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

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**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

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**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

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cmH20, 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

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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

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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 cancer[14-19], colorectal cancer[20], oesophago-gastric cancer[21], abdominal cancer[22,23], or any cancer[24]), or specific procedures (cardiac surgery [25], vascular surgery [26], colorectal surgery[27] or major abdominal surgery[28-30]. 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.

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# Methods

## Protocol and Registration

This review is reported according to the PRISMA statement [32] 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-MAStARI 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.

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**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 (peak$VO_2$), maximal inspiratory pressure (MIP), six-minute walking test (6MWT), forced expiratory volume in the first second [$FEV_1$],

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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 peak$VO_2$, MIP and 6MWT, we calculated

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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

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(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] France[64] 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

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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, $FEV_1$ 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 scale[62] 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%)

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(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 al[58] 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

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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 $cmH_20$ and 81 $cmH_20$, 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 $ml.kg^{-1}.min^{-1}$, 99%CI 0.33 to 3.11) and in MIP (WMD +15.5 $cmH_20$, 99%CI 12.5 to 18.4) with no significant change at the 6MWT (WMD +30.7 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%).

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## 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.

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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 $cmH_20$, 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

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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 peak$VO_2$ during CPET (11% gain in peak$VO_2$, compared with baseline). In agreement with previous analyses, such training failed to produce any gain in functional lung capacity and $FEV_1$ 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-F 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]

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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 al[59] found no favourable clinical effect of preoperative RMT whereas Yamana et al[61] 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.

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**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.

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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.

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**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

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**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 |

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| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 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 |

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| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 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.

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**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) | $I^2$ | P value overall effect* |
|---|---|---|---|---|
| **Peak $VO_2$ (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 ($cmH_2O$)** | | | | |
| 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 |
| **$FEV_1$ (% 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 |

Peak$VO_2$, peak oxygen consumption; $FEV_1$, 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

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**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) | $I^2$ % | 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.

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

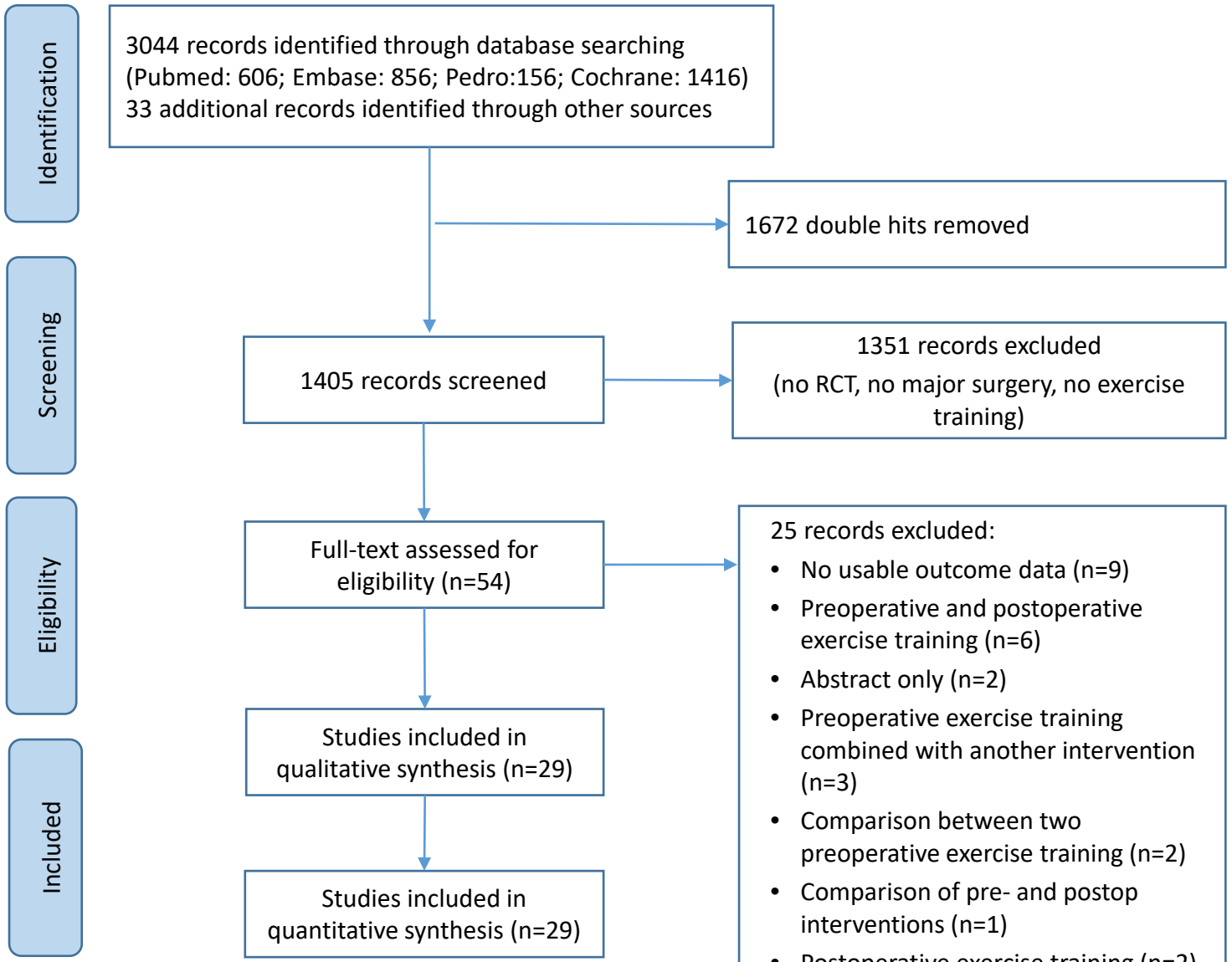


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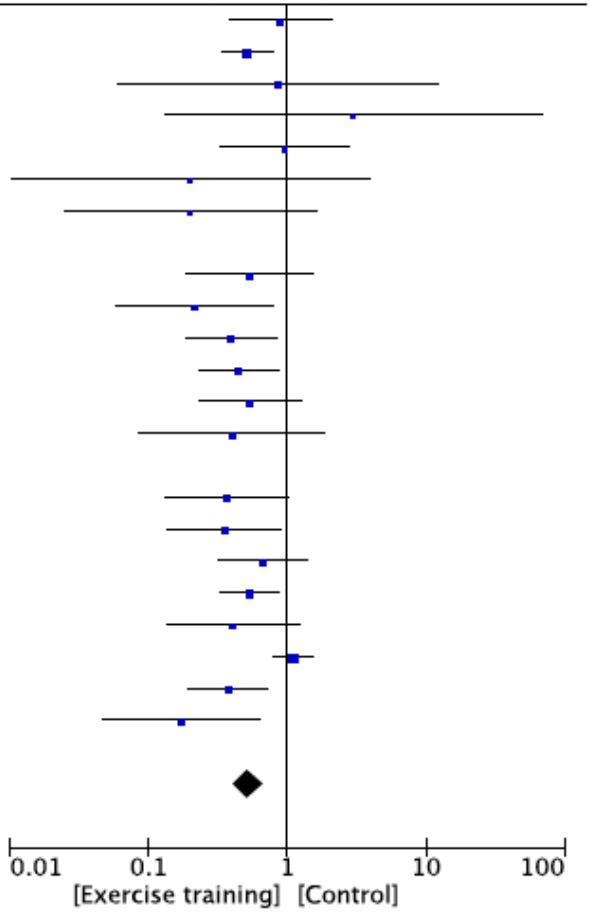
**Figure 2 .** Forrest plot of the effect of preoperative exercise training on postoperative pulmonary complications, including all randomized controlled trials

