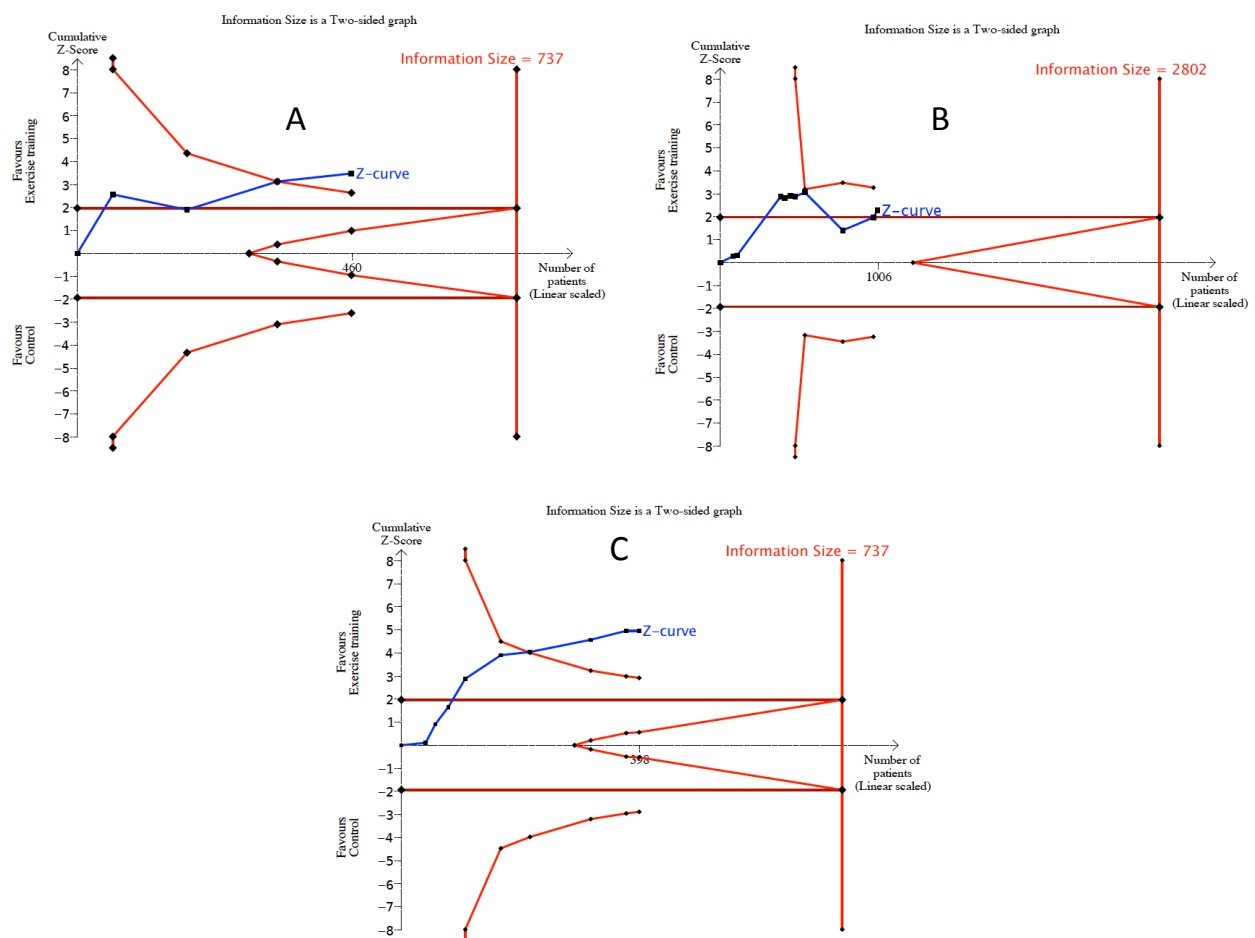
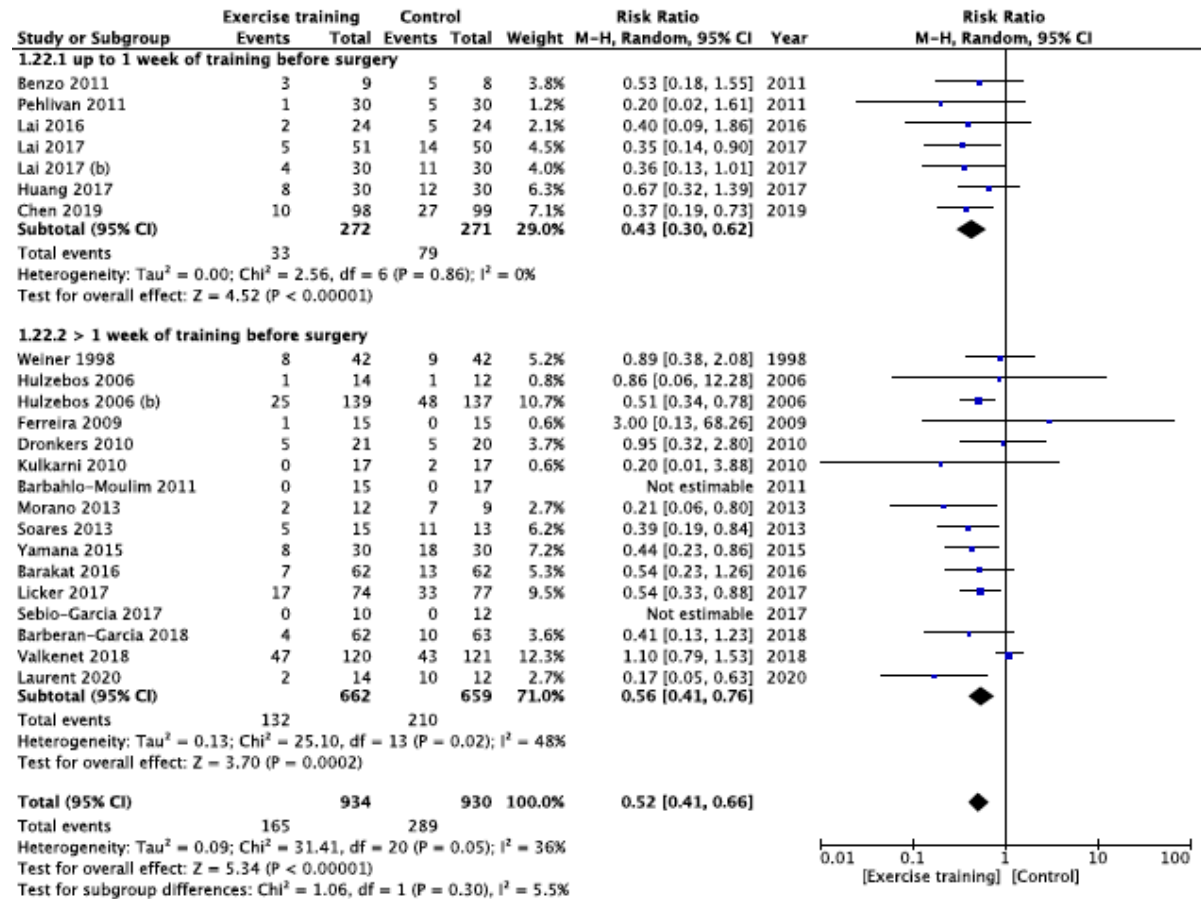


