Appendix 1. Search strategies

Embase

(postoperative complication/ or perioperative period/ or peroperative care/ or preoperative care/ or postoperative care/ or anesthesia/ or intra*operative complication*.mp or post*operative complication*.mp or peri*operative complication*.mp or pre*operative care.mp or intra*operative care.mp or peri*operative care.mp or post*operative care.mp or an*esthesia.mp)

Combined with the AND Boolean operator for the following descriptive terms relevant to post-operative respiratory complications and based on the EPCO definitions:

(pneumonia/ or respiratory tract infection/ or lung infection/ or respiratory failure/ or atelectasis/ or pleural effusion/ or pneumonia.mp or respiratory infection.mp or pulmonary infection.mp or respiratory failure.mp or atelectasis.mp or pleural effusion.mp or respiratory complication*.mp)

Limits

Human studies only

Year of publication: 1990 to December 12 2017

Randomized controlled trial

MEDLINE

(Postoperative complications/ or Intraoperative care/ or Postoperative care/ or Perioperative care/ or Preoperative care/ or Intraoperative complications/ or Anesthesia/ or intra*operative complication*.mp or post*operative complication*.mp or peri*operative complication*.mp or pre*operative care.mp or intra*operative care.mp or peri*operative care.mp or post*operative care.mp or an*esthesia.mp)

Combined with the AND Boolean operator for the following descriptive terms relevant to post operative respiratory complications and based on the EPCO definitions:

(Respiratory tract infections/ or Respiratory insufficiency/ or Pneumonia/ or Pulmonary atelectasis/ or Pleural effusion/ or pneumonia.mp or respiratory infection.mp or pulmonary infection.mp or respiratory failure.mp or atelectasis.mp or pleural effusion.mp or respiratory complication*.mp)

Limits

Human studies only

Year of publication: 1990 to December 12 2017

Randomised controlled trial

CINHAL

(intra*operative complication* or post*operative complication* or peri*operative complication* or pre*operative care or intra*operative care or peri*operative care or post*operative care or an*esthesia)

Combined with the AND Boolean operator for the following descriptive terms relevant to post operative respiratory complications and based on the EPCO definitions:

(pneumonia or respiratory infection or pulmonary infection or respiratory failure or atelectasis or pleural effusion or respiratory complication*)

Limits

Year of publication: 1990 to December 12 2017

Randomised controlled trial

CENTRAL

(intra*operative complication* or post*operative complication* or peri*operative

complication* or pre*operative care or intra*operative care or peri*operative care or post*operative care or an*esthesia)

Combined with the AND Boolean operator for the following descriptive terms relevant to post operative respiratory complications and based on the EPCO definitions:

(pneumonia or respiratory infection or pulmonary infection or respiratory failure or atelectasis or pleural effusion or respiratory complication*)

Limits

Year of publication: 1990 to December 12 2017

Trials

Inclusion/exclusion criteria

The inclusion criteria are:

- Studies of patients aged 18 or over
- Studies of patients undergoing elective and emergency non-cardiac surgery
- Studies published with primary data in full peer reviewed journals

The following will be excluded from the review:

- Studies of patients under the age of 18
- Studies of patients undergoing cardiac surgery
- Studies published before 1990
- Studies lacking explicitly defined criteria or definitions for PPCs
- Studies of organ transplantation surgery, due to the effects of immunosuppressive drugs on the likelihood of developing PPCs

- Studies of only physiological (e.g. lung volumes and flow measurements) or only biochemical (e.g. lung inflammatory markers) parameters, rather than clinical outcomes measures
- Studies where the intervention is directly related to surgical technique

Citation searching of reference lists

In addition, the clinical trials identified in the primary search were then snowballed by hand searching of references lists and searching for citations on Web of Science.

Appendix 2. Characteristics of studies and meta-analysis of trials according to intervention group

1. Incentive spirometry

Study Author and Year	Study Sample and Country	Intervention description	Timing of Intervention Delivery	Pulmonary Outcomes	Risk of bias
Agostini 2013	n=180, UK, single centre	Post-operative supervised use of incentive spirometry once or twice daily until hospital discharge	Post-operative	Composite PPC	Some concerns
Gosselink 2000	n=67, Belgium, single centre	Post-operative supervised use of incentive spirometry with target volume set daily by a physiotherapist	Post-operative	Composite PPC	High risk
Hall 1991	n=876, Australia, single centre	Prophylactic use of incentive spirometry for at least 5 mins in every waking hour, when possible started before surgery	Pre-operative and post-operative	Composite PPC, respiratory failure	High risk
Hall 1996	n=63, Australia, single centre	Prophylactic use of incentive spirometry pre and post surgery	Pre-operative and post-operative	Composite PPC, respiratory infection, respiratory failure, atelectasis	High risk
Lunardi 2015	n=137, Brazil, single centre	Post-operative use of 2 different types of incentive spirometry and deep breathing exercises for 5 days	Post-operative	Composite PPC	High risk
Pantel 2017	n=224, USA, single centre	Postoperative supervised use of incentive spirometry In addition, preoperative teaching and postoperative coaching and prompting.	Post-operative	Composite PPC, respiratory infection, respiratory failure, atelectasis	High risk

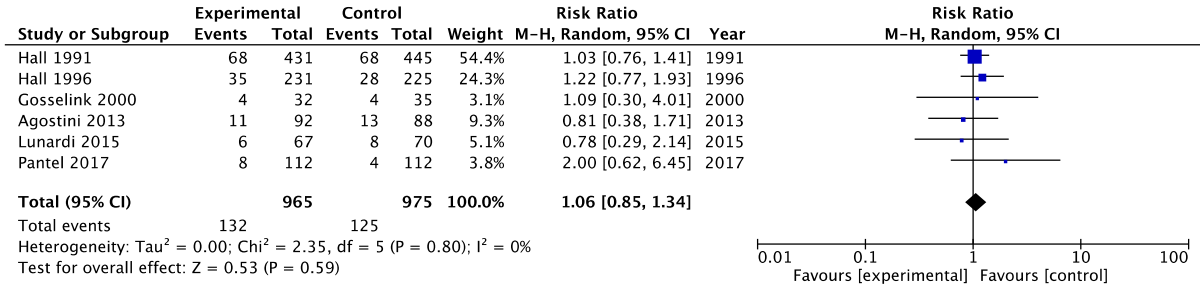

Figure 1.1 Forest plot comparing proportions of patient developing PPCs in RCTs of prophylactic incentive spirometry compared with standard medical care.

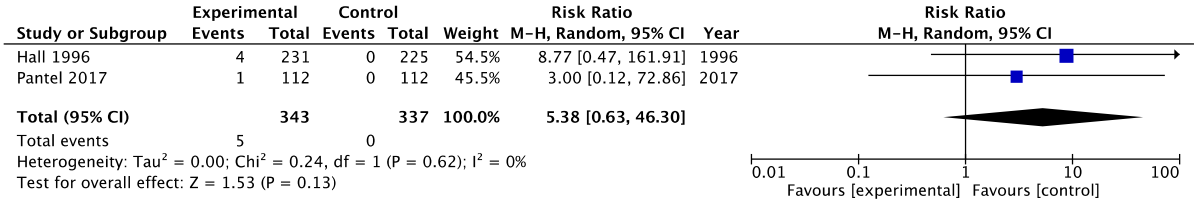

Figure 1.2 Forest plot comparing proportions of patient developing respiratory infections in RCTs of prophylactic incentive spirometry compared with standard medical care.

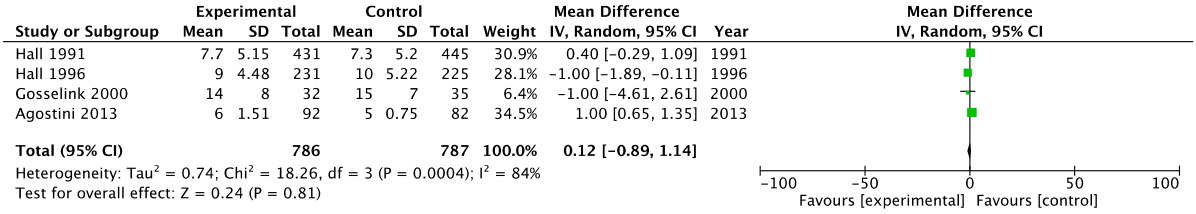

Figure 1.3 Forest plot comparing hospital length of stay (days) in RCTs of prophylactic incentive spirometry compared with standard medical care.

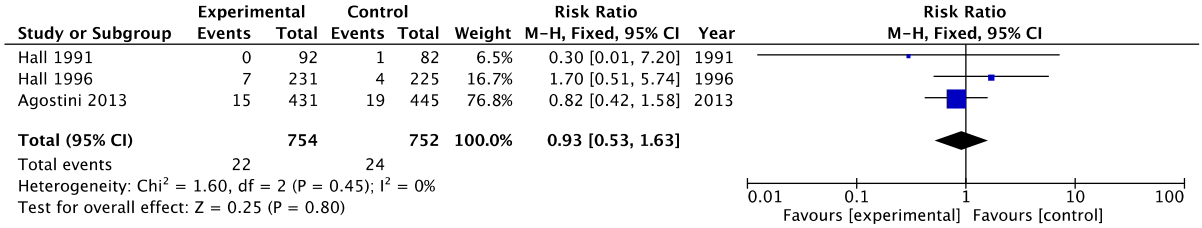

Figure 1.4 Forest plot comparing mortality in RCTs of prophylactic incentive spirometry compared with standard medical care.