| Study or Subgroup | Exercise training Events | Total | Control Events | Total | Weight | Risk Ratio M-H, Random, 95% CI | Year |
|---|---|---|---|---|---|---|---|
| Weiner 1998 | 8 | 42 | 9 | 42 | 5.2% | 0.89 [0.38, 2.08] | 1998 |
| Hulzebos 2006 (b) | 25 | 139 | 48 | 137 | 10.7% | 0.51 [0.34, 0.78] | 2006 |
| Hulzebos 2006 | 1 | 14 | 1 | 12 | 0.8% | 0.86 [0.06, 12.28] | 2006 |
| Ferreira 2009 | 1 | 15 | 0 | 15 | 0.6% | 3.00 [0.13, 68.26] | 2009 |
| Dronkers 2010 | 5 | 21 | 5 | 20 | 3.7% | 0.95 [0.32, 2.80] | 2010 |
| Kulkarni 2010 | 0 | 17 | 2 | 17 | 0.6% | 0.20 [0.01, 3.88] | 2010 |
| Pehlivan 2011 | 1 | 30 | 5 | 30 | 1.2% | 0.20 [0.02, 1.61] | 2011 |
| Barbahlo-Moulim 2011 | 0 | 15 | 0 | 17 | | Not estimable | 2011 |
| Benzo 2011 | 3 | 9 | 5 | 8 | 3.8% | 0.53 [0.18, 1.55] | 2011 |
| Morano 2013 | 2 | 12 | 7 | 9 | 2.7% | 0.21 [0.06, 0.80] | 2013 |
| Soares 2013 | 5 | 15 | 11 | 13 | 6.2% | 0.39 [0.19, 0.84] | 2013 |
| Yamana 2015 | 8 | 30 | 18 | 30 | 7.2% | 0.44 [0.23, 0.86] | 2015 |
| Barakat 2016 | 7 | 62 | 13 | 62 | 5.3% | 0.54 [0.23, 1.26] | 2016 |
| Lai 2016 | 2 | 24 | 5 | 24 | 2.1% | 0.40 [0.09, 1.86] | 2016 |
| Sebio-Garcia 2017 | 0 | 10 | 0 | 12 | | Not estimable | 2017 |
| Lai 2017 (b) | 4 | 30 | 11 | 30 | 4.0% | 0.36 [0.13, 1.01] | 2017 |
| Lai 2017 | 5 | 51 | 14 | 50 | 4.5% | 0.35 [0.14, 0.90] | 2017 |
| Huang 2017 | 8 | 30 | 12 | 30 | 6.3% | 0.67 [0.32, 1.39] | 2017 |
| Licker 2017 | 17 | 74 | 33 | 77 | 9.5% | 0.54 [0.33, 0.88] | 2017 |
| Barberan-Garcia 2018 | 4 | 62 | 10 | 63 | 3.6% | 0.41 [0.13, 1.23] | 2018 |
| Valkenet 2018 | 47 | 120 | 43 | 121 | 12.3% | 1.10 [0.79, 1.53] | 2018 |
| Chen 2019 | 10 | 98 | 27 | 99 | 7.1% | 0.37 [0.19, 0.73] | 2019 |
| Laurent 2020 | 2 | 14 | 10 | 12 | 2.7% | 0.17 [0.05, 0.63] | 2020 |
| **Total (95% CI)** | | **934** | | **930** | **100.0%** | **0.52 [0.41, 0.66]** | |
| Total events | 165 | | 289 | | | | |

Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 31.41$, df = 20 (P = 0.05); $I^2 = 36\%$

Test for overall effect: Z = 5.34 (P < 0.00001)

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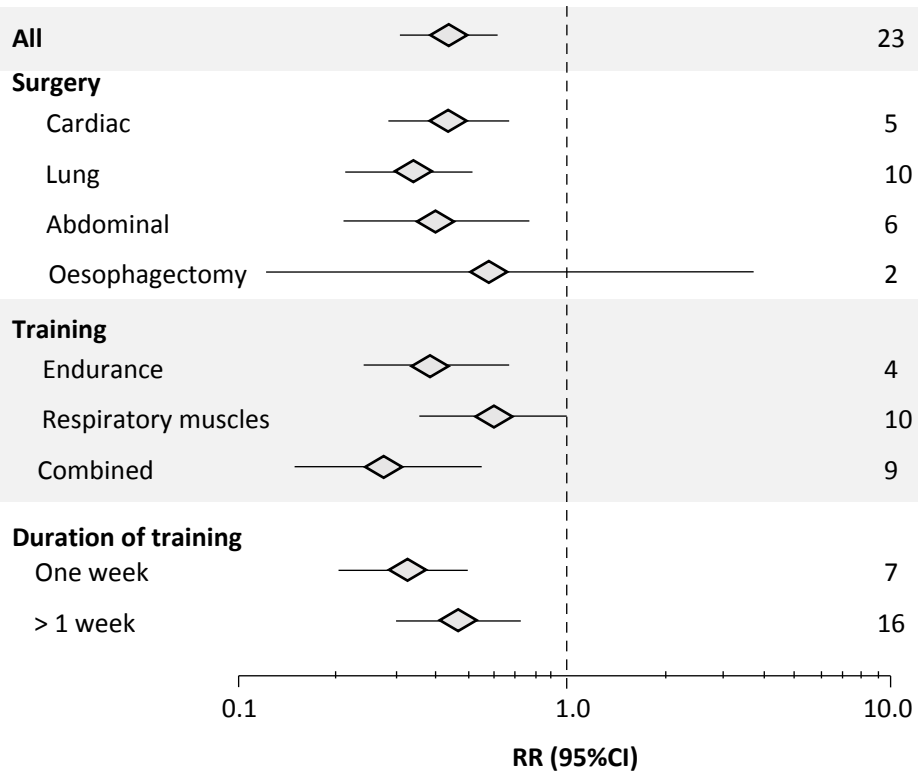


| | N RCTs | N events / total patients (%) intervention | control | RR(95%CI) | TSA |
|---|---|---|---|---|---|
| **All** | 23 | 165/934 (17%) | 289/930 (31%) | 0.52 (0.41 to 0.66) | Conclusive |
| **Surgery** | | | | | |
| Cardiac | 5 | 45/308 (15%) | 85/305 (28%) | 0.53 (0.38 to 0.73) | Conclusive |
| Lung | 10 | 44/284 (15%) | 102/282 (36%) | 0.45 (0.33 to 0.60) | Conclusive |
| Abdominal | 6 | 21/192 (11%) | 41/192 (21%) | 0.50 (0.32 to 0.78) | Unclear |
| Oesophagectomy | 2 | 55/150 (37%) | 61/151 (40%) | 0.73 (0.30 to 1.78) | --- |
| **Training** | | | | | |
| Endurance | 4 | 29/228 (13%) | 61/232 (26%) | 0.50 (0.34 to 0.74) | Conclusive |
| Respiratory muscles | 10 | 102/504 (20%) | 152/502 (30%) | 0.61 (0.39 to 0.94) | Unclear |
| Combined | 9 | 34/202 (17%) | 76/196 (39%) | 0.43 (0.31 to 0.60) | Conclusive |
| **Duration of training** | | | | | |
| One week | 7 | 33/272 (12%) | 79/271 (29%) | 0.43 (0.30 to 0.62) | Conclusive |
| > 1 week | 16 | 142/662 (20%) | 210/659 (32%) | 0.56 (0.41 to 0.76) | Conclusive |

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**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

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**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).