Figure S8: Postoperative pulmonary complications in patients receiving preoperative exercise training or usual care. (A) Forrest plot with subgroup analysis according to duration of training (up to one week; more than one week). (B) Trial sequential analysis according to the duration of training (A=up to one week; B=more than one week).

S8A



S8B

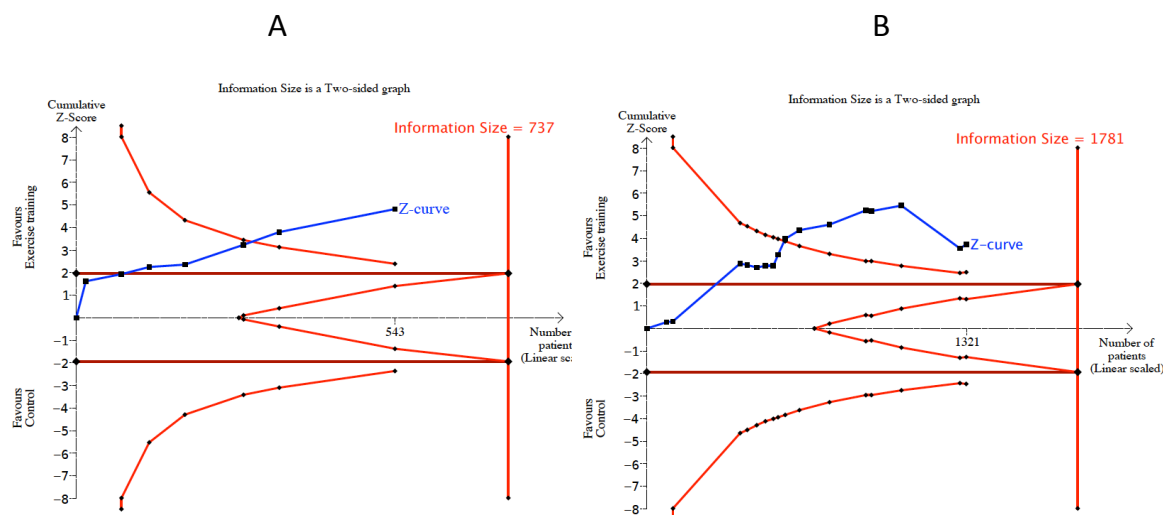


Figure S9: Grade of the evidence for the postoperative pulmonary complications

Preoperative exercise training compared to control in major surgeries

Bibliography: . [Rehab] versus [Control] for [major surgeries]. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With control	With preoperative exercise training		Risk with control	Risk difference with preoperative exercise training
1864 (23 RCTs)	serious a	not serious	not serious	not serious	none	⊕⊕⊕○ MODERATE	279/930 (30.0%)	163/934 (17.5%)	RR 0.53 (0.43 to 0.69)	300 per 1000	141 fewer per 1000 (from 171 fewer to 93 fewer)

CI: Confidence interval; RR: Risk ratio

Explanations

a. Only 10 of the 23 RCTs included were classified as low risk of bias.

Table S1: Authors who were contacted to obtain additional information. 6MWT: 6- minute walking test, VO2 max: maximal oxygen consumption, FEV1: Forced Expiratory Volume in 1 second, FVC: Forced Vital Capacity, MIP: Maximum Inspiratory Pressure