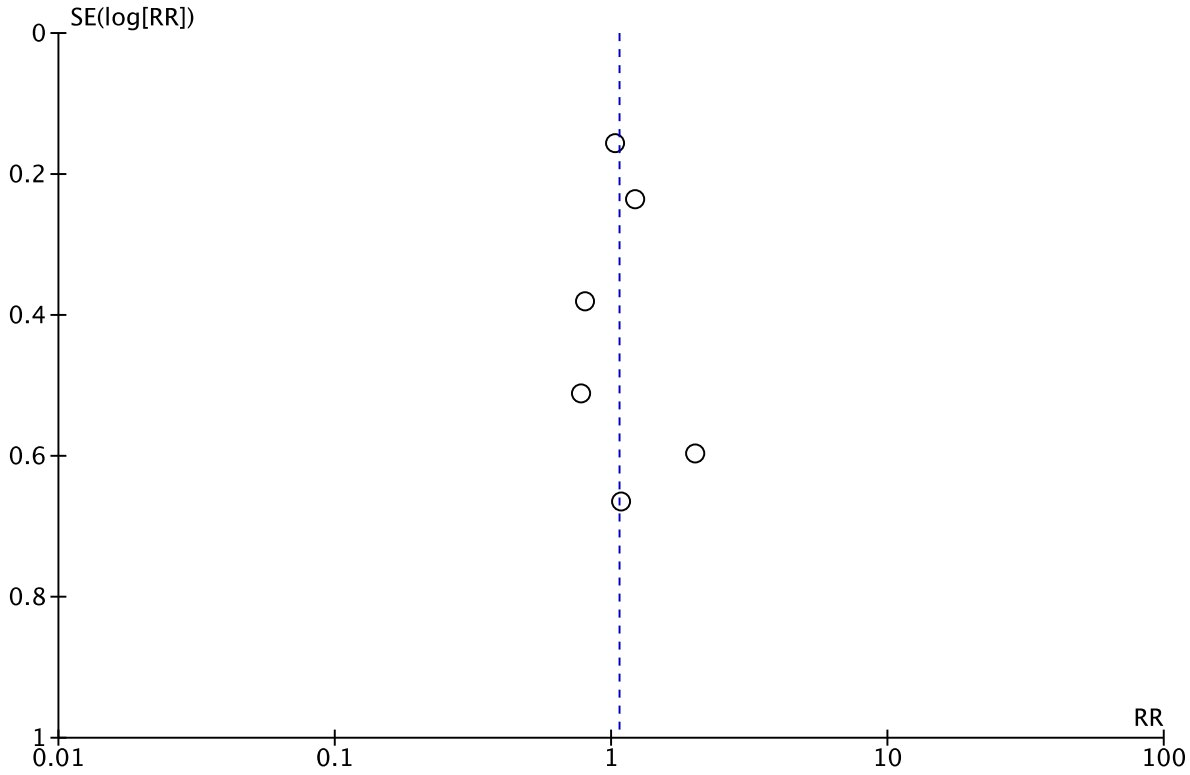

Figure 1.5 Funnel plot for random effects meta-analysis of PPCs outcomes in RCTs of incentive spirometry.

2. Supervised physiotherapy

Study Author and Year	Study Sample and Country	Intervention description	Timing of Intervention Delivery	Pulmonary Outcomes	Risk of bias
Brocki, 2016	n=69, Denmark, single centre	Preoperative and postoperative supervised chest physiotherapy including at home post discharge for up to two weeks	Pre-operative and post-operative	Composite PPC, respiratory infection, respiratory failure, atelectasis	High risk
Chumillas, 1998	n=81, Spain, single centre	Supervised chest physiotherapy pre-operatively and until discharge, with early post-operative ambulation	Pre-operative and post-operative	Composite PPC	High risk
Condie, 1993	n=310, European, multi-centre	Postoperative supervised respiratory physiotherapy and early postoperative ambulation	Pre-operative and post-operative	Respiratory infection	High risk
Dronkers, 2008	n=20, Netherlands, single centre	Preoperative respiratory inspiratory muscle training	Pre-operative	Atelectasis	Some concerns
Kulkarni, 2010	n=49, UK, single centre	Supervised preoperative repiratory physiotherapy	Pre-operative	Respiratory infection	High risk
Ludwig	n=135, Germany, single centre	Postoperative respiratory physiotherapy from postoperative day one until discahrge	Post-operative	Composite PPC, respiratory infection	High risk
Mackay 2005	n=50, Australia, single centre	Postoperative respiratory physiotherapy	Post-operative	Composite PPC	High risk

Olsen 1997	n=364, Sweden, single centre	Pre-operative education and postoperative supervised respiratory physiotherapy	Pre-operative and post-operative	Composite PPC, respiratory infection	High risk
Olsen 1999	n=80, Sweden, single centre	Preoperative education and postoperative supervised respiratory physiotherapy until discharge	Pre-operative and post-operative	Respiratory infection, respiratory failure	High risk
Reeve 2010	n=76, New Zealand, single centre	Supervised and non-supervised postoperative respiratory physiotherapy. Exercises continued at home post-discharge	Post-operative	Composite PPC	High risk
Silva 2013	n=56, Australia, single cente	Postoperative supervised respiratory physiotherapy and early ambulation	Post-operative	Composite PPC	Low risk
Van Adrichem 2014	n=39, Netherlands, single centre	preoperative respiratory high intensity muscle training	Pre-operative	Composite PPC, respiratory infection	High risk

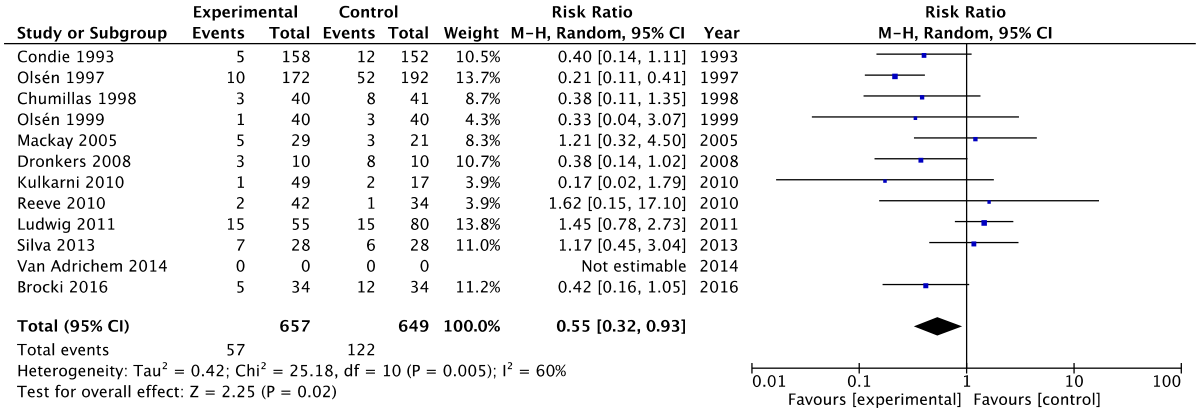

Figure 2.1 Forest plot comparing proportions of patients developing PPCs in RCTs of prophylactic supervised respiratory physiotherapy compared with standard medical care. Van Adrichem 2014 was not included in the meta-analysis because there was no standard medical care group.

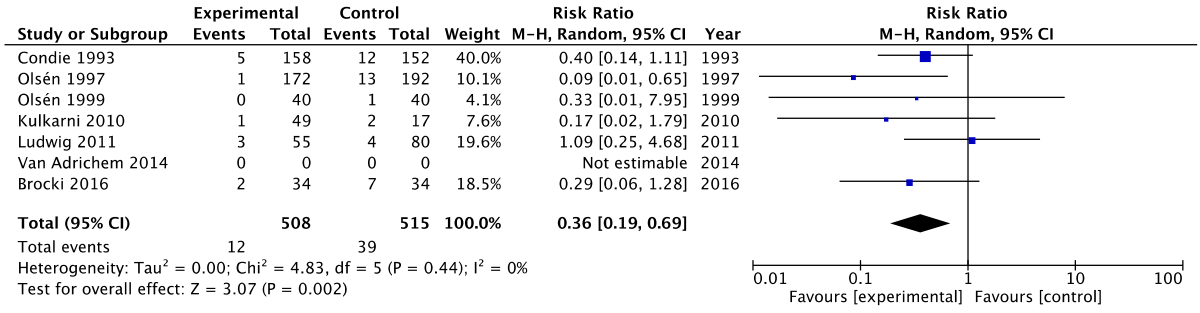

Figure 2.2 Forest plot comparing proportions of patient developing respiratory infections in RCTs of prophylactic supervised respiratory physiotherapy compared with standard medical care. Van Adrichem 2014 was not included in the meta-analysis because there was no standard medical care group.

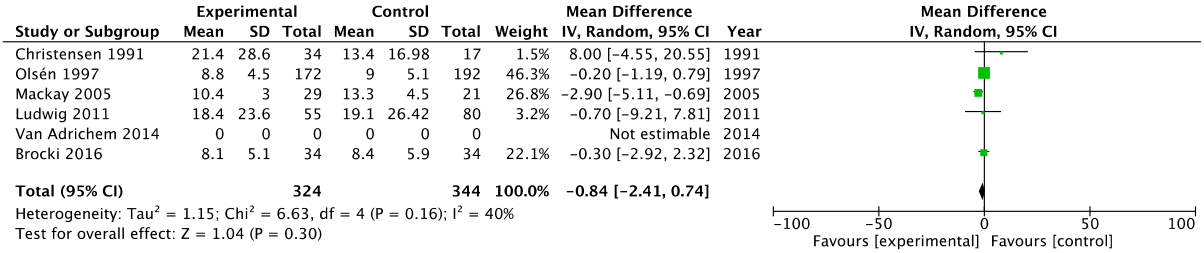

Figure 2.3 Forest plot comparing hospital length of stay (days) in RCTs of prophylactic supervised respiratory physiotherapy compared with standard medical care.

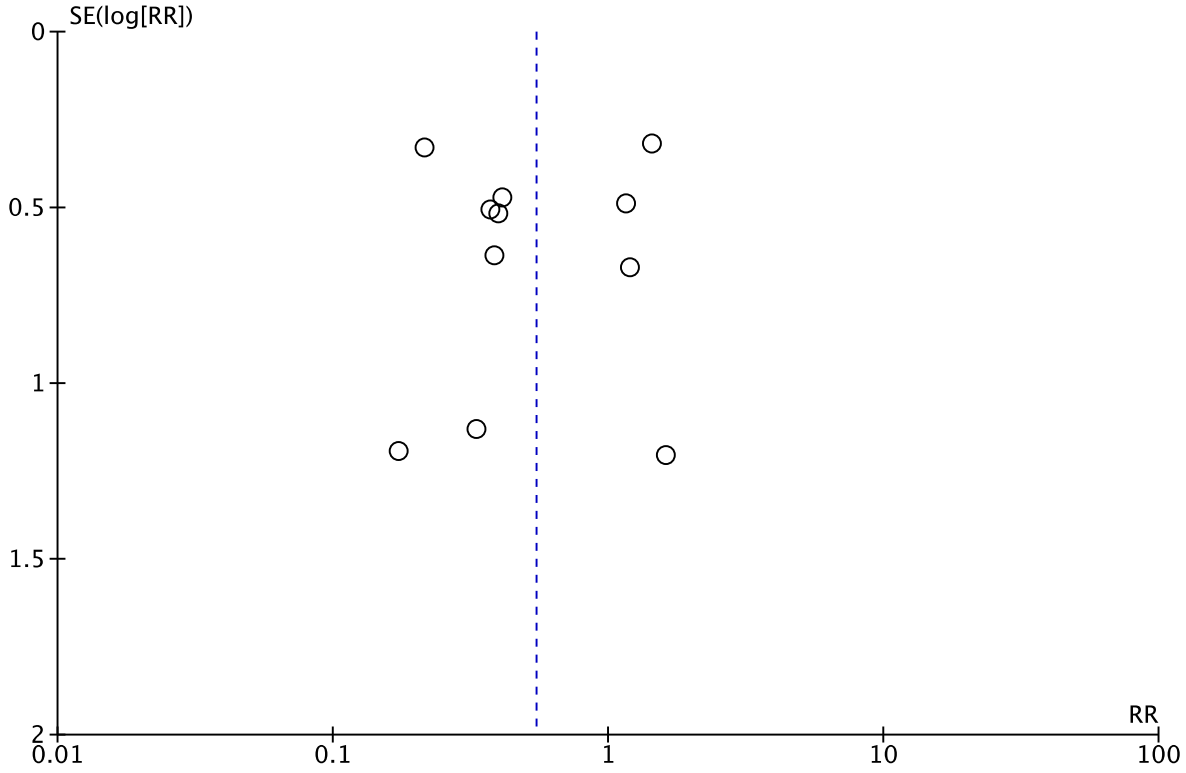

Figure 2.4 Funnel plot for random effects meta-analysis of PPCs outcomes in RCTs of incentive spirometry.