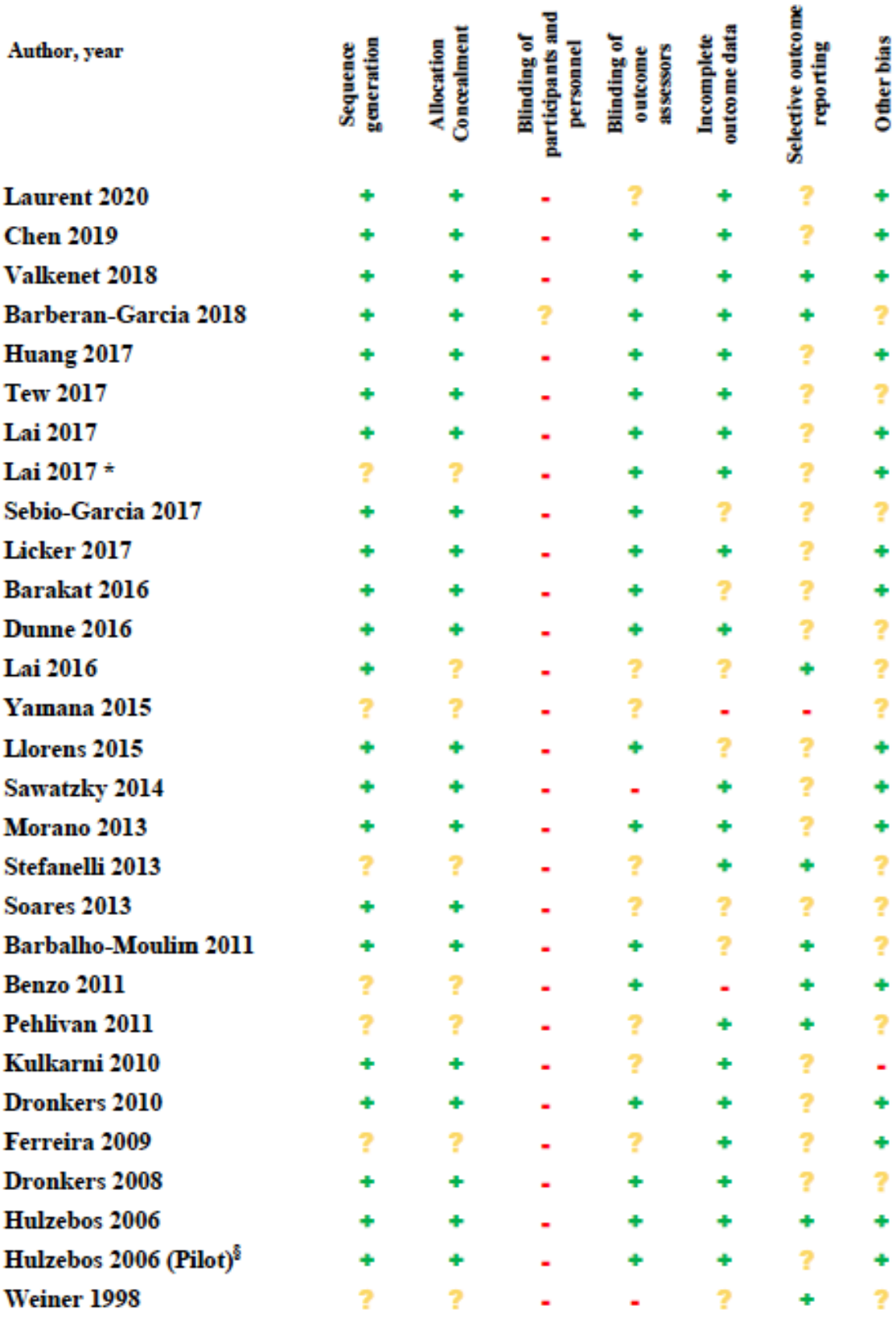




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**Fig. S2.** Summary of risk of bias of across the 23 trials reporting on the primary endpoint and included in the systematic review. Information for every study characteristic was pooled from every trial (green: low risk of bias; yellow: unclear risk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

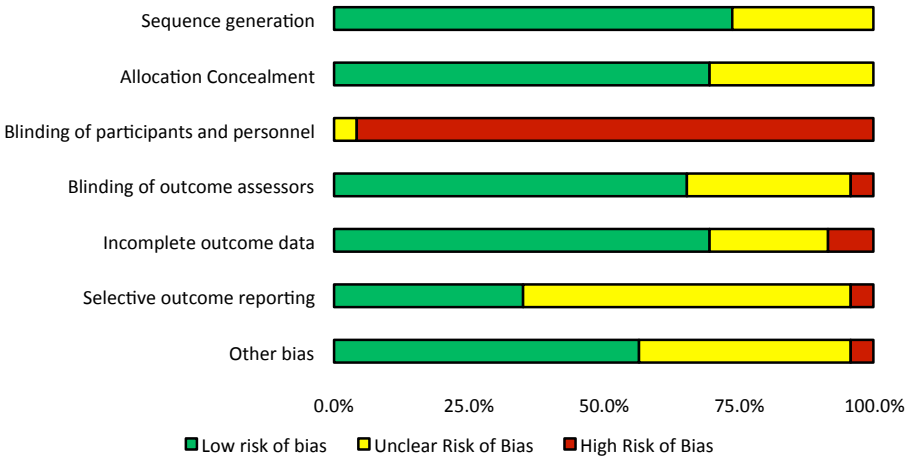




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**Fig S3:** Funnel plot for postoperative pulmonary complications

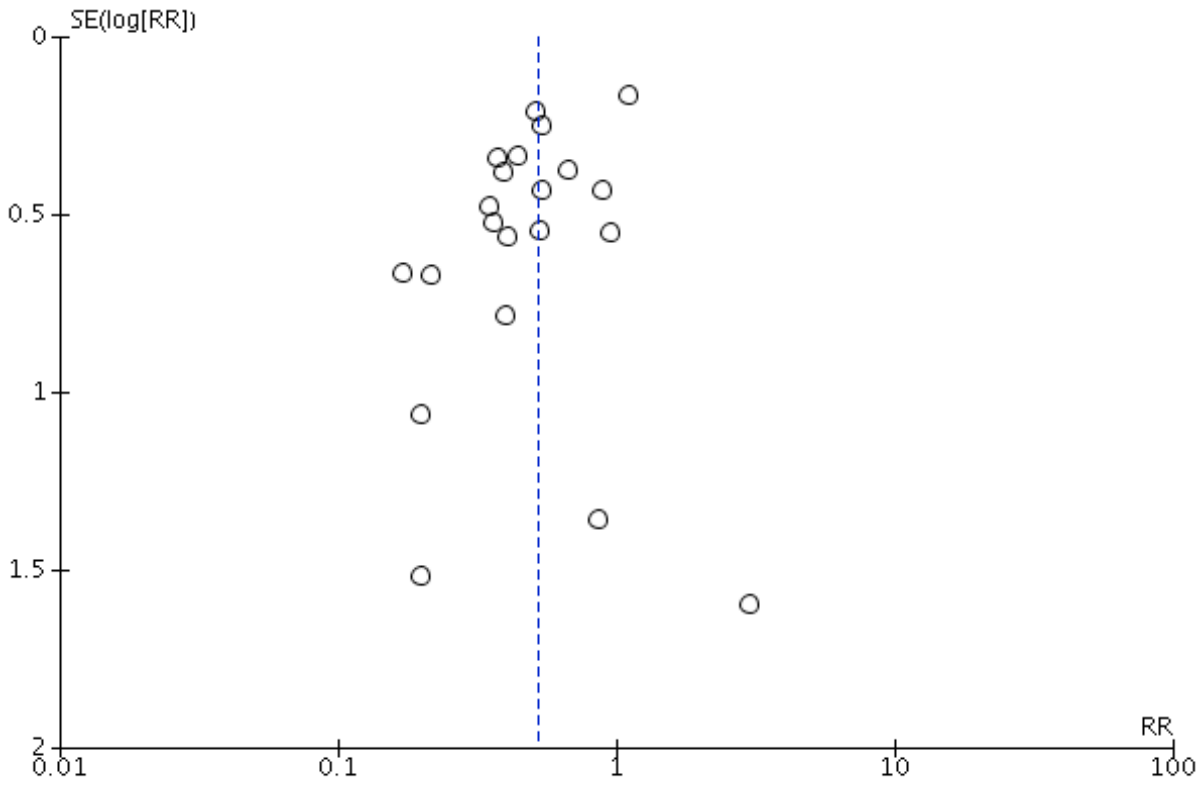




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**Figure S4:** Trial sequential analysis of 23 trials comparing intervention with control for postoperative pulmonary complications (scaled trial distance). This figure illustrates that the cumulative Z curve (blue line) crosses the conventional boundary 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%.