Author	When ?	Question	Answer
Soares 2013	29/5/2017 3/10/2017	- Full text - 30- day mortality - Mean and SD for 6MWT	- Full text received - No response
Dunne 2016	3/10/2017	- 30- day mortality - Place of exercises? Supervision?	- No mortality after 30 days - Supervised, hospital
Barbalho- Moulim 2011	3/10/2017	- 30- day mortality	- No mortality after 30 days
Benzo 2011	3/10/2017 11/11/2018	- 30- day mortality - Protocol for study 1	- No data available - No response
Stefanelli 2013	3/10/2017	- 30- day mortality - Delta VO2max	- No response
Lai 2017	3/10/2017	- 30- day mortality - Delta 6MWT	- No response
Morano 2013	3/10/2017	- 30- day mortality	- No response
Pehlivan 2011	3/10/2017	- 30- day mortality	- No response
Barberan- Garcia 2017	5/1/2018	- Full text	- Full text received
Barakat 2016	29/1/2018	- Mean and standard deviation of VO2 max	- No response
Sawatsky 2014	6/8/2018	- Full text	- Full text received
Sebio Garcia 2017	6/8/2018	- 6MWT	- No data available
Kulkarni 2010	10/8/2018	- Mean and standard deviation of FEV1, FVC and MIP	- No data available
Valkenet 2018	10/12/2018	- Check number of pulmonary complications without pneumonia	- No data
Laurent 2020	14/7/2020	- VO2max - MIP	- Answer received

Table S2: Articles excluded after full-text screening

Article	Journal	Title	Main reason for non-inclusion
Jonsson 2019	Physiotherapy 2019;105(4):434-441.	In-hospital physiotherapy improves physical activity level after lung cancer surgery: a randomized controlled trial	Preoperative and postoperative intervention
Bhatia 2019		Preoperative high-intensity interval training is effective and safe in deconditioned patients with lung cancer: A randomized clinical trial	No usable outcome data, duplicated results
Kim 2019	J Rehabil Med 2019 Oct 3;51(9):712-718.	Effects of a 12-week home-based exercise program on quality of life, psychological health, and the level of physical activity in colorectal cancer survivors: a randomized controlled trial.	No usable outcome data
Petersen 2019	Support Care Cancer. 2019 Aug;27(8):2933-2940.	A comparison of high versus low dose of exercise training in exercise-based cardiac rehabilitation: a randomized controlled trial with 12-months follow-up.	No usable outcome data
O'Neil 2018	S. Clin Rehabil. 2020 Jan;34(1):69-81	The RESTORE RCT: impact of a multidisciplinary rehabilitative program on cardiorespiratory fitness in oesophagogastric cancer survivorship	Postoperative intervention
Bousquet-Dion G 2018	Acta Oncol 2018; 57:849-59	Evaluation of supervised multimodal prehabilitation program in cancer patients undergoing colorectal surgery	No usable outcome data
Minnella 2018	JAMA Surg 2018 153:1081-89	Effect of Exercise and Nutrition Prehabilitation on Functional Capacity in Oesophagogastric Cancer Surgery: A Randomized Clinical Trial	Preoperative exercise training combined with other intervention
Jensen 2016	Support Care Cancer 2016 24:3325-31	Exercise- based prehabilitation is feasible and effective in radical cystectomy pathways: secondary results from a RCT	Feasibility study No usable outcome data
Sommer	Integr Cancer Ther 20	Perioperative rehabilitation in operation	Preoperative and

2016	16;15:455-466	for lung cancer (PROLUCA), a feasibility study	postoperative intervention
Shakouri 2015	J Cardiovasc Thorac Res 2015; 7:13-7	Effect of Respiratory Rehabilitation Before Open Cardiac Surgery on Respiratory Function: A Randomized Clinical Trial	Preoperative and postoperative intervention
Xu 2015 Y	Oncologists 2015;20:1216-22	A walk-and-et intervention improves outcomes for patients with oesophageal cancer undergoing neoadjuvant chemoradiotherapy	Low grade exercise, no surgery, no usable outcome data
Gillis C 2014	Anesthesiology 2014; 121:937-947	Prehabilitation versus rehabilitation: a randomized control trial in patients undergoing colorectal resection for cancer.	Preoperative intervention compared with postoperative intervention
Van Aldrichem 2014	Ann Surg Oncol 2014; 21:2353-60	Comparison of two preoperative inspiratory muscle training programs to prevent pulmonary complications in patients undergoing esophagectomy: a randomized controlled pilot study.	Comparison of two preoperative interventions
Kaibori M 2013	Am J Surg 2013; 206:202-209	Perioperative exercise for chronic liver injury patients with hepatocellular carcinoma undergoing hepatectomy	No usable outcome data; preoperative and postoperative interventions
Bridevaux 2012	Eur Respir J 2012; 40: 3306	Effect of preoperative short-term rehabilitation on peak VO2 in patients with NSCLC	Abstract only
Benzo 2011	Lung Cancer 2011; 74:441-5	Preoperative pulmonary rehabilitation before lung cancer resection: results from two randomized studies	No usable outcome data
Carvalho 2011	Eur Heart J 2011; 32 Suppl:328	Preoperative respiratory muscle training reduces complications in coronary artery bypass surgery	Abstract only
Rosenfeldt 2011	BMC Complement Altern Med 2011;11:2	Physical conditioning and mental stress reduction--a randomised trial in patients undergoing cardiac surgery	Preoperative exercise training combined with another intervention
Savci 2011	Scand Cardiovasc J 2011; 45:286-293	Short-term effects of inspiratory muscle training in coronary artery bypass graft surgery: A randomized controlled trial	Preoperative and postoperative interventions