3. Drug therapies to improve pulmonary function

Study Author and Year	Study Sample and Country	Intervention description	Timing of Intervention Delivery	Pulmonary Outcomes	Risk of bias
Dilworth 1994	n=43, UK single, centre	5mg nebulised Salbutamol from 1hour preoperatively, then at 6 h intervals for 2 days postoperatively	Pre-operative and post-operative (beta blocker)	Composite PPC	High risk
Fegiz 1991	n=252, Italy, multi-centre	1000mg Ambroxol administered intravenously for 3 days before surgery, on the day of surgery and 2 days after surgery	Pre-operative and post-operative (secretolytic)	Respiratory infection	High risk

Gao 2014	n=60, China, single centre	1000mg Ambroxol administered intravenously on the day of surgery and for four days after surgery	Pre-operative and post-operative (secretolytic)	Composite PPC, respiratory infection, atelectasis	High risk
Li 2014	n=40, China, single centre	1mg Budesonide nebulised twice daily from postoperative day one to day three after surgery	Post-operative (inhaled steroid)	Composite PPC, respiratory infection	High risk
Ong 2004	n=73, New Zealand, single centre	1200mg Co-amoxiclav administered intravenously for five days postoperatively	Post-operative (prophylactic antibiotics)	Composite PPC, respiratory infection, atelectasis	Low risk
Perkins 2014	n=362, UK, multi-centre	100mcg Salmeterol inhaled by spacer device 2 hours before surgery and every 12 hours for 72 hours after surgery	Pre-operative and post-operative (inhaled beta agonist)	Respiratory infection, respiratory failure	Low risk
Refai 2009	n=140, Italy, single centre	1000mg Ambroxol administered intravenously on the day of surgery and for three days after surgery	Pre-operative and post-operative (secretolytic)	Composite PPC, respiratory infection, respiratory failure, atelectasis	Some concerns
Sohn 2017	n=62, South Korea, single centre	MgSO4 50 mg/kg administered intravenously fover 10 minutes, followed by a continuous infusion of 15 mg/kg/h during surgery	Intra-operative (magnesium sulphate)	Respratory infection, pulmonary effusion	Low risk

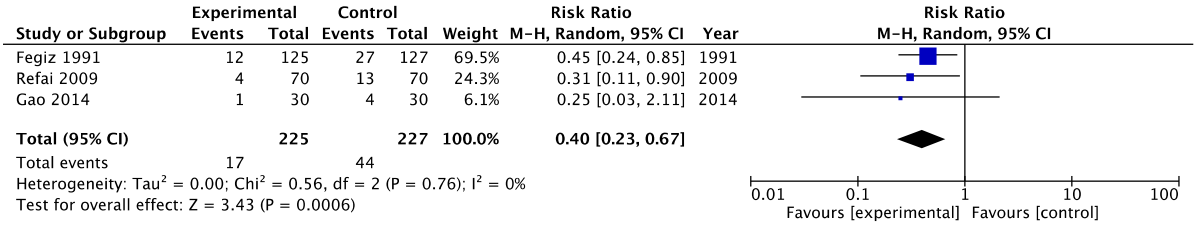

Figure 3.1 Forest plot comparing proportions of patients developing PPCs in RCTs of prophylactic mucolytic (Ambroxol) with placebo.

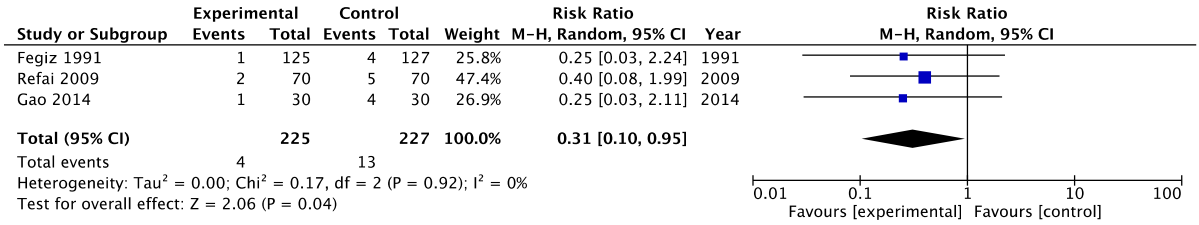

Figure 3.2 Forest plot comparing proportions of patients developing respiratory infection in RCTs of prophylactic mucolytic (Ambroxol) with placebo.

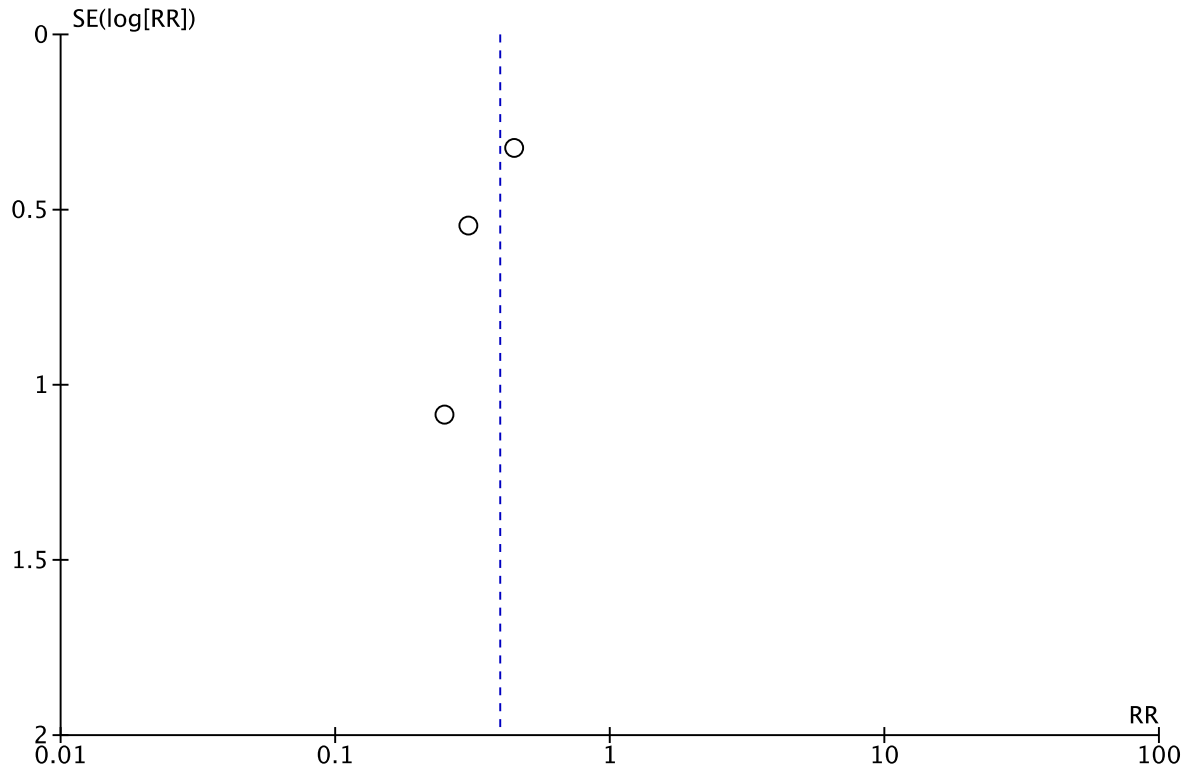

Figure 3.3 Funnel plot for random effects meta-analysis of PPCs outcomes in RCTs of prophylactic mucolytic (Ambroxol).

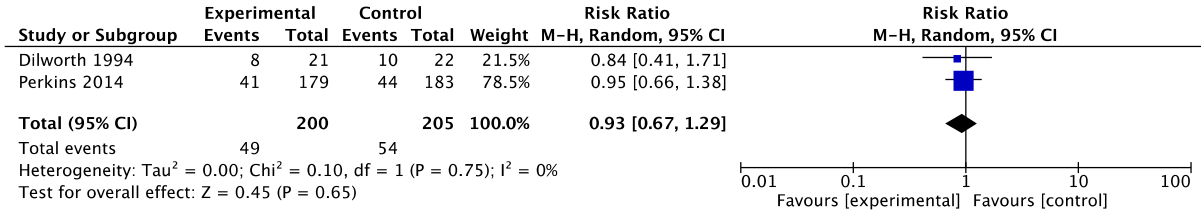

Figure 3.4 Forest plot comparing proportions of patients developing respiratory infection in RCTs of inhaled beta agonists with placebo.