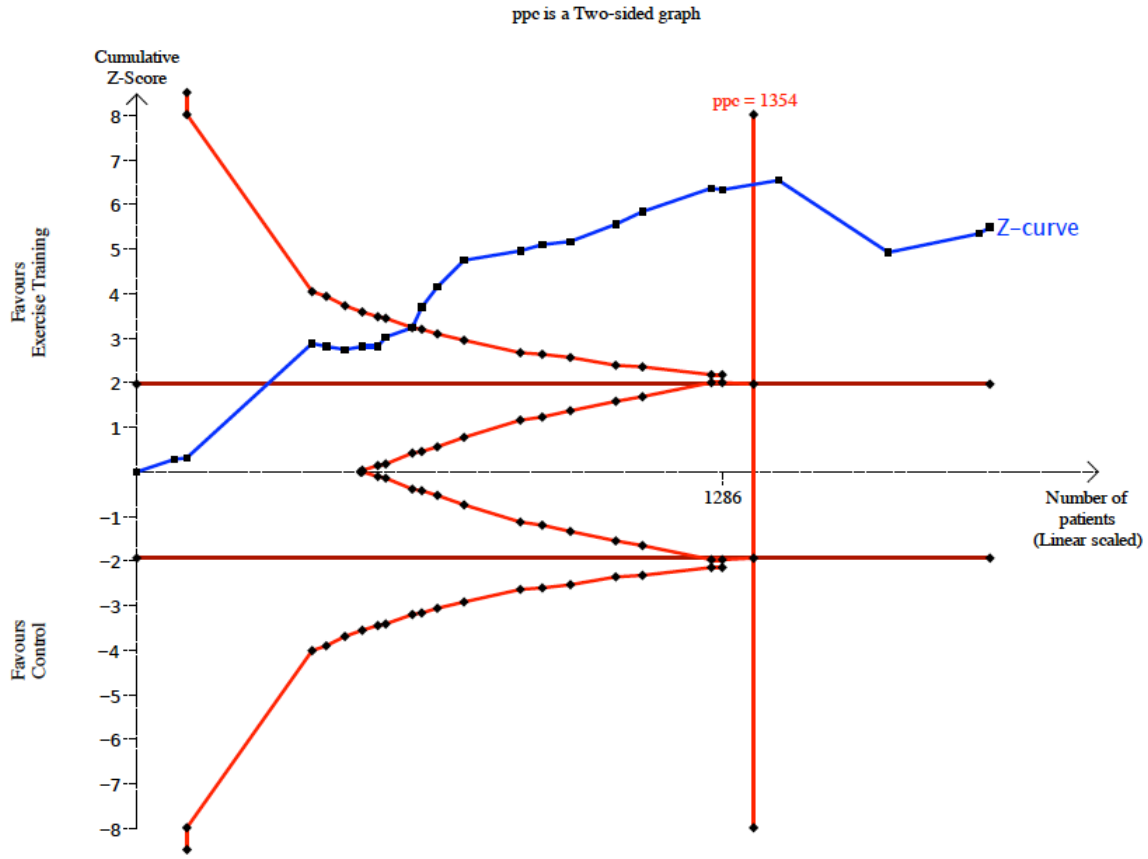




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**Fig S5:** Forrest plot of the effect of preoperative exercise training on postoperative pulmonary complications, including randomized controlled trials with low risk of bias.