Carli F 2010	Br J Surg 2010; 97:1187-97	Randomized clinical trial of prehabilitation in colorectal surgery	Comparison of 2 preoperative interventions (structured endurance and strengthening program vs walking and breathing exercises)
Kim 2009	Tohoku J Exp Med 2009; 217:109-115	Responsive measures to prehabilitation in patients undergoing bowel resection surgery	No usable outcome data
Herdy 2008	Am J Phys Med Rehabil 2008;87:714- 9	Pre- and postoperative cardiopulmonary rehabilitation in hospitalized patients undergoing coronary artery bypass surgery	Preoperative and postoperative interventions
Arthur 2000	Ann Intern Med 2000; 133: 253-62	Effect of a preoperative intervention on preoperative and postoperative outcomes in low-risk patients awaiting elective coronary artery bypass graft surgery	No usable outcome data
Rajendran AJ, 1998	Indian Heart J 1998;50:531-4	Pre-operative short-term pulmonary rehabilitation for patients of chronic obstructive pulmonary disease undergoing coronary artery bypass graft surgery	Low grade intensity exercise program, combined with relaxation training (mental stress reduction)
Chumillas 1998	Arch Phys Med Rehabil 1998;79:5-9	Prevention of postoperative pulmonary complications through respiratory rehabilitation: a controlled clinical study	Preoperative and postoperative interventions

Table S3: Modalities of care in the intervention and control groups

Study, year	Intervention group	Cumulated training time	Usual or standard of care	Preoperative time delay
Laurent 2020	<ul style="list-style-type: none"> - 12 sessions (30 min/day) of respiratory muscle endurance training based on isocapnic hyperpnea (Spirotiger®, Idiag, Feraltorf, CH) with one supervised session per week by physiotherapist; starting at 30% of maximal voluntary ventilation and increasing the respiratory rate by one cycle every session whenever possible - usual chest physical therapy 	270-360 min	usual chest physical therapy including airway clearance techniques, deep breathing exercises and thoracic stretching	Three weeks
Chen 2019	<ul style="list-style-type: none"> - Hospital-based, 5-days of intensive respiratory muscle training. - Use of IMT: started at 30% MIP for 20 min twice a day (Threshold IMT, HS730-010; Philips Respironics), inspiratory load increased incrementally, based on the RPE score (>5). - Diaphragmatic breathing (5 breaths followed by 5-10 seconds rest and repeat for 20 minutes, twice a day) 	200 min	Routine preoperative preparation including education and instructions on coughing and abdominal breathing (20 min, twice a day) and information on the need for postop mobilization.	One week
Valkenet 2018	<ul style="list-style-type: none"> - Home-based (diary), supervised (phone call) by physiotherapist. - Oral instruction by a physiotherapist and with video-assistance - Use of IMT device (PowerBreath KH1-KH2), starting with 60% MIP and increase based on RPE>5; 30 breaths, 2 times/day until surgery (at least 2 weeks), post-neoadjuvant chemoradiotherapy 	At least 120 min	Routine care in each participating center (not standardized) and preoperative instruction on postoperative physical therapy. Advice to stay active or seek training guidance	At least two weeks

Huang 2017	<ul style="list-style-type: none"> - Hospital-based, supervised training by trained nurses - Use of volumetric spirometry (Voldyne 5000 Sherwood Med, St Louis, MO), inspiration through the suction nozzle of the respiratory training device, hold a few seconds and calm exhalation; 20 min 4 times/day - Abdominal and thoracic breathing training ; inspiration up to maximal lung capacity and slow exhalation; 15-20min, 2-3 times/day 	840 min	Routine preoperative preparation including information, education, and psychological support	One week
Lai 2017	<ul style="list-style-type: none"> - Hospital-based, supervised training - Thoracic expansion and incentive spirometry (deep breathing using HUDSON RCI 2500 Teleflex, Temecula, CA), 20 breaths/session, 3 times/day; - Abdominal breathing to strengthen the diaphragm, 15-30 min, 2 times/day - Aerobic endurance training (Nu-Step Inc. Ann Arbor, MI) up to Borg scale 6, 30 min/day 	385 min	Routine preoperative preparation including information, education, and psychological support	One week
Lai 2017	<ul style="list-style-type: none"> - Hospital-based, supervised training - Abdominal and thoracic breathing training; inspiration up to maximal lung capacity and slow exhalation, 15-20min, 2-3 times /day; expiration exercise with respiratory training device (Voldyne 5000, Inc. Ann Arbor, MI), 20 min/session, 3 times/day - Lower limb aerobic endurance training (Nu-step) exercise up to Borg score 5-7; 30 min/day 	385 min	Routine preoperative preparation including information, education, and essential encouragement or psychological support	One week
Licker 2017	<ul style="list-style-type: none"> - Hospital-based, supervised training by physiotherapists - Aerobic endurance high-intensity interval training with cycle ergometer; two 10 min series of 15sec sprint up to 80-100% peak work rate, with 15 sec rest (4 min between 2 series); 2-3 times/week 	480 min	Advice regarding active mobilization, risk factor management (e.g. healthy nutrition, smoking, alcohol cessation)	Two to four weeks

Tew 2017	<ul style="list-style-type: none"> - Hospital-based, supervised training - Aerobic endurance high-intensity training with cycle ergometer (Optibike Med); Ergoline Bitz, Germany; 8 times 2 min or 4 times work intervals with power guided by RPE (up to 5-7/10 Borg scale); 3 sessions/week 	360 min	Evidence-based medical optimization (no details), no specific exercise	Four weeks
Barberan- Garcia 2017	<ul style="list-style-type: none"> - Home-based training - Personalized rehabilitation, motivational interview, nutritional counselling; advice on smoking cessation and reduction of alcohol intake - Instructions for physical exercise and specific thoracic expansion maneuvers - Aerobic endurance high-intensity interval training with cycle ergometer (Jaeger ER 550; Wuerzburg, D), warm up/cool down 10 min, 7-8 series of 2min high intensity (70-85% peak work rate) and 3 min rest (30-40% peak work rate); total of 60 min, 1-3 session/week 	560 min	<p>Routine preoperative care,</p> <p>Recommendation on physical activity (use pedometer); nutritional counselling;</p> <p>Advice on smoking cessation and reduction of alcohol intake</p>	Four to six weeks
Sebio Garcia 2017	<ul style="list-style-type: none"> - Aerobic endurance moderate-intensity interval training with cycle ergometer (Monark); 30 min (1 min at 80% peak work rate, 4 min active rest at 50% peak work rate); - Resistance training using elastic bands (Thera-Band, Hygienic Corp., Ohio, USA) and body weight exercises (six different types) - IMT using volume-oriented incentive spirometer (Coach 2 Incentive spirometer 22-400 HD, Smith Medicals, USA); Breathing exercises included 30 sustained inspirations up to 80% maximal ventilatory capacity (6 cycles x 5 rep, 1 min pause/cycle; 2 sessions/day) - Median of 16 sessions (3-5 times/week) 	660 min	Usual care	At least two weeks
Barakat 2016	<ul style="list-style-type: none"> - Hospital-based, supervised training. - Aerobic endurance training with cycle ergometer, treadmill (moderate intensity) and additional exercises (flexion, knee bending, 	1080 min	Continue usual lifestyle, avoid additional unsupervised exercises	Six weeks