4. Intraoperative anaesthetic gas composition

Study Author and Year	Study Sample and Country	Intervention description	Timing of Intervention Delivery	Pulmonary Outcomes	Risk of bias
Akca 1999	n=30, Austria single centre	80% FiO2 during and for two hours following surgery	Intra-operative and post-operative	Atelectasis	Low risk
Meyhoff 2009	n=1386, Denmark, multi-centre	80% FiO2 during and for two hours following surgery	Intra-operative and post-operative	Respiratory infection, respiratory failure, atelectasis	Low risk
Myles 2007	n=2012, multi-national, multi-centre	Anaesthesia with a nitrous oxide-free gas mixture (80% O2, 20% N2)	Intra-operative	Composite PPC, respiratory infection,	Low risk

				atelectasis	
Stæhr 2011	n=166, Denmark, multi-centre	Subgroup analysis of obese patients from the PROXI trial. 80% FiO2 during and for 2 hours following surgery	Intra-operative	Respiratory infection, respiratory failure, atelectasis	Low risk

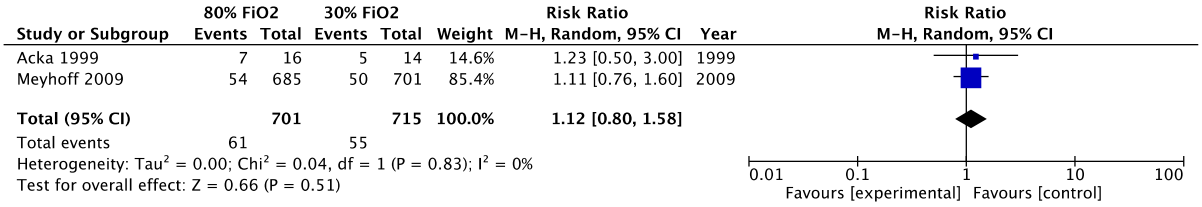

Figure 4.1. Forest plot comparing proportions of patients developing PPCs in RCTs of high (0.8) versus low (0.3) perioperative inspired oxygen fraction.

5. Intraoperative ventilation strategies

Study Author and Year	Study Sample and Country	Intervention description	Timing of Intervention Delivery	Pulmonary Outcomes	Risk of bias
Aretha 2017	n=81, Greece, single centre	Tidal volume 8ml/kg, Zero PEEP - then immediately after induction pressure-control mode was started and inspiratory time was increased to 50% (inspiratory: expiratory ratio was set to 1:1). Peak airway inspiratory pressure (Ppeak) was initially set to 20 cmH2O for three breaths, then PEEP was increased in four steps from 0 to 5 cmH2O for three breaths, from 5 to 10 cmH2O for five breaths, from 10 to 15 cmH2O for seven breaths and from 15 to 20 cmH2O for 10 breaths while Ppeak increased to 45 cmH2O and was maintained for three more breaths. Followingthe recruitment manoever, volume control was re-established using Vt 6 mL/kg and step-wise reductions in PEEP from 20 to 15 cmH2O for three breaths, and then to 8 cmH2O until the end of surgery.	Intra-operative	Respiratory infection	Some concerns
Choi 2017	n=51, S. Korea, single centre	Tidal volume of 6–8 mL/kg of predicted body weight, ventilatory rate of 10 breaths/min, FIO2 of 0.4, and inspiratory:expiratory ratio of 1:2 in pressure control mode. Lungs were recruited by increasing the PEEP gradually, from 4 cmH2O (2 breaths) to 6 cmH2O (2 breaths), 8 cmH2O (2 breaths), and finally 16	Intra-operative	Respiratory infection and atelectasis	High risk

		cmH2O (10 breaths). After 10 breaths with 16 cmH2O, PEEP was decreased stepwise as before.			
Futier 2013	n=400, Europe, multicentre	Tidal volume of 6-8 mL/kg (IBW), PEEP 6-8 cm H2O, and recruitment manoeuvres repeated every 30 minutes after tracheal intubation (30 cm H2O for 30 seconds)	Intra-operative	Composite PPC, respiratory infection and atelectasis	Some concerns
Goda Choi 2006	n=40, Netherlands, single centre	Tidal volume 6 mls/kg and PEEP of 10cmH2O	Intra-operative	Composite PPC	High risk
Hongwei Cai 2007	n=16, China, single centre	Tidal volume 6ml/kg	Intra-operative	Atelectasis	High risk
Lucangelo 2009	n=44, Italy, single centre	High frequency percussive ventilation. FiO2 1.0, 500 cycles per minute, mean pulsatile pressure 5cmH20, inspiratory time-10.5 and expiratory time-1.5.	Intra-operative	Respiratory infection	High risk
Mikyung Yang 2011	n=100, S. Korea, single centre	FiO2 0.5, tidal volume 6 ml/kg and PEEP 5	Intra-operative	Composite PPC, respiratory failure, pleural effusion and pneumothorax	High risk
Park 2016	n=39, S. Korea, single centre	Tidal volume of 6 ml/kg with positive end-expiratory pressure (PEEP) of 5 cmH2O,	Intra-operative	Composite PPC, respiratory infection and atelectasis	Some concerns
PROVE Network investigators 2014	n=894, multinational, multicentre	12cm H2O PEEP + RMs after intubation at the start of ventilation; before tracheal extubation; after each accidental disconnection from the ventilator. RMs were performed as follows: peak inspiratory pressure limit was set at 45 cmH2O; tidal volume was set at 8 ml kg 1 predicted body weight (PBW), respir- atory rate at 6 to 8 breaths min 1 (or lowest respiratory rate that the anaesthesia ventilator allows), and PEEP was set at 12 cmH2O; inspiratory to expiratory (I:E) ratio was set at 1 : 2; tidal volumes were increased in steps of 4 ml kg 1 PBW until a plateau pressure of 30 to 35cmH2O was attained; three breaths were administered with a plateau pressure of 30 to 35cmH2O; peak inspiratory pressure limit, respiratory rate, I:E ratio, and tidal volume were reset to the settings preceding each recruitment manoeuver.	Intra-operative	Composite PPC, respiratory infection, pleural effusion and atelectasis	Low risk
Qutub 2014	n=26, Saudi Arabia, single centre	Tidal volume 4mls/kg v 6 mls/kg	Intra-operative	Respiratory infection, respiratory failure and atelectasis	High risk
Remistico 2011	n=30, Brazil, single centre	PEEP 30cmH2O and inpsiratory plateau pressure 45 cmH2O for 2 mins after pneumoperitoneum deflated	Intra-operative	Composite PPC	High risk
Severgnini 2013	n=53, Italy, single cente	Tidal volumes of 7ml/kg ideal body weight, 10cm H2O positive end-expiratory pressure, and recruitment maneuvers (pro- tective ventilation strategy)	Intra-operative	Composite PPC, respiratory infection and atelectasis	High risk

Shen 2013	n=101, China, single centre	Tidal volume 5mls/kg and peep 5cmH2O	Intra-operative	Composite PPC	High risk
Talab 2009	n=58, Saudi Arabia, single	Use of 5 and 10 cm H2O PEEP	Intra-operative	Composite PPC and atelectasis	High risk
Treschen 2012	n=101, Germany, single centre	low (6 ml/kg) tidal volumes	Intra-operative	Composite PPC, respiratory infection, respiratory failure and pneumothorax	Low risk
Treschen 2017	n=57, Germany, single centre	As per PROVILHO trial (PROVE et al 2014)	Intra-operative	Composite PPC, respiratory infection, pleural effusion, atelectasis and pneumothorax	Low risk
Weingarten 2010	n=40, USA, single centre	Recruitment manoeuvres, tidal volume 6 ml/kg predicted body weight, and 12 cm H2O PEEP	Intra-operative	Respiratory infection and atelectasis	High risk
Wetterslev 2001	n=40, Denmark, single centre	5-10cm H2O PEEP	Intraoperative	Respiratory infection and respiratory failure	Low risk

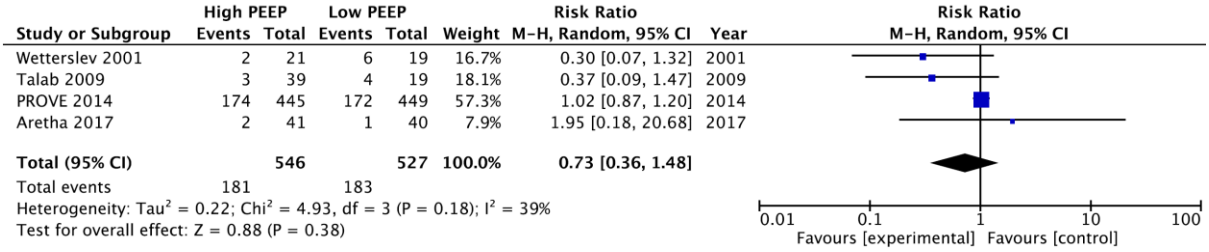

Figure 5.1. Forest plot comparing proportions of patients developing PPCs in RCTs of high PEEP (≥5cm H_2O) versus low PEEP (≤2cm H_2O) during intra-operative mechanical ventilation.

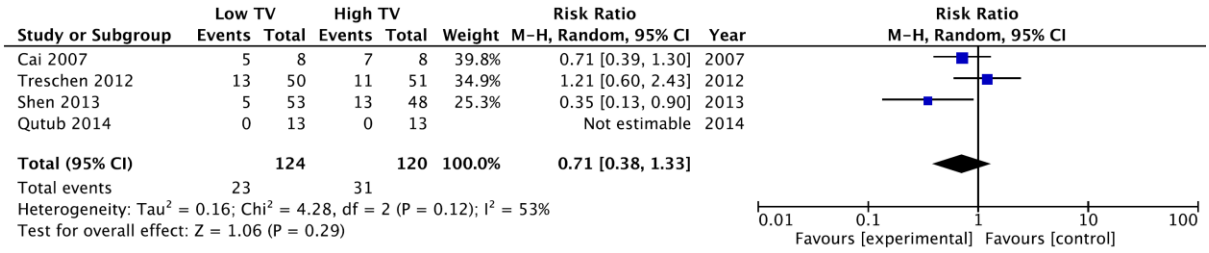

Figure 5.2. Forest plot comparing proportions of patients developing PPCs in RCTs of low tidal volume (≤ 6ml/kg predicted body weight) versus high tidal volume (≥ 8ml/kg) during intra-operative mechanical ventilation.