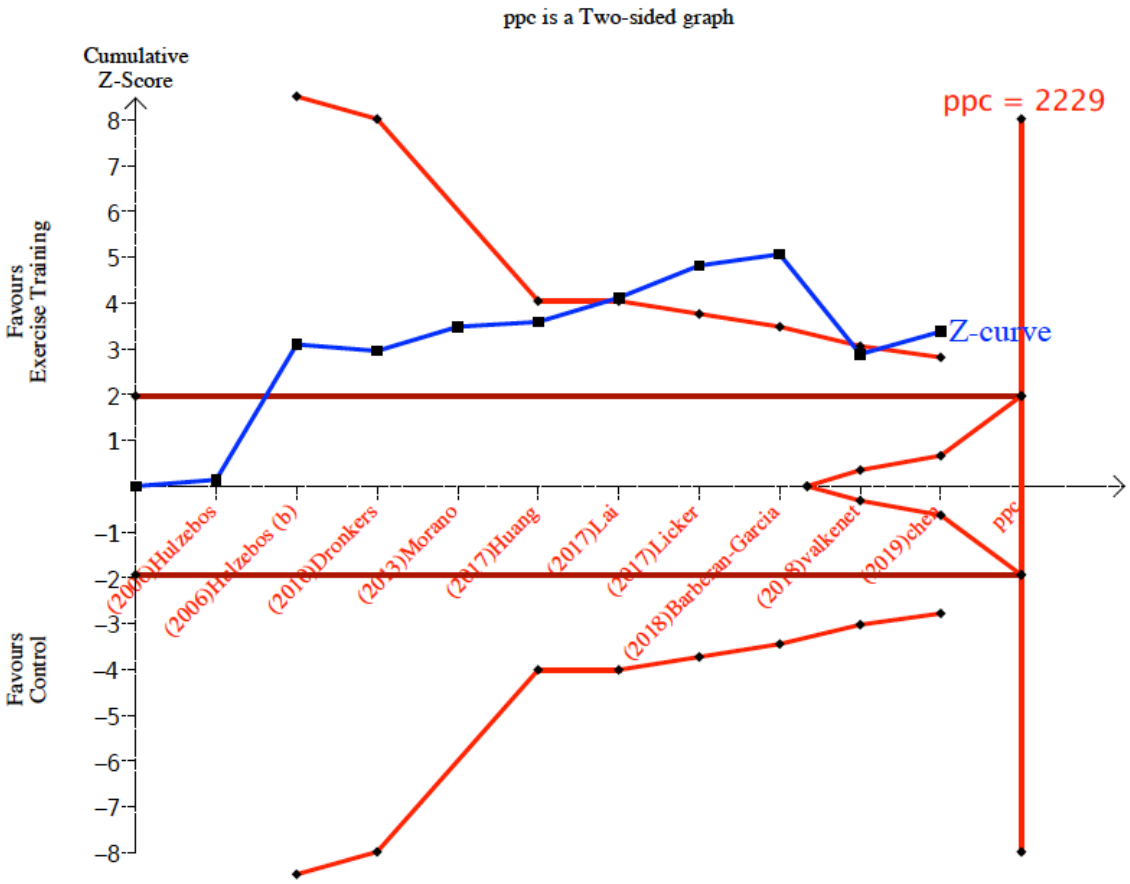




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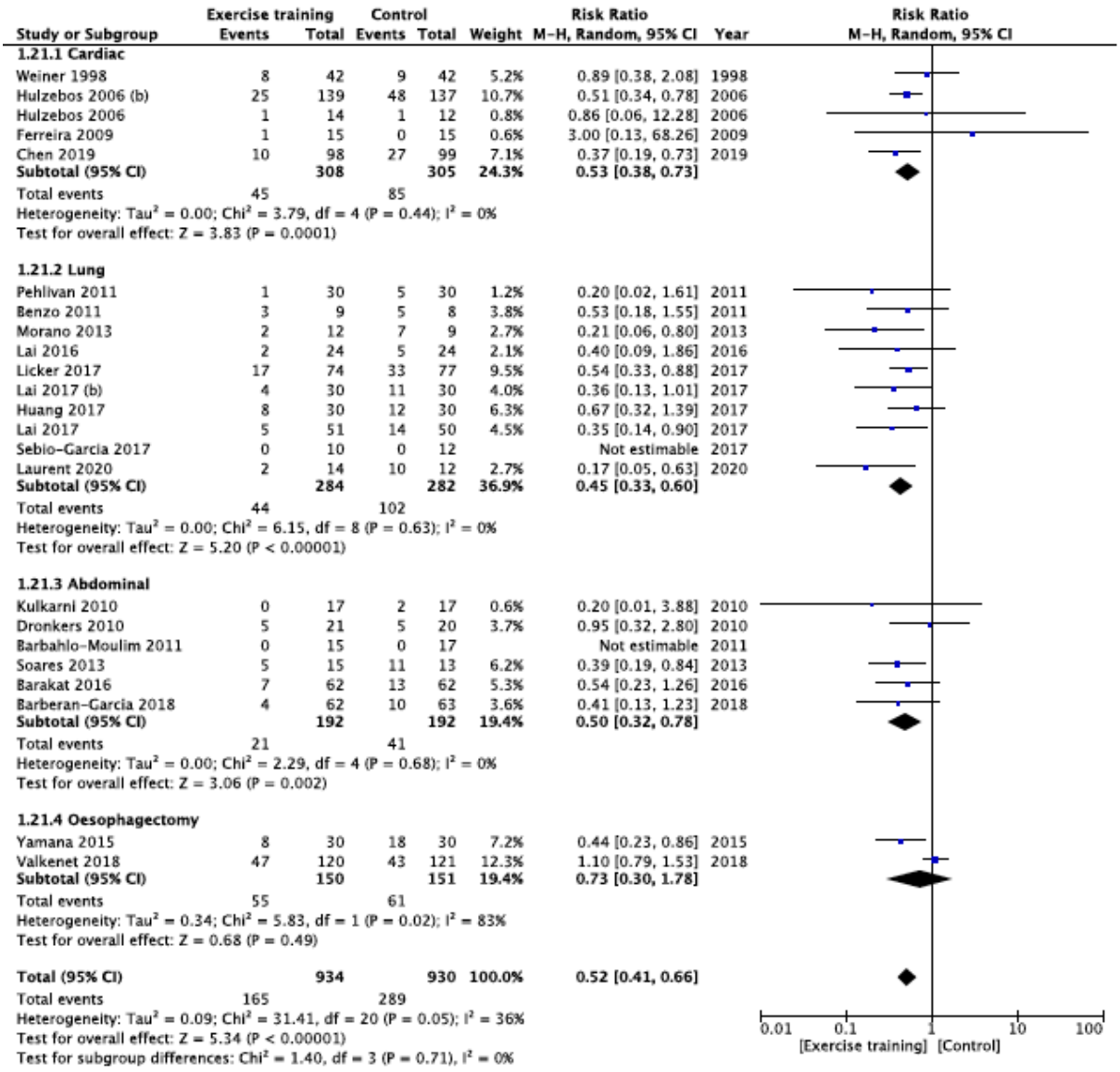
**Fig S6**: Postoperative pulmonary complications in patients receiving intervention training or usual care. (A) Forrest plot with subgroup analysis according to type of surgery (cardiac, lung, abdominal, esophageal). (B) Trial sequential analysis for surgical subgroups (A=Cardiac; B=Lung; C= Abdominal)