	body weight lifting, step-up, stretching); 3 times/week			
Dunne 2016	<ul style="list-style-type: none"> - Hospital-based, supervised training with personalized exercise program (on anaerobic threshold) - Aerobic endurance high-intensity interval training with cycle ergometer (Optibike; Ergoline, Bitz, Germany), alternating work at 60% and 90% peak VO₂), 12 sessions (30-40 min) over 4 weeks 	420 min	Advice for regular exercise	Four weeks
Lai 2016	<ul style="list-style-type: none"> - Hospital-based, supervised training - Respiratory training in supine position: inspiration up to maximal lung capacity and slow exhalation (2-3 times /day for 15-20min); volumetric spirometry (Voldyne E5000) in sitting position, deep inspiration then breath hold for 3 seconds and slow exhalation, 12-20 times/day; inhalation therapy with beta-2 adrenergic agonist, glucocorticoid and mucolytic drugs, 2 times/day - Lower limb endurance training (Nu-step) exercise up to Borg score 5-7; 15-20 min/day; stair climbing 15-30min/day 	385 min	Routine preoperative preparation including information, education, and essential information, general advices and psychological support	One week
Llorens 2015	<ul style="list-style-type: none"> - Home-based with one session supervised/week - Use of IMT device (Threshold, Respiroics Inc. Pittsburgh, PA), starting from 30% MIP and increased based on Borg scale (<5) - Use volumetric spirometry (Voldyne 5000, Teleflex medical); once/day, 40 min 	600 min	Instructions about preoperative usual care	Four weeks
Yamana 2015	<ul style="list-style-type: none"> - Hospital-based, supervised intensive respiratory, for 60 min per day during more than 7 days - Deep inspiration, deep diaphragmatic breathing and thoracic cage stretching; efficient coughing and contractions of abdominal muscles - Aerobic endurance on cycle ergometer (20 min with increasing workload); strengthening exercises of lower limbs 	420 min	Routine preoperative protocol	More than one week

Sawatzky 2014	<ul style="list-style-type: none"> - Supervised training in a medical fitness facility - Aerobic endurance exercises (walking, cycling, light resistance exercise with body weight and resistance bands and stretching): 85% VO₂max; - Additional voluntary exercise sessions, counselling on healthy life style behaviours and cardiovascular risk management (12 class-based education sessions) 	900 min	Counselling on healthy lifestyle behaviour	Eight weeks
Soares 2013	<ul style="list-style-type: none"> - Hospital supervised training (2 sessions of 50 min/week) and home-based unsupervised training sessions. - Use of IMT (Threshold, Respironics, NJ), 20% MIP, increased by 2cmH₂O ; 15 min, 4 times/week - Stretching, relaxation and trunk rotation exercises; guidance on coughing and huffing - Lower limb aerobic training, walking up to Borg scale<15 on flat ground; 10min, 4 times/week 	550 min	Routine preoperative protocol	Two to three weeks
Stefannelli 2013	<ul style="list-style-type: none"> - In-hospital supervised sessions - Respiratory exercises (mattress, bench & wall bars) - High-intensity aerobic endurance of the upper limbs (rowing and ergometer) and the lower limbs (treadmill and cycle ergometer) starting at 70% maximal load of CPET, then increase by 10W; 3h session, 5 times/week 	1700 min	Routine preoperative protocol	Three weeks

Morano 2013	<ul style="list-style-type: none"> - Hospital-based, supervised training - Use of IMT device (Threshold Inspiratory Muscle Trainer, HealthScan Products Inc), starting at 20% MIP and increase up to 60% of MIP (load increased by 5- 10%/session); once a day, 10-30min, 5 sessions/week. - Lower limb aerobic training on treadmill up to 80% WR (10 to 30 min) - Upper limb using proprioceptive neuromuscular facilitation method (diagonal movement), (initial load of 0.5kg, the increase 0.5kg/min, 15 repetition/min, 10-30 min; additional flexibility, stretching, and balance exercises; 	600 min	Instructions about the techniques for lung expansion	Four weeks
Benzo 2011	<ul style="list-style-type: none"> - Hospital-based, supervised sessions - Use of IMT (Threshold Inspiratory Muscle Trainer IMT or the P-Flex valve (Philips Healthcare); slow breathing; 10 sessions, 2 times/day for 1 week - Lower extremity endurance training on treadmill or NuStep (20 min); Upper extremity endurance performed by arm-R-size exercises, the use of an arm ergometer or the NuStep (Inc. Ann Arbor); strengthening exercises with Thera-band 	420 min	Routine preoperative protocol	One week
Pehlivan 2011	<ul style="list-style-type: none"> - Hospital-based, supervised sessions - Intensive physical therapy (chest physiotherapy, breathing/diaphragmatic exercise, incentive spirometry, coughing) - Lower limb aerobic training on a treadmill (walking), increasing the load to achieve 65 to 80% maximal heart rate, 3 times a day 	NR	Routine home-based physical therapy (advice)	One week
Barbalho- Moulim 2011	<ul style="list-style-type: none"> - Hospital-based, supervised (one in three) and unsupervised sessions - Use of IMT (Threshold, Respiroics, Pittsburgh, PA), starting at load 30% MIP, re-calculated after a new measure of this variable at each visit to the physiotherapist, 15 min session, 6 times/week 	270 min	Instructions about postoperative care, importance of cough and early ambulation	Two to four weeks