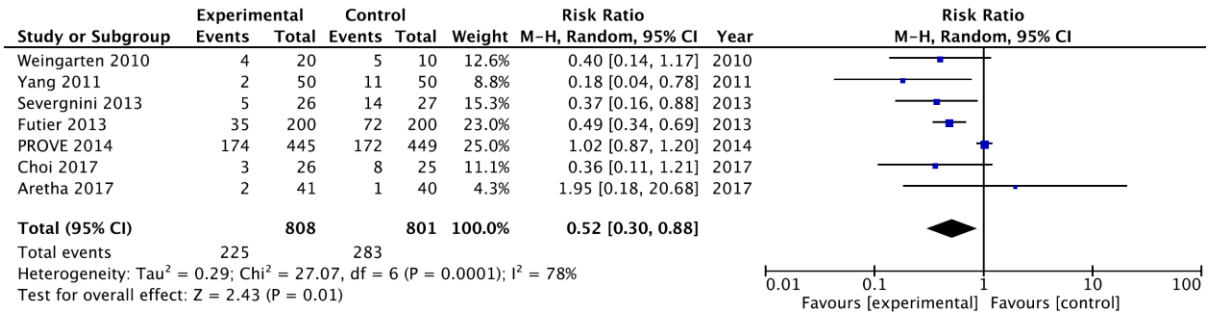

Figure 5.3. Forest plot comparing proportions of patients developing PPCs in RCTs of a lung protective ventilation strategy (PEEP ≥ 5 cm H_2O + TV ≤ 8ml/kg PBW + recruitment manoeuvres) versus no protective strategy during intra-operative mechanical ventilation.

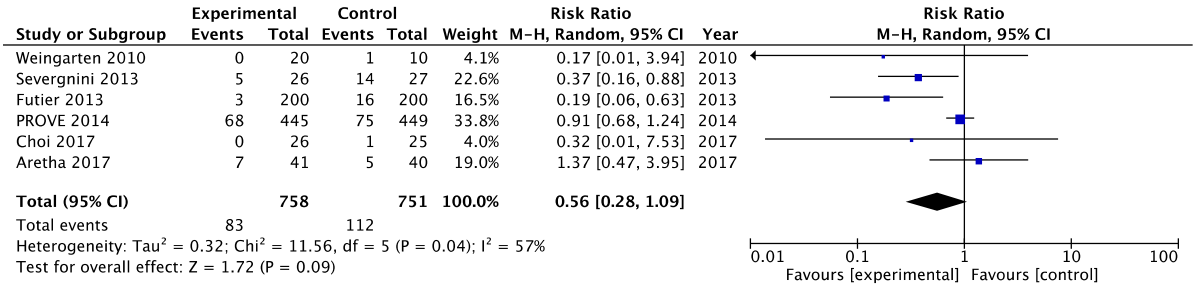

Figure 5.4. Forest plot comparing proportions of patients developing respiratory infection in RCTs of a lung protective ventilation strategy (PEEP ≥ 5 cm H2O + TV ≤ 8ml/kg PBW + recruitment manoeuvres) versus no protective strategy during intra-operative mechanical ventilation.

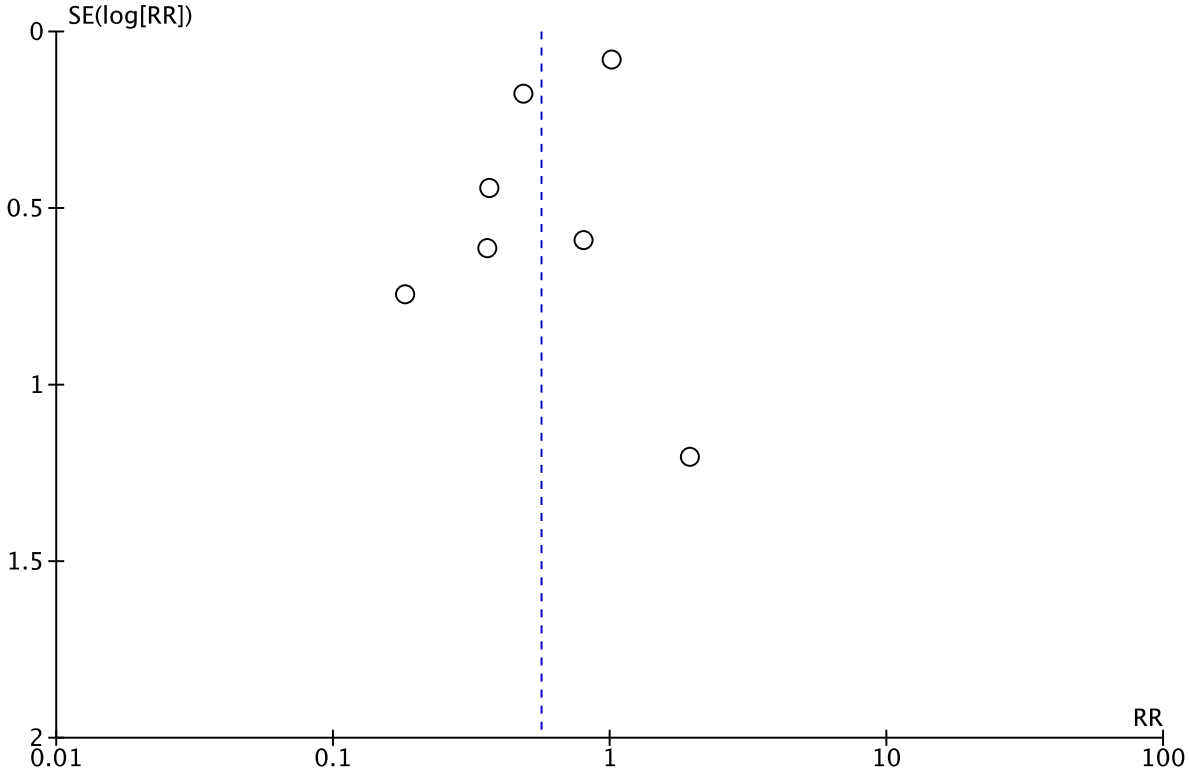

Figure 5.5 Funnel plot for random effects meta-analysis of PPCs outcomes in RCTs of lung protective ventilation.

6. Prophylactic non-invasive ventilation

Study Author and Year	Study Sample and Country	Intervention description	Timing of Intervention	Pulmonary Outcomes	Risk of bias

		Delivery			
Barbagallo 2012	n=50, Italy, single centre	2 cycles of helmet CPAP for 120 min, alternating with air-entrainment mask oxygen therapy (at FiO2 0.4) every 4 hours; post operatively for the first day only	Post-operative	Composite PPC, respiratory infection	Poor
Böhner 2002	n=204, Germany, single centre	Nasal CPAP with mask pressure of 10 cm H2O. Initial FiO2 of 0.4 thereafter adjusted according to the arterial blood gas analyses to achieve oxygen saturation >95%.	Post-operative	Respiratory infection, respiratory failure	Poor
Christensen 1991	n=51, Denmark, single centre	5 to 15 cmH20 CPAP given preoperatively and continued during postoperative period for 3 days.	Pre-operative and post-operative	Composite PPC	Poor
Denehy 2001	n=50, Australia, single centre	Two groups received CPAP for either 15 min or 30 min 4 times a day. 10 cm H2O on 30% oxygen at a total flow rate of 30 l/min.	Post-operative	Composite PPC	Poor
Futier 2016	n=206, France, multi-centre	High-flow nasal CPAP at 50–60 L/min. In each group, oxygen flow was titrated by the bedside nurse to maintain a peripheral oxygen saturation of 95 % or more. Allocated therapy was delivered continuously until 7.00–8.00 a.m. on post-operative day 1	Post-operative	Composite PPC, respiratory infection, respiratory failure, atelectasis	Fair
Hewidy 2016	n=46, Egypt, single centre	CPAP (8–12 cm H2O) for at least 8h on the first postoperative day; applied immediately following extubation	Post-operative	Respiratory infection, respiratory failure, atelectasis	Poor
Kindgen-Milles 2005	n=50, Germany, single centre	Following extubation in the ICU, oxygen therapy was applied at ambient pressure via a non-occlusive facemask and intermittent mask CPAP therapy at a pressure of 10 cm H2O every 4 h for 10 min; duration of between 12 and 24 h following extubation	Post-operative	Composite PPC, respiratory infection, atelectasis	Poor
Lorut 2014	n=360, France, multi-centre	Bilevel pressure support ventilation provided for 1 h x6/d. Physicians were responsible for prophylactic NIV implementation, which included choice and fitting of masks, adjustment of ventilator settings, and initial patient adjustment. Maintained daily whilst an inpatient.	Post-operative	Composite PPC, respiratory infection, respiratory failure	Poor
Perrin 2007	n=32, France, single centre	BiPAP for 7 days preoperatively - IPAP was initially set at 8cmH2O and then was increased until the maximal level tolerated by the patient was reached. EPAP was set at 2–4cmH2O. Postoperatively, the same NIPSV regimen was required with the exception of the first 2 h following surgery during which the patients were not wearing NIPSV.	Pre-operative and post-operative	Atelectasis	Fair
Yu 2016	n=110, China, multi-centre	High-flow nasal CPAP at 35 to 60 L/min and FiO2 was titrated (from 45% to 100%) by the treating clinician to maintain a peripheral SpO2 of 95% or more.	Post-operative	Respiratory infection, respiratory failure, atelectasis	Poor

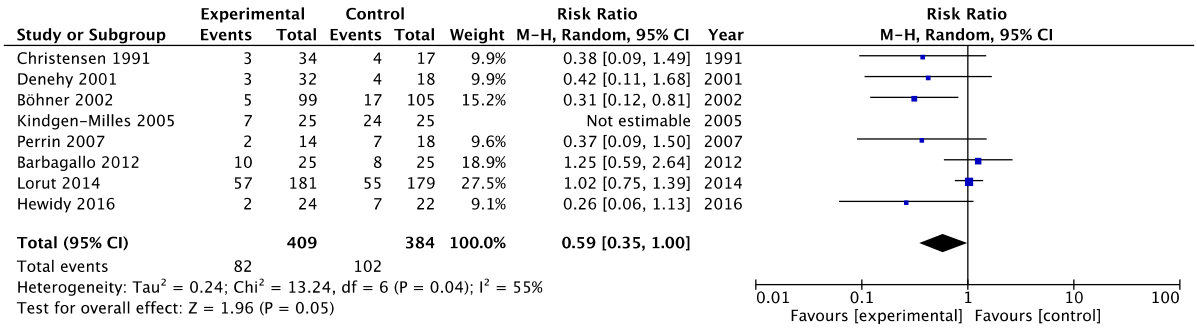

Figure 6.1. Forest plot comparing proportions of patients developing PPCs in RCTs of prophylactic non-invasive ventilation (bilevel and CPAP) with oxygen administered at ambient pressure.