**S6-A.**



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**S6-B.**

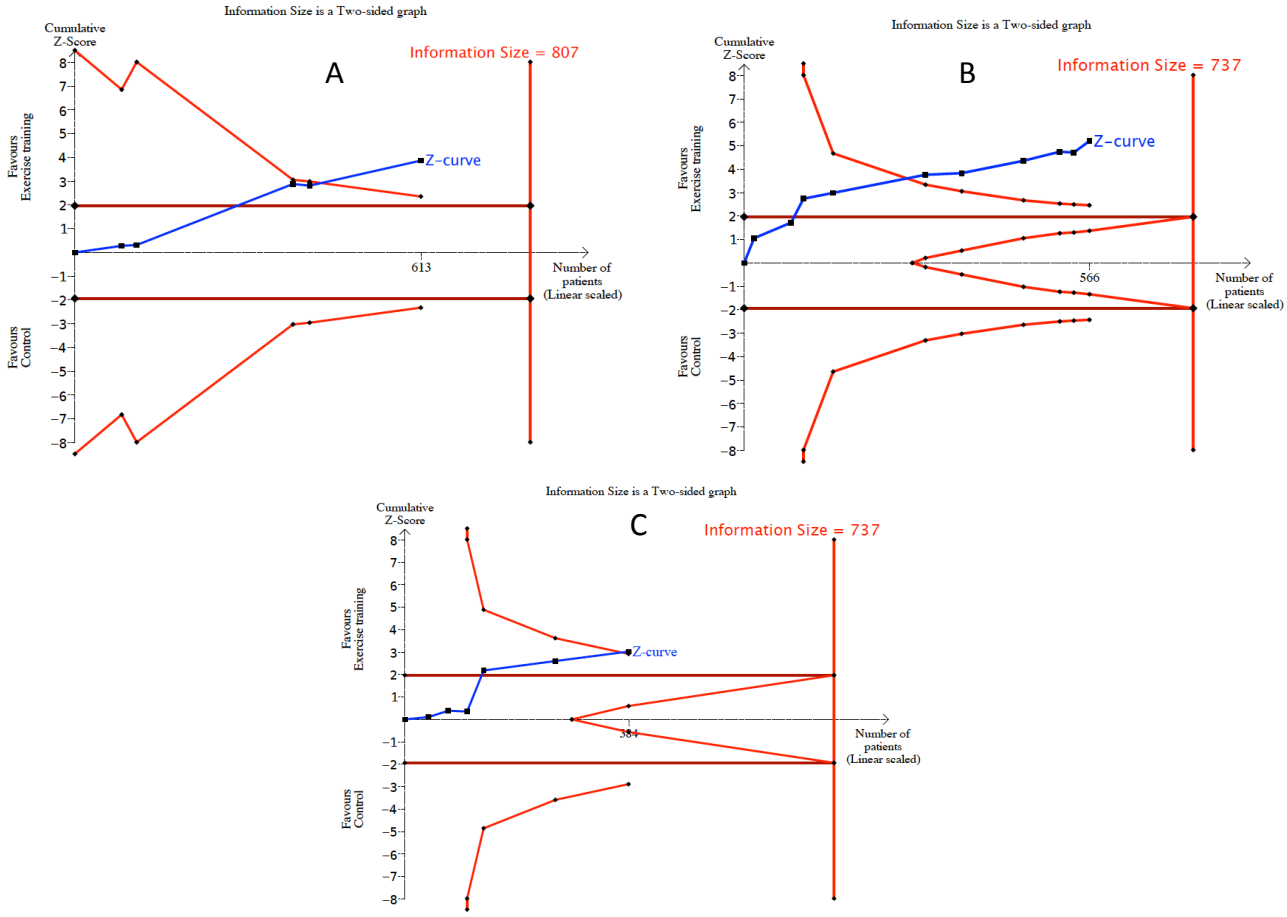




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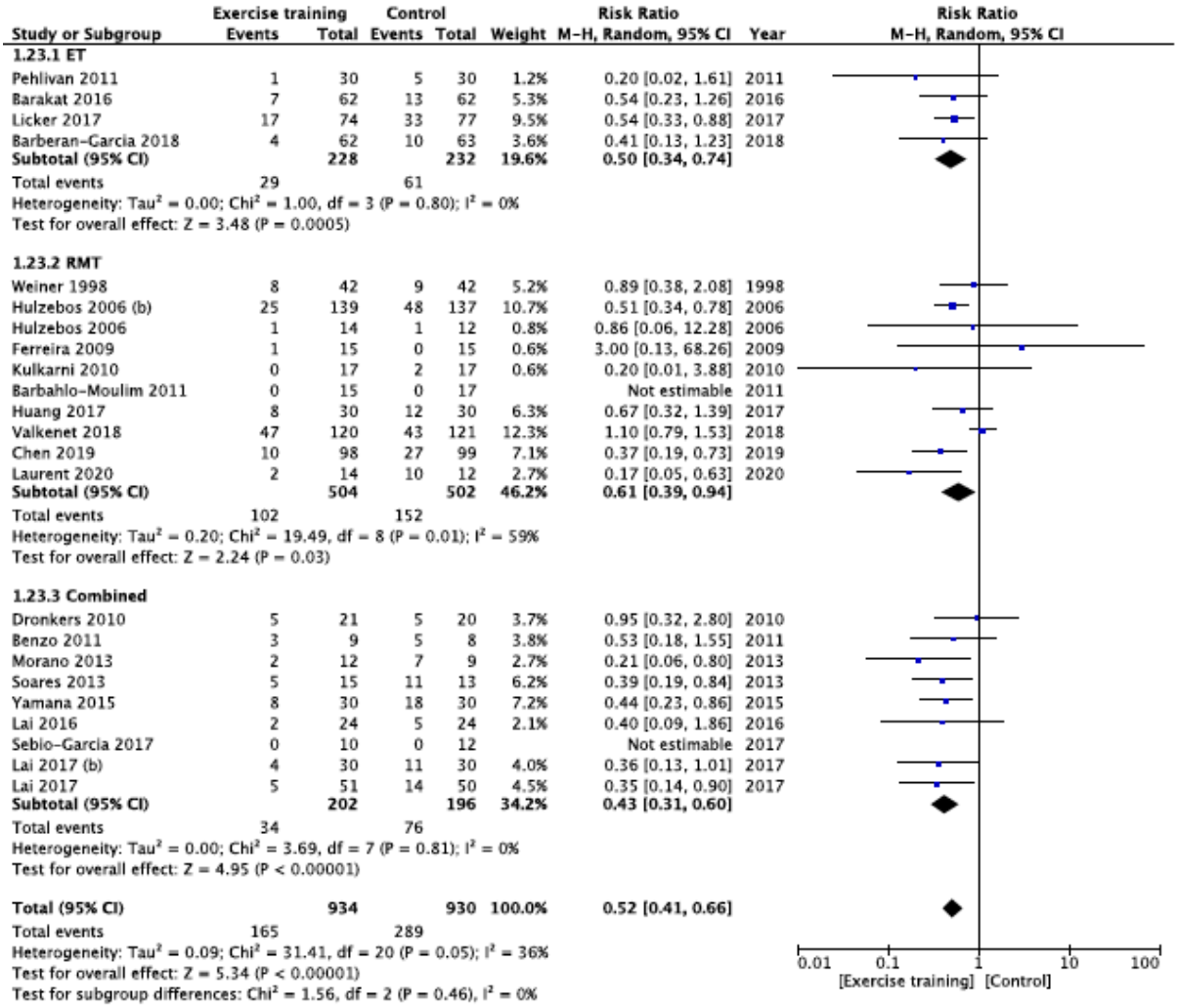
**Fig S7:** Postoperative pulmonary complications in patients receiving preoperative exercise training or usual care. (A) Forrest plot with subgroup analysis according to type of training (ET, endurance training; RMT, inspiratory muscle training; Combined). (B) Trial sequential analysis according to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