Kulkarni 2010	<ul style="list-style-type: none"> - Home-based sessions - Use of IMT device (PowerBreath) , starting at 20-30% MIP then increase by half a level daily for the first week, 15 min, 2 times/day, for 2-5 weeks 	420	Routine preoperative protocol	Two weeks
Dronkers 2010	<ul style="list-style-type: none"> - In-hospital supervised training sessions (60 min, 2 times/week) and home-based sessions (45 min/day) - Use of IMT device : 1) supervised sessions with variable resistance from 10% to 60% of MIP (15 min, 240 breathing cycles), 2) unsupervised sessions with resistance starting at 20% MIP and increase by 10% up to 100% MIP based on RPE (<13) - Aerobic supervised training with moderate intensity endurance exercise (55-75% maximal heart rate or RPE on Borg scale 11-13, 20-30min) and with lower limb resistance (up to 60-80% maximum load). - Unsupervised home session including walking (pedometer) or/and cycling (> 30 m min/day) 	360 min supervised 675 min un-supervised	Home-based exercise advice, minimum 30 min active/day (pedometer) Instructions about diaphragmatic breathing, deep inspirations using incentive spirometry, coughing and forced expiration techniques	Two to four weeks
Ferreira 2009	<ul style="list-style-type: none"> - Home-based training program - Use of IMT device (Threshold Respiroics Cedar Grove, NJ) at 40% MIP, 5 series of 10 deep inspirations, 3 times/day - Information about risk of surgery and advice on deep inspiration, smoking cessation and active mobilization (walking) 	NR	Information about risk of surgery and advice on deep inspiration, smoking cessation and active mobilization (walking)	At least two weeks
Dronkers 2008	<ul style="list-style-type: none"> - Hospital based, supervised training sessions (1/week) with unsupervised sessions (5/week) 2-3 weeks before surgery. Instructions about diaphragmatic breathing, deep inspirations using incentive spirometry, coughing and forced expiration techniques - Use of IMT Threshold (Respiroics Pittsburgh, PA) from MIP 20% increase based on RPE >5); 15 min, 6 sessions/week, at least 2 week before surgery 	225 min	Routine preoperative protocol One day before surgery: instructions about diaphragmatic breathing, deep inspirations using incentive spirometry, coughing and forced expiration techniques	Two to three weeks

Hulzebos 2006	<ul style="list-style-type: none"> - Home-based training (diary recording) with one supervised session/week. - Instruction on breathing techniques with an incentive spirometer (Coach 2, DHD Healthcare, Wampsville, NY) and forced expiration manoeuvre. - Use of IMT device (Threshold IMT, PT Medical, Leek, the Netherlands) starting at > 30% MIP and increase based on RPE (>5/10), 20 min/day, at least 2 weeks before surgery 	490 min	<p>Routine preoperative protocol</p> <p>Instructions on deep breathing, coughing and early mobilization</p>	Two to four weeks
Hulzebos 2006	<ul style="list-style-type: none"> - Home-based training with one supervised session/week - Use of IMT device (Threshold IMT, PT Medical, Leek, the Netherlands) starting at > 30% MIP and increase based on RPE (>5/10), 20 min/day for 2-4 weeks before surgery 	490 min	<p>Routine preoperative protocol and one day before surgery: education about early mobilization and coughing with wound support</p>	Two to four weeks
Weiner 1998	<ul style="list-style-type: none"> - Hospital-based, supervised training by a physician. - Use of IMT device (Threshold Inspiratory Muscle Trainer, Healthscan) from 15% to 60% MIP, 30 min, 6 times/week for 2-4 weeks before surgery - IMT was continued at low level (15% of MIP) for 1 week postoperatively 	540 min	<p>Breathing exercises without resistance, 6 times a week, for 2-4 weeks</p>	Two to four weeks

CPET, cardiopulmonary exercise test; IMT, inspiratory muscle training; MIP, maximal inspiratory pressure; RPE, rate perceived exercise; VO₂peak, peak oxygen consumption