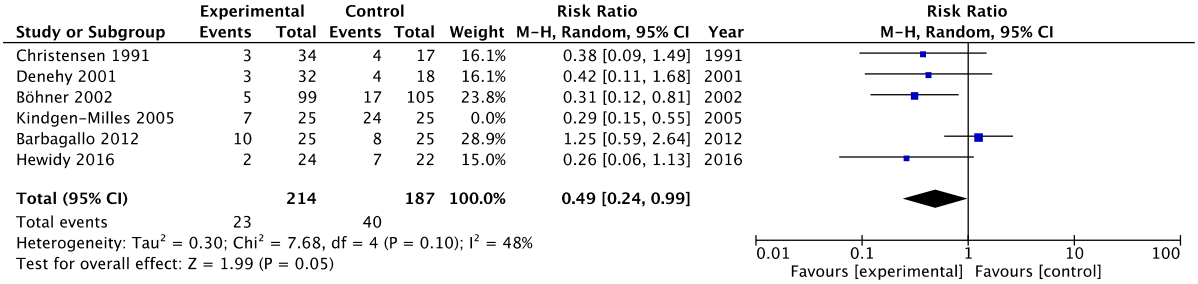

Figure 6.2. Forest plot comparing proportions of patients developing PPCs in RCTs of prophylactic CPAP with oxygen administered at ambient pressure.

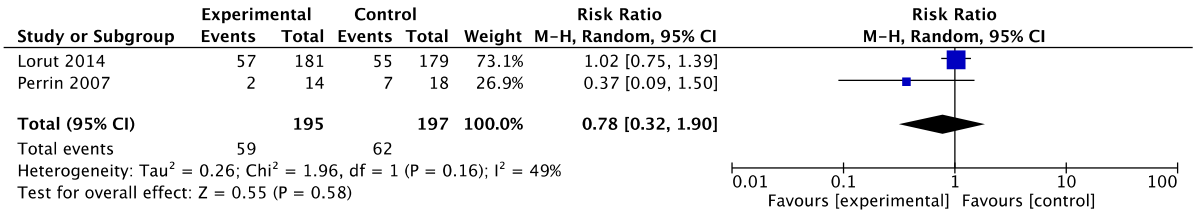

Figure 6.3. Forest plot comparing proportions of patients developing PPCs in RCTs of bilevel non-invasive ventilation with oxygen administered at ambient pressure.

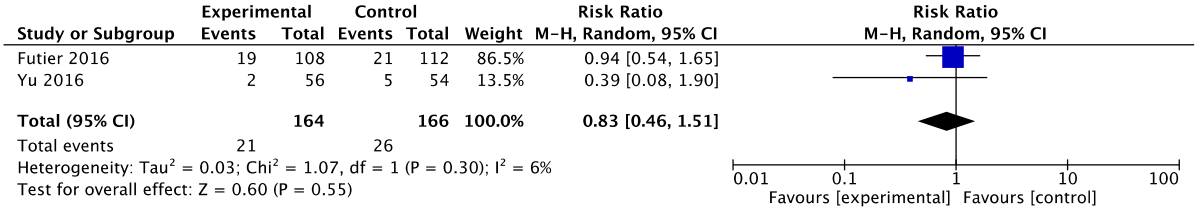

Figure 6.4. Forest plot comparing proportions of patients developing PPCs in RCTs of prophylactic high flow nasal cannula oxygen with oxygen administered by air entrainment devices (nasal prongs or facemask).

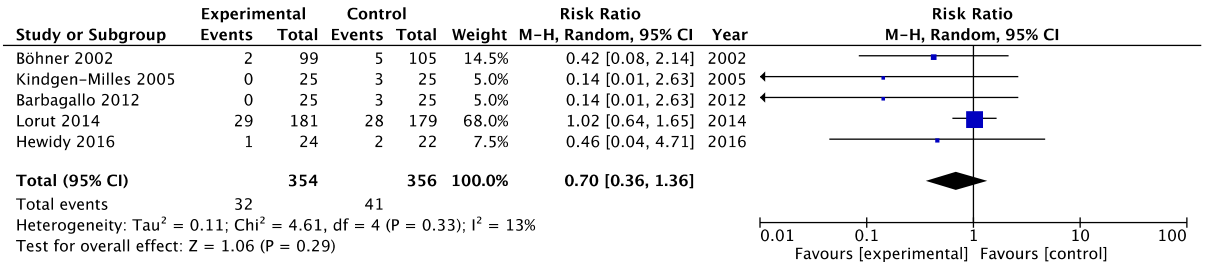

Figure 6.5. Forest plot comparing proportions of patients developing respiratory infection in RCTs of prophylactic non-invasive ventilation (bilevel and CPAP) with oxygen administered at ambient pressure.

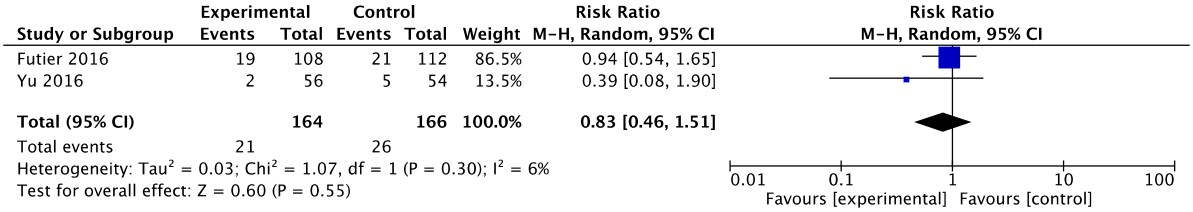

Figure 6.6. Forest plot comparing proportions of patients developing respiratory infection in RCTs of prophylactic high flow nasal cannula oxygen with oxygen administered by air entrainment devices (nasal prongs or facemask).

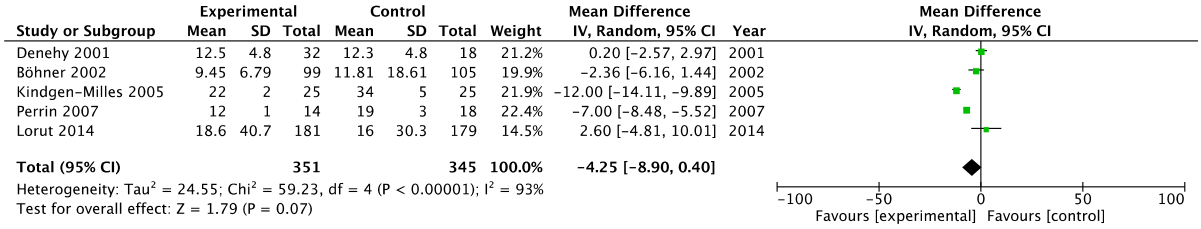

Figure 6.7. Forest plot comparing hospital length of stay in RCTs of prophylactic non-invasive ventilation with oxygen administered at ambient pressure.

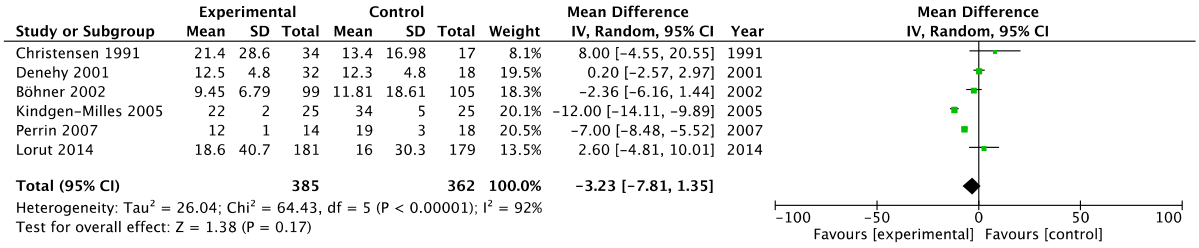

Figure 6.8. Forest plot comparing mortality in RCTs of prophylactic non-invasive ventilation with oxygen administered at ambient pressure.

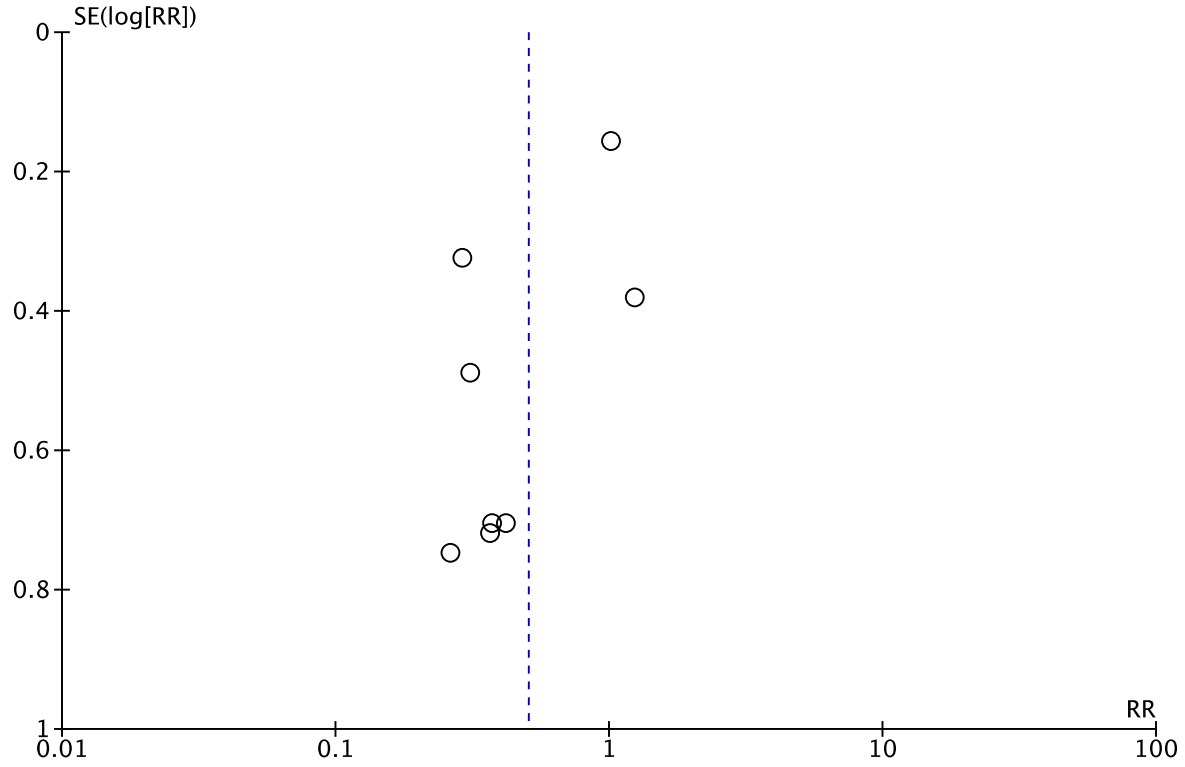

Figure 4.3 Funnel plot for random effects meta-analysis of PPCs outcomes in RCTs of prophylactic non-invasive ventilation.