**S 7A**



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**S7B**

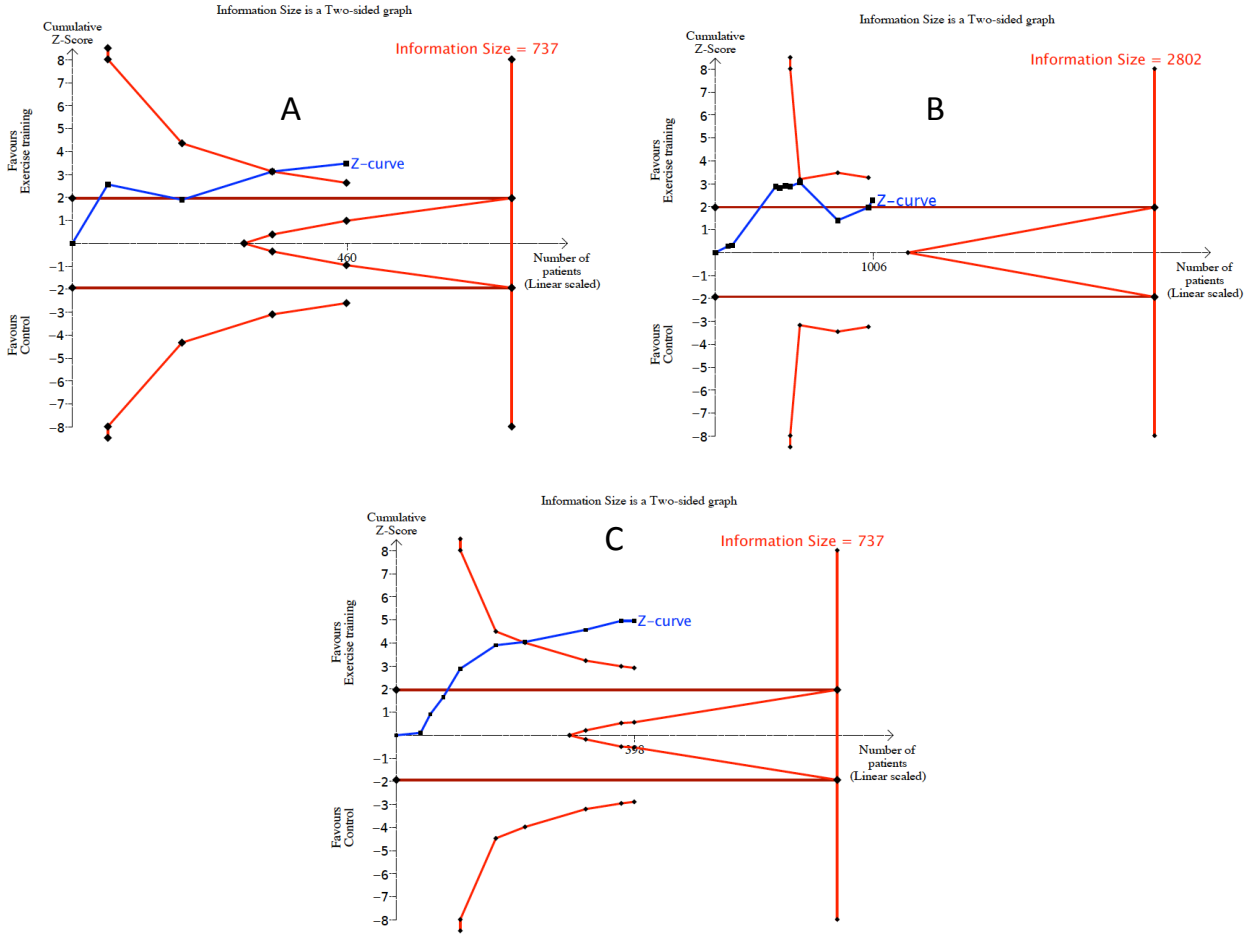




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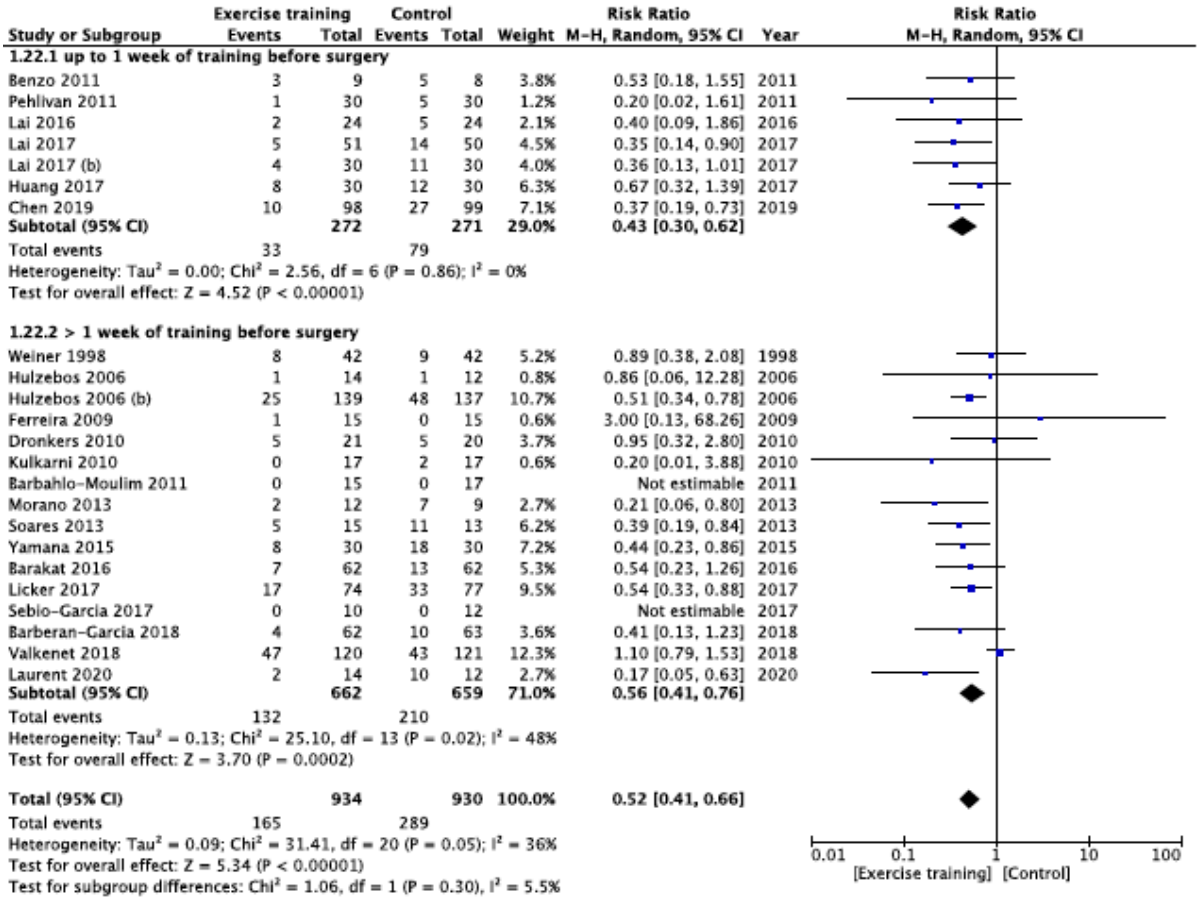
**Figure S8:** Postoperative pulmonary complications in patients receiving preoperative exercise training or usual care. (A) Forrest plot with subgroup analysis according to duration of training (up to one week; more than one week). (B) Trial sequential analysis according to the duration of training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

**S8A**



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**S8B**

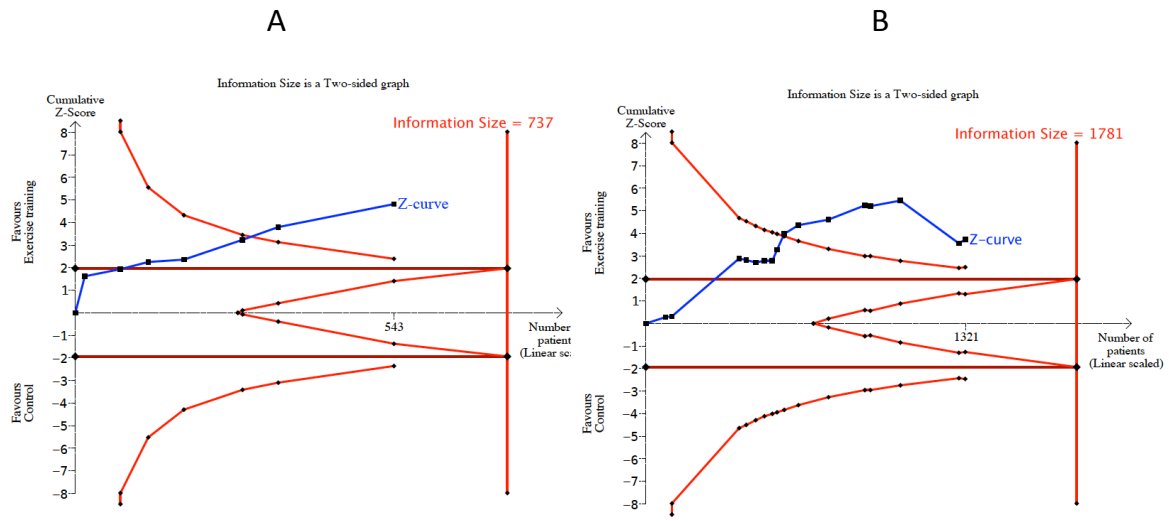


Figure S9: Grade of the evidence for the postoperative pulmonary complications

**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 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Study event rates (%) | | | Anticipated absolute effects | |
| Participants (studies) Follow up | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Overall certainty of evidence | With control | With preoperative exercise training | Relative effect (95% CI) | Risk with control | Risk difference with preoperative exercise training |
| **Postoperative Pulmonary complications** | | | | | | | | | | | |
| 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 1 000 | **141 fewer per 1 000** (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 biais.



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**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<br>3/10/2017 | - Full text<br>- 30- day mortality<br>- Mean and SD for 6MWT | - Full text received<br>- No response |
| Dunne 2016 | 3/10/2017 | - 30- day mortality<br>- Place of exercises? Supervision? | - No mortality after 30 days<br>- Supervised, hospital |
| Barbalho-Moulim 2011 | 3/10/2017 | - 30- day mortality | - No mortality after 30 days |
| Benzo 2011 | 3/10/2017<br>11/11/2018 | - 30- day mortality<br>- Protocol for study 1 | - No data available<br>- No response |
| Stefanelli 2013 | 3/10/2017 | - 30- day mortality<br>- Delta VO2max | - No response |
| Lai 2017 | 3/10/2017 | - 30- day mortality<br>- 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<br>- MIP | - Answer received |



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**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 | J Rehabil Med 2019 Oct 3;51(9):712-718. | 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 | Support Care Cancer. 2019 Aug;27(8):2933-2940. | 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 | S. Clin Rehabil. 2020 Jan;34(1):69-81 | 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 | Ann Surg 2018; 268: 747–55 | 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<br>No usable outcome data |
| Sommer | Integr Cancer Ther 20 | Perioperative rehabilitation in operation | Preoperative and |



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| | | | |
|---|---|---|---|
| 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,<br>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 |



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| | | | |
|---|---|---|---|
| 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 pulmonarycComplications through respiratoryrRehabilitation: a controlled clinical study | Preoperative and postoperative interventions |



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**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 | - 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<br>- 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 | - Hospital-based, 5-days of intensive respiratory muscle training.<br>- 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).<br>- 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 | - Home-based (diary), supervised (phone call) by physiotherapist.<br>- Oral instruction by a physiotherapist and with video-assistance<br>- 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 |



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| | | | | |
|---|---|---|---|---|
| Huang 2017 | - Hospital-based, supervised training by trained nurses<br>- 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<br>- 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 | - Hospital-based, supervised training<br>- Thoracic expansion and incentive spirometry (deep breathing using HUDSON RCI 2500 Teleflex, Temecula, CA), 20 breaths/session, 3 times/day;<br>- Abdominal breathing to strengthen the diaphragm, 15-30 min, 2 times/day<br>- 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 | - Hospital-based, supervised training<br>- 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<br>- 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 | - Hospital-based, supervised training by physiotherapists<br>- 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 |