Table S4: Study endpoints of analyzed studies

Author, year	PPC	Peak VO ₂	MIP	6 MWT	FVC	FEV ₁	Hosp LOS	CVC	Postop ventilation	Death 30-day
Laurent 2020	1	1	1	-	-	-	1	1	-	1
Chen 2019	1		1		1	1	1	-	-	-
Valkenet 2018	1	-	1	-	-		-	1	-	1
Tew 2017	-	1	-	-	-		-	-	-	1
Barberan- Garcia 2017	1	-	-	1	-		1	1	-	1
Huang 2017	1	-	-	1	-		-	1	1	1
Lai 2017	1	-	-	1	-		1	1	1	-
Lai 2017	1	-	-	1	-		1	1	1	-
Licker 2017	1	1	-	1	-		1	1	1	1
Sebio Garcia 2017	1	-	-	-			1	-	-	-
Barakat 2016	1	-	-	-	-		-	1	-	1
Dunne 2016	-	1	-	-	-		-	-	-	1
Lai 2016	1	-	-	-	-		-	1	-	-
Yamana 2015	1	-	-	-	-	-	-	-	-	1
Llorens 2015	-	-	1	-	-		-	-	-	-
Sawatzky 2014	-	-	-	1	-		-	-	-	-
Soares 2013	1	-	-	-	-		-	-	-	-
Stefannelli 2013	-	1	-	-	-		-	-	-	-
Morano 2013	1	-	1	1	-	1	1	-	1	-
Benzo 2011	1	-	-	-	-		1	-	-	-
Pehlivan 2011	1	-	-	-	-	1	1	1	-	-
Barbalho-Moulim 2011	1	-	1	-	1	1	-	-	-	-
Kulkarni 2010	1	-	-	-	-		-	-	-	-
Dronkers 2010	1	-	-	-	-		1	-	-	-
Ferreira 2009	1	-	-	-	1	1	-	-	1	1
Dronkers 2008	-	-	1	-	-		-	-	-	-
Hulzebos 2006	1	-	1	-	-		1	-	-	1
Hulzebos 2006	1	-	1	-	1	1	-	-	-	-
Weiner 1998	1	-	1	-	-		-	-	1	-

CVC, cardiovascular complications; FVC, forced vital capacity; FEV₁, forced expiratory volume att 1 sec; MIP, maximal inspiratory pressure; LOS, length of stay; PPC, postoperative pulmonary complications; 6MWT, six minute walk test

Table S5: Definition criteria of postoperative pulmonary complications

Author	Definition criteria of postoperative pulmonary complications
- Laurent 2020	Clavien-Dindo classification (grades II to V) ²
- Lai 2017 ¹ Barberan-Garcia 2017 Huang 2017 Licker 2017 Yamana 2015	<p>Clavien-Dindo classification or Thoracic Morbidity and Mortality classification for all complications (grades I to V) in Barberan-Garcia and Yamana; complications with grade II-V in Huang, Lai and Licker</p> <p><i>Grade I:</i> complication without need for pharmacologic treatment or other intervention.</p> <p><i>Grade II:</i> complication requiring pharmacologic treatment or minor intervention.</p> <p><i>Grade III:</i> complication requiring surgical, radiologic, endoscopic intervention, or multi-therapy.</p> <p><i>Grade IIIa:</i> invasive treatment with no need for general anesthesia</p> <p><i>Grade IIIb:</i> invasive treatment under general anesthesia</p> <p><i>Grade IV:</i> complication requiring intensive care unit management and life support.</p> <p><i>Grade IVa:</i> single organ major dysfunction.</p> <p><i>Grade IVb:</i> multiorgan major dysfunction.</p> <p><i>Grade V:</i> complication leading to the death of the patient.</p>
- Lai 2016, Lai 2017 ³	<p>(i) <i>Atelectasis</i>, (ii) <i>acute respiratory distress syndrome</i>, (iii) <i>respiratory failure</i>, (iv) <i>mechanical ventilation at 48 h postoperatively</i>, (v) <i>deep vein thrombosis/pulmonary embolism</i> and (vi) <i>empyema or pneumonia</i> (at least 3 of the following: leucocytosis >11'200/mm³ or <3000/mm³, temperature >38.5 °C, purulent sputum, persistent infiltrate on chest X-rays or pathogenic microorganisms cultured from endotracheal aspirate).</p>
- Sebio Garcia 2017	<p>Melbourne Group scale⁴; PPC diagnosed by ≥ 4 of the following criteria:</p> <ol style="list-style-type: none"> 1. Chest radiograph report of atelectasis/consolidation 2. Unexplained leucocytosis (>11'200/mm³) or administration of antibiotics postoperatively (in addition to those administered routinely postoperatively). 3. Fever (>38°C) with no focus outside of the lungs. 4. Positive signs of infection on sputum microbiology. 5. Production of purulent (yellow or green) sputum differing from preoperative status 6. SpO₂ < 90% on room air 7. Diagnosis of pneumonia/chest infection by attending physician.

¹ Lai Y, Huang J, Yang M, Su J, Liu J, Che G. *J Surg Res* 2017;209:30-36

² Dindo D, Demartines N, Clavien PA. *Ann Surg* 2004; 240 :205-13

³ Lai Y, Su J, Qiu P, et al. *Interact Cardiovasc Thorac Surg*. 2017;25:476-483

⁴ Reeve JC, Nicol K, Stiller K, McPherson KM and Denehy L. *J Cardiothorac Surg* 2008; 3: 48.

8. Re-admission to the ITU/HDU with problems which are respiratory in origin or a prolonged stay on the ITU/HDU (over 36 hours) with problems which are respiratory in origin.

- Hulzebos 2006⁵ Definition and grading of complications according to Kroenke et al⁶
Chen 2019

Grade II:

Bronchospasm: new wheezing or preexistent wheezing resulting in change therapy

Hypoxemia: alveolar-arterial gradient >29 mmHg and symptoms of dyspnea or wheezing

Atelectasis: radiological confirmation associated with elevated temperature (>37.5°C) or abnormal lung findings

Hypercarbia, requiring temporary treatment with IV naloxone or ventilatory support

Adverse reaction to pulmonary medication

Grade III:

Pleural effusion, resulting in thoracentesis

Pneumonia, suspected: radiological evidence without bacteriological confirmation

Pneumonia, proved: radiological evidence and documentation of pathological organism by Gram stain or culture

Pneumothorax

Reintubation postoperative, with period of ventilator dependence \leq 48h

Grade 4:

Ventilatory failure: postoperative ventilator dependence > 48 hours, or reintubation with subsequent period of ventilator dependence > 48 hours

- Hulzebos 2006⁷ *Bronchitis*: normal chest X-rays, temperature > 37.5°, rales on auscultation, abundant and clear sputum

Atelectasis: collapsed areas, diaphragmatic elevation on chest X-rays, temperature < 38°C, diminished or abolished vesicular murmur on auscultation: diminished or abolished

Pneumonia : consolidation, pleurisy on chest X-rays, temperature >38°C (at least 4 days), rales on auscultation, abundant and purulent sputum

- Barakat 2016 *Pneumonia*:clinical history with positive sputum culture or infiltrate on chest X- rays)

⁵ Hulzebos EH, Helders PJ, Favie NJ, et al. *JAMA*. 2006;296:1851-1857

⁶ Kroenke K, Lawrence VA, Theroux JF, Tuley MR. *Arch Intern Med*. 1992;152:967-971.