7. Analgesia

Study Author and Year	Study Sample and Country	Intervention description	Timing of Intervention Delivery	Pulmonary Outcomes	Risk of bias
Boisseau 2001	n=50, France, single centre	T4/5 Thoracic epidural, continuous infusion of ropivicaine 0.2% with sufentanil 1 or 0.5 micrograms per ml started 1 hour befor the end of surgery	Intra-operative and post-operative	Composite PPC, respiratory infection and atelectasis	High risk
Esmea 2012	n=45, Turkey, single centre	At the end of the operation and every 4 h thereafter, the patients received 1.5 mg kg−1 bupivacaine epidural boluses	Intra-operative and post-operative	Composite PPC, atelectasis and pulmonary infection	High risk
Fleron 2003	n=217, France, single	1 microgram/kg sufentanil with 8 micrograms/kg preservative-free morphine injected at the L4/5 interspace	Pre-operative	Respiratory infection, atelectasis and respiratory failure	High risk
Lee 2016	n=100, South Korea, single centre	Dexmedetomidine loading dose 1mcg/kg IV for 20 mins prior to end of surgery	Intra-operative	Pulmonary function	High risk
Mann 2000	n=70, France, single centre	Continuous intraoperative epidural infusion of a 0.25% bupivacaine and 1-mcg/ml sufentanil mixture, followed by postoperative administration of a 0.125% bupivacaine and 0.5mcgg/ml sufentanil mixture provided with a PCEA pump programmed to deliver a 2- or 3-ml bolus with a lockout interval of 12 min and a background infusion of 3-5 ml/h.	Intra-operative and post-operative	Composite PPC and atelectasis	High risk

Norris 2001	n=79, USA, single centre	Epidural (preoperative bolus and intra/postoperative infusion) and general anaesthesia versus general anaesthesia and postoperative patient controlled intravenous or epidural analgesia	Intra-operative and post-operative	Respiratory infection and respiratory failure	Low risk
Park 2001	n=1021, USA, multi-centre	Continuous lumbar or thoracic epidural anesthesia using 0.5% bupivacaine with epinephrine. Epidural morphine (0.5 mg/mL, 3– 6 mg) immediately before or after surgery. Additional epidural morphine (3–6 mg) was given every 12 to 24 hours, or continuously, for as long as it was needed.	Pre-operative, intra-operative and post operative	Respiratory infection and respiratory failure	High risk
Radovanovic 2017	n=60, Serbia, single centre	T8-T12 epidural catheter with Levobupivacaine 0.5% to a maximum of 0.1-0.15 mL/kg. Neural blockade was maintained during surgery with additional 5 mL of levobupivacaine 0.25% administered hourly. Epidural infusion of levobupivacaine 1 mg/mL with fentanyl 3 μg/mL and adrenaline 2 μg/mL at a rate between 5 and 10 mL/h started at the end of surgery and continued up to postoperative day 3.	Pre-operative, intra-operative and post operative	Composite PPC	High risk
Rigg 2002	n=882, Australia, East-Asia and Middle East, mulitcentre	General anaesthesia with intraoperative and postoperative epidural analgesia for 72 hours	intra-operative and post-operative	Respiratory failure	High risk
Sagrioglu 2014	n=110, Turkey, single centre	T4-6, Patient Controlled epidural analgesia 0.1 mL/kg/h, with 2 mL on demand, and a lock-out interval of 30 min in the 24 hours postoperative period	Post-operative	Atelectasis, reintubation	High risk
Sen 2009	n=70, Turkey, single centre	1 g (2 ml) etofenamate intramuscularly, administered 1 hour before surgery	Pre-operative	Respiratory infection, atelectasis	High risk
Yildrim 2007	n=60, Turkey, single centre	18-gauge intra-pleural catheter in all patients at the end of the operation. Infusion of 10 mL ropivacaine 0.2% during a 30-min period. A continuous infusion (0.1 mL/kg per hour) with 0.2% ropivacaine supplemented with fentanyl 2 μg/mL was maintained for a minimum of 3 days.	Intra-operative and post-operative	Atelectasis	High risk
Zhu 2013	n=60, China, single centre	T8–9 epidural. Iinfusion of 0.05 % bupivacaine and 100 lg/mL morphine at 4 mL/h for 48 h, supplemented by rescue boluses of 4 mL, with a 30-min lock-out period, using an electronic patient-controlled analgesia (PCA) pump.	Post-operative	Pulmonary infection	High risk
Garnett 1996	n=99, Canada, single	Lumbar epidural. GA + Lumbar epidural (bupivacaine 0.1% + meperidine 2 mg/ml) at 5-15 ml/h.	Intra-op, post-op	Respiratory infection	High risk
Davies 1993	n=50, Australia, single	Thoracic epidural (T9-10) with 0.5% bupivacaine at a rate of 5ml bolus each hour. Infusion rate not specified.	Intra-op, post-op	Respiratory infection, prolonged ventilation	Some concerns
Kilbride 1992	n=43, USA, single	Lumbar epidural	Intra-op, post-op	Respiratory infection	Some concerns
Tuman 1991	n=80, USA, single	Lumbar and thoracic epidural. Bupivacaine 0.1% + fentanyl 0.001% at 5-8 ml/h initiated at least 30 min before anticipated completion of the surgical procedure	Intra-op, post-op	PPC	High risk

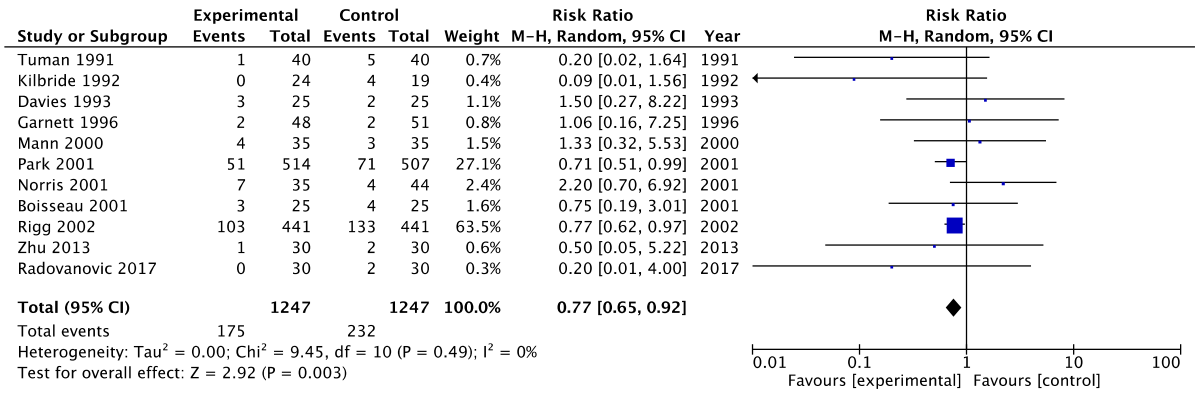

Figure 7.1. Forest plot comparing proportions of patients developing PPCs in RCTs of epidural analgesia therapies against morphine patient controlled analgesia.

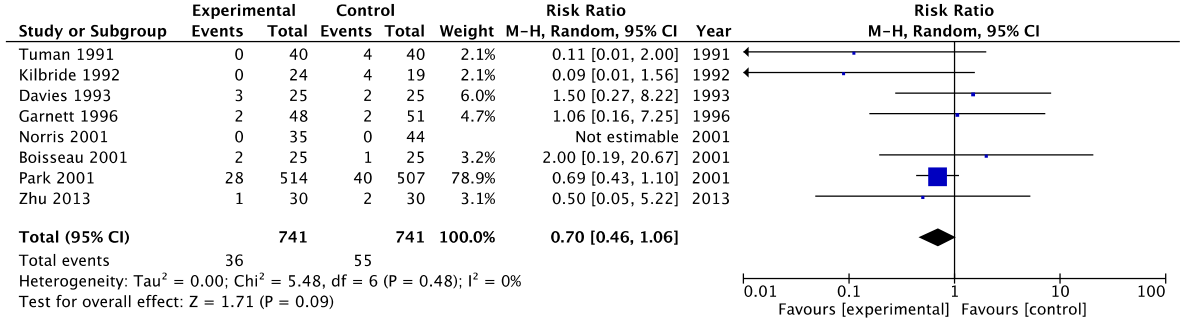

Figure 7.2. Forest plot comparing proportions of patients developing respiratory infections in RCTs of epidural analgesia therapies against morphine patient controlled analgesia.

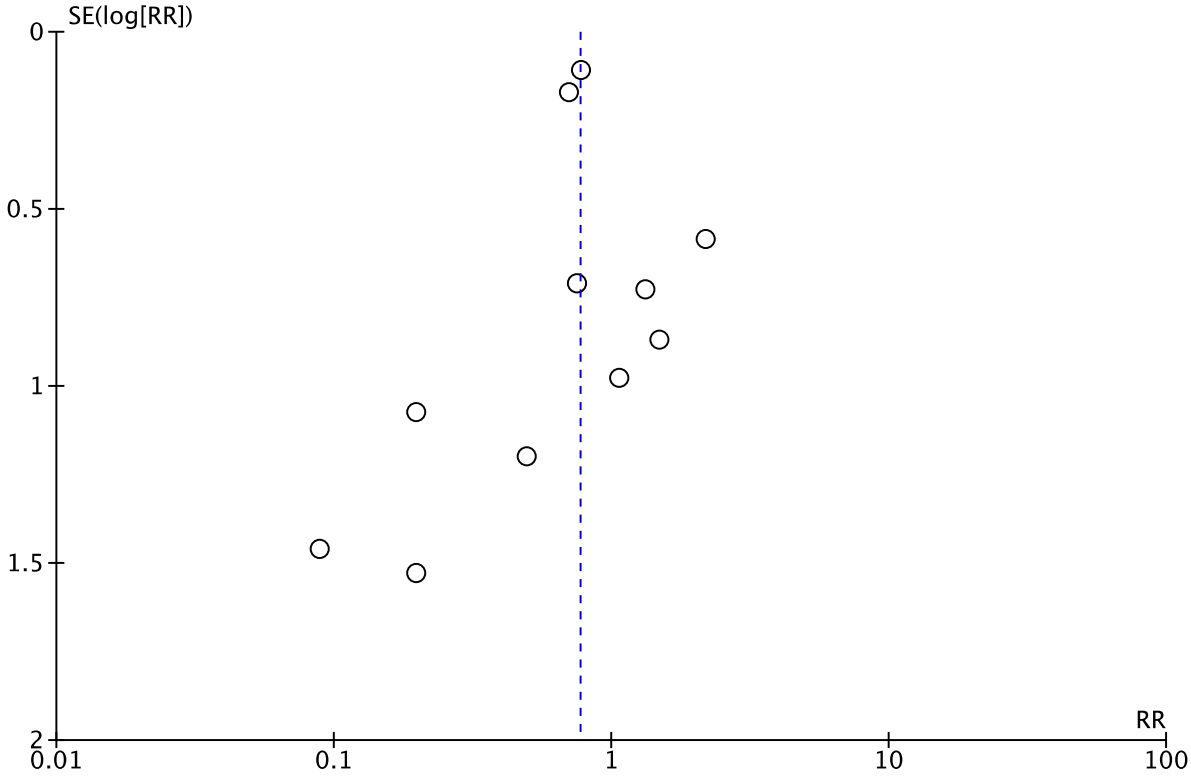

Figure 7.3 Funnel plot for random effects meta-analysis of PPCs outcomes in RCTs of epidural analgesia.