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| | | | | |
|---|---|---|---|---|
| Tew 2017 | - Hospital-based, supervised training<br>- 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 | - Home-based training<br>- Personalized rehabilitation, motivational interview, nutritional counselling; advice on smoking cessation and reduction of alcohol intake<br>- Instructions for physical exercise and specific thoracic expansion maneuvers<br>- 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 | Routine preoperative care,<br>Recommendation on physical activity (use pedometer); nutritional counselling;<br>Advice on smoking cessation and reduction of alcohol intake | Four to six weeks |
| Sebio Garcia 2017 | - 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);<br>- Resistance training using elastic bands (Thera-Band, Hygienic Corp., Ohio, USA) and body weight exercises (six different types)<br>- 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)<br>- Median of 16 sessions (3-5 times/week) | 660 min | Usual care | At least two weeks |
| Barakat 2016 | - Hospital-based, supervised training.<br>- 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 |



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| | | | | |
|---|---|---|---|---|
| | body weight lifting, step-up, stretching); 3 times/week | | | |
| Dunne 2016 | - Hospital-based, supervised training with personalized exercise program (on anaerobic threshold)<br>- Aerobic endurance high-intensity interval training with cycle ergometer (Optibike; Ergoline, Bitz, Germany), alternating work at 60% and 90% peak $VO_2$), 12 sessions (30-40 min) over 4 weeks | 420 min | Advice for regular exercise | Four weeks |
| Lai 2016 | - Hospital-based, supervised training<br>- 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<br>- 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 | - Home-based with one session supervised/week<br>- Use of IMT device (Threshold, Respironics Inc. Pittsburgh, PA), starting from 30% MIP and increased based on Borg scale (<5)<br>- Use volumetric spirometry (Voldyne 5000, Teleflex medical); once/day, 40 min | 600 min | Instructions about preoperative usual care | Four weeks |
| Yamana 2015 | - Hospital-based, supervised intensive respiratory, for 60 min per day during more than 7 days<br>- Deep inspiration, deep diaphragmatic breathing and thoracic cage stretching; efficient coughing and contractions of abdominal muscles<br>- Aerobic endurance on cycle ergometer (20 min with increasing workload); strengthening exercises of lower limbs | 420 min | Routine preoperative protocol | More than one week |



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| | | | | |
|---|---|---|---|---|
| Sawatzky 2014 | - Supervised training in a medical fitness facility<br>- Aerobic endurance exercises (walking, cycling, light resistance exercise with body weight and resistance bands and stretching): 85% $VO_2$max;<br>- 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 | - Hospital supervised training (2 sessions of 50 min/week) and home-based unsupervised training sessions.<br>- Use of IMT (Threshold, Respironics, NJ), 20% MIP, increased by 2cmH2O ; 15 min, 4 times/week<br>- Stretching, relaxation and trunk rotation exercises; guidance on coughing and huffing<br>- 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 | - In-hospital supervised sessions<br>- Respiratory exercises (mattress, bench & wall bars)<br>- 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 |



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| | | | | |
|---|---|---|---|---|
| Morano 2013 | - Hospital-based, supervised training<br>- 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.<br>- Lower limb aerobic training on treadmill up to 80% WR (10 to 30 min)<br>- 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 | - Hospital-based, supervised sessions<br>- 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<br>- 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 | - Hospital-based, supervised sessions<br>- Intensive physical therapy (chest physiotherapy, breathing/diaphragmatic exercise, incentive spirometry, coughing)<br>- 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 | - Hospital-based, supervised (one in three) and unsupervised sessions<br>- Use of IMT (Threshold, Respironics, 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 |



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| | | | | |
|---|---|---|---|---|
| Kulkarni 2010 | - Home-based sessions<br>- 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 | - In-hospital supervised training sessions (60 min, 2 times/week) and home-based sessions (45 min/day)<br>- 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)<br>- 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).<br>- Unsupervised home session including walking (pedometer) or/and cycling (> 30 m min/day) | 360 min supervised<br>675 min un-supervised | Home-based exercise advice, minimum 30 min active/day (pedometer)<br>Instructions about diaphragmatic breathing, deep inspirations using incentive spirometry,coughing and forced expiration techniques | Two to four weeks |
| Ferreira 2009 | - Home-based training program<br>- Use of IMT device (Threshold Respironics Cedar Grove, NJ) at 40% MIP, 5 series of 10 deep inspirations, 3 times/day<br>- 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 | - 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<br>- Use of IMT Threshold (Respironics 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<br>One day before surgery: instructions about diaphragmatic breathing, deep inspirations using incentive spirometry, coughing and forced expiration techniques | Two to three weeks |



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| | | | | |
|---|---|---|---|---|
| Hulzebos 2006 | - Home-based training (diary recording) with one supervised session/week.<br>- Instruction on breathing techniques with an incentive spirometer (Coach 2, DHD Healthcare, Wampsville, NY) and forced expiration manoeuvre.<br>- 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 | Routine preoperative protocol<br>Instructions on deep breathing, coughing and early mobilization | Two to four weeks |
| Hulzebos 2006 | - Home-based training with one supervised session/week<br>- 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 | Routine preoperative protocol and one day before surgery: education about early mobilization and coughing with wound support | Two to four weeks |
| Weiner 1998 | - Hospital-based, supervised training by a physician.<br>- Use of IMT device (Threshold Inspiratory Muscle Trainer, Health-scan) from 15% to 60% MIP, 30 min, 6 times/week for 2-4 weeks before surgery<br>- IMT was continued at low level (15% of MIP) for 1 week postoperatively | 540 min | Breathing exercises without resistance, 6 times a week, for 2-4 weeks | Two to four weeks |

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



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**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



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**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]<br>Barberan-Garcia 2017<br>Huang 2017<br>Licker 2017<br>Yamana 2015 | 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<br><br>*Grade I*: complication without need for pharmacologic treatment or other intervention.<br><br>*Grade II*: complication requiring pharmacologic treatment or minor intervention.<br><br>*Grade III*: complication requiring surgical, radiologic, endoscopic intervention, or multi-therapy.<br><br>*Grade IIIa*: invasive treatment with no need for general anesthesia<br><br>*Grade IIIb*: invasive treatment under general anesthesia<br><br>*Grade IV*: complication requiring intensive care unit management and life support.<br><br>*Grade IVa*: single organ major dysfunction.<br><br>*Grade IVb*: multiorgan major dysfunction.<br><br>*Grade V*: complication leading to the death of the patient. |
| - Lai 2016,<br>Lai 2017[3] | (i) *Atelectasis*, (ii) *acute respiratory distress syndrome*, (iii) *respiratory failure*, (iv) *mechanical ventilation at 48 h postoperatively*, (v) *deep vein thrombosis/pulmonary embolism* and (vi) *empyema or pneumonia* (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). |
| - Sebio Garcia 2017 | Melbourne Group scale[4]; PPC diagnosed by $\geq$ 4 of the following criteria:<br>1. Chest radiograph report of atelectasis/consolidation<br>2. Unexplained leucocytosis (>11'200/mm3) or administration of antibiotics postoperatively (in addition to those administered routinely postoperatively).<br>3. Fever (>38°C) with no focus outside of the lungs.<br>4. Positive signs of infection on sputum microbiology.<br>5. Production of purulent (yellow or green) sputum differing from preoperative status<br>6. SpO2 < 90% on room air<br>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.



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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 2006[5] Chen 2019

Definition and grading of complications according to Kroenke et al[6]

**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 48 hours

- Hulzebos 2006[7]

*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



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| | |
|---|---|
| | *Mechanical ventilation*: postoperative ventilator support >48h, |
| | *Unplanned reintubation* |
| - Morano 2013 | *Pneumonia*: new infiltrate plus temperature≥ 38°C, white blood cell count >10'000 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°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 C) and white cell count >11,000/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 ≤ 38.4°C: 0; ≤ 36·0 and ≥ 38·5°C: 1), Leucocyte count (≥ 4·0 and ≤ 11·0 × $10^9$ /l: 0; < 4·0 or > 11·0 × $10^9$ /l: 1), chest X-rays (No infiltrate: 0; Diffused (or patchy) infiltrate: 1; Well circumscribed infiltrate: 2) |



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| | |
|---|---|
| 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 | |



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**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 |



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| | | |
|---|---|---|
| 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 |



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