⁷ Hulzebos EH, van Meeteren NL, van den Buijs BJ, et al. *Clin Rehabil*. 2006;20:949-959

- Mechanical ventilation*: postoperative ventilator support >48h,
- Unplanned reintubation*
- Morano 2013 *Pneumonia*: new infiltrate plus temperature $\geq 38^{\circ}\text{C}$, white blood cell count $>10^4$ or fever and purulent secretions
- Bronchopleural fistula*
- Bronchospasm*
- Severe atelectasis*: confirmed by chest X- rays, requiring physiotherapy or bronchoscopy
- Prolonged need for chest tubes*: >7 days drainage
- Prolonged mechanical ventilation*, >48h
- Barbalho-Moulim 2011 *Pneumonia*: temperature $>38^{\circ}\text{C}$, productive cough with purulent sputum, presence of pulmonary infiltration on chest X- ray, increased leukocyte count)
- Atelectasis*: based on chest X- rays and associated with respiratory discomfort
- Acute respiratory failure*: poor gas exchange and requirement for mechanical ventilation
- Benzo 2011 *Pneumonia*, new infiltrate with either fever ($>38.5\text{ C}$) and white cell count $>11,000/\text{ml}$ or fever and purulent secretions
- Severe atelectasis*, requiring bronchoscopy
- Prolonged chest tubes*, >7days
- Prolonged mechanical ventilation*, >24hours
- Dronkers 2010 *Atelectasis*, diagnosed on chest-XRays by a “blinded” radiologist
- Pneumonia*, fever, cough, and development of purulent sputum, in conjunction with radiologic evidence of a new or progressive pulmonary infiltrate, a suggestive Gram stain, and positive cultures of sputum, tracheal aspirate, pleural fluid, or blood
- Acute respiratory failure*, need for mechanical ventilation
- Dronkers 2008 *Atelectasis*, diagnosed on chest-XRays by a “blinded” radiologist
- Pehlivan 2011 *Atelectasis*: based on chest-X rays Fever, Dyspnoea, Haemorrhagic drainage, *Pneumonia*,
- Pulmonary embolism
- Valkenet 2018 *Pneumonia*: a score of 2 points or more with at least 1 point assigned based on Temperature (≥ 36.1 and $\leq 38.4^{\circ}\text{C}$: 0; ≤ 36.0 and $\geq 38.5^{\circ}\text{C}$: 1), Leucocyte count (≥ 4.0 and $\leq 11.0 \times 10^9 /\text{l}$: 0; < 4.0 or $> 11.0 \times 10^9 /\text{l}$: 1), chest X-rays (No infiltrate: 0; Diffused (or patchy) infiltrate: 1; Well circumscribed infiltrate: 2)

Soares 2013 *Pneumonia*: based on clinical, laboratory and chest X-rays as well as the need for antibiotic therapy

Atelectasis, based on chest X-rays and need for bronchoscopy

Kulkarni 2010 *Pneumonia*: based on positive sputum culture and antibiotic treatment

Ferreira 2009 No specific criteria to diagnose pneumonia, atelectasis and other complications

Weiner 1998

Table S6: Adherence to treatment and adverse effect during training session

Study	Adherence	Adverse effects
Laurent 2020	86% to prescribed training sessions	None
	Not reported	Not reported
Chen 2019		
Valkenet 2018	67.5% to prescribed training sessions	None
	28.3% achieved the prescribed intensity of training	
Barberan- Garcia 2017	Not reported	None
Huang 2017	Not reported	Not reported
Tew 2017	76% to prescribed training sessions	Angina pectoris (1 patient), dizziness (1 patient)
Lai 2017 (JOR)	Not reported	Not reported
Lai 2017	Not reported	Not reported
Barakat 2016	77% to at least 75% of prescribed training sessions	None
Dunne 2016	95% of the prescribed training sessions	None
Licker 2017	87% of the prescribed training sessions	None
Sebio Garcia2017	A median of 16 sessions (range 8 to 25) were attended over a mean period of 54 days (SD 15)	None
Lai 2016	Not reported	Not reported
Yamana 2015	Not reported	None
Llorens 2015	Not reported	Not reported
Sawatzky 2014	Not reported	none
Stefanelli 2013	Not reported	Not reported
Soares 2013	Not reported	Not reported

Morano 2013	Not reported	Not reported
Barbalho-Moulim 2011	Not reported	Not reported
Benzo 2011	100% % to prescribed training sessions	None
Pehlivan 2011	Not reported	Not reported
Kulkarni 2010	100% % of the prescribed training sessions	Not reported
Dronkers 2010	97% of the prescribed training sessions	None
Ferreira 2009	Not reported	None
Dronkers 2008	Not reported	None
Hulzebos 2006	Not reported	None
Hulzebos 2006 (Pilot)	Not reported	None
Weiner 1998	Not reported	Not reported