8. Lifestyle modifications

Study Author and Year	Study Sample and Country	Intervention description	Timing of Intervention Delivery	Pulmonary Outcomes	Risk of bias
Lindström 2008	n=102, Sweden, single centre	Weekly sessions, face-to-face or by telephone, with a trained smoking cessation counsellor and nicotine replacement therapy 4 weeks pre- and 4 weeks postoperatively.	Pre-operative and post-operative (smoking cessation)	Composite PPC	High risk
Møller 2002	n=102, Denmark, multi-centre	Pre-operative smoking intervention was weekly nurse-led counselling and nicotine replacement therapy	Pre-operative (smoking cessation)	Respiratory failure	High risk
Sorensen 2003	n=57, Denmark, single-centre	2-3 weeks before surgery, patients were given smoking cessation advice, nurse-led counselling and nicotine replacement	Pre-operative (smoking cessation)	Respiratory infection, respiratory failure	Some concerns
Wong 2012	n=304, Canada, single centre	Varenicline initiated 1 week before the target quit date (24 hours before surgery) and continued for a total of 12 weeks	Pre-operative and post-operative (smoking cessation)	Composite PPC	Some concerns

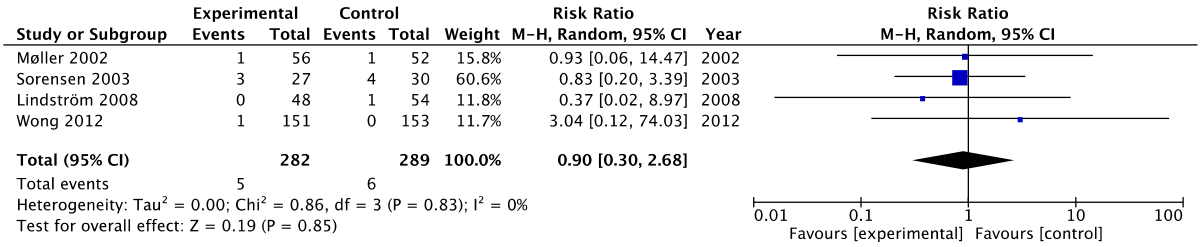

Figure 8.1 Forest plot comparing proportions of patients developing PPCs in RCTs of smoking cessation therapies against standard medical care.

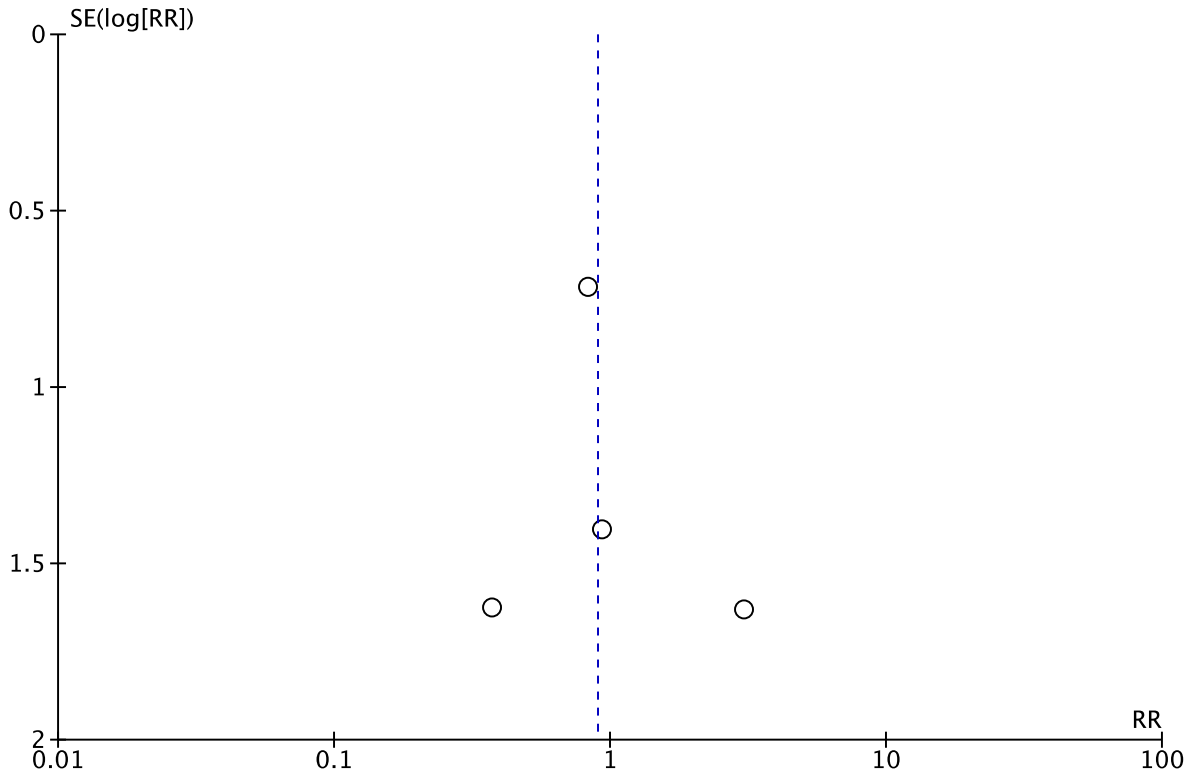

Figure 8.2 Funnel plot for random effects meta-analysis of PPCs outcomes in RCTs of smoking cessation therapies.

9. Enhanced post-operative recovery pathways

Study Author and Year	Study Sample and Country	Intervention description	Timing of Intervention Delivery	Pulmonary Outcomes	Risk of bias
Feng 2013	n=119, China, single centre	Modified fast-track protocol consisting of: Pre-op: Intake of 1000 mL 14% carbohydrate drink 12 h before and 350 mL 14% carbohydrate drink 3 h before surgery. Intra-op: tracheal intubation and general anesthesia, thermal insulation of the body and extremities, body temperature was maintained at 36 ℃; standard laparotomy approach; no routine use of abdominal drainage tube; infiltration of surgical wounds with ropivacaine at the end of surgery and 24 h after surgery. Post-op: Oral intake of 200 mg celecoxib twice daily, encourage patients to mobilize out of bed, oral intake of 500-1000 mL glucose saline on the day of surgery, intake of 2000-3000 mL liquid food containing 1000 kcal to 1200 kcal per day from the 1st day after surgery, infusion of parenteral nutrition (25 kcal/kg of body weight) iv before oral intake. Appropriate level of iv fluid intake based on the volume of liquid intake and output and physiological need. Infusion of parenteral nutrition iv if oral intake is not adequate. Appropriate level of iv fluid intake based on the volume of liquid	Pre-operative, intra-operative and post-operative	Respiratory infection	High risk

		intake and output, and physiological need; removal of nasogastric tube within 24 h after surgery; removal of urine catheter within 24 h after surgery; standard use of antibiotics before and once after surgery			
Gonenc 2014	n=47, Turkey, single centre	Protocolised evidence based pre-, intra- and post-op care pathway consistent with ERAS guidelines. Pre-op: Information and counselling, optimisation of organ function, smoking and alcohol abstinence, no bowel preparation, carbohydrate loading Intraoperative: Fluid optimisation, maintenance of normothermial, regional anesthesia where possible, short-acting opioids, minimally invasive surgery, oxygen therapy, antibiotic prophylaxis, thromboprophylaxis Postoperative: Multimodal and opioid-sparing analgesia, prevention of nausea and vomiting, prevention of ileus, early enteral nutrition, early mobilization, early removal of catheters, drains, and tubes, discharge criteria	Pre-operative, intra-operative and post-operative	Composite PPC, pleural effusion, atelectasis	High risk
HIP ATTACK investigators 2014	n=60, multi-national, multi-centre	Accelerated surgical procedure and accelerated medical clearance of fitness for surgery, with a goal of surgery within 6 h of diagnosis	Pre-operative	Respiratory infection	High risk
Jia 2014	n=133, China, single centre	Pre-op: bowel preparation with oral purgatives instead of amechanical enema. Intra-op: thoracic epidural anesthesia and postoperative analgesic maintenance via the epidural catheter (ropivacaine, 2 mg/ml maintained for 48 h, controlled to 6–10 ml (12–20 mg) per hour and opium-derived agents were excluded, no nasogastric tube insertion, no drainage tube placement with the exception of low rectal anastomosis; Post-op: water was allowed from 6 h post operation, liquid diet in the morning and semi-liquid diet at noon and evening of the first and second postoperative days (POD) with regular diet on POD 3, early urine catheter withdrawal (at POD1–2), early out-of-bed mobilization (i.e., walking).	Pre-operative, intra-operative and post-operative	Respiratory infection	High risk
Sokouti 2011	n=60, Iran single centre	Preoperatively inserted epidural catheter which was placed in intervertebral spaces T5-T6. At the end of surgery, 0.25% epidural marcaine and 2μg/ml fentanyl were infused. Marcaine (2-2.5 μg/hour) was transfused at the rate of 5ml/hour postoperatively via patient controlled epidural analgesia (PCEA) in the ICU. Diclofenac suppository (100 mg) was also administered when needed. Feeding and ambulation started the night after and one day after surgery, respectively.	Pre-operative, intra-operative and post-operative	Composite PPC, pleural effusion, atelectasis	High risk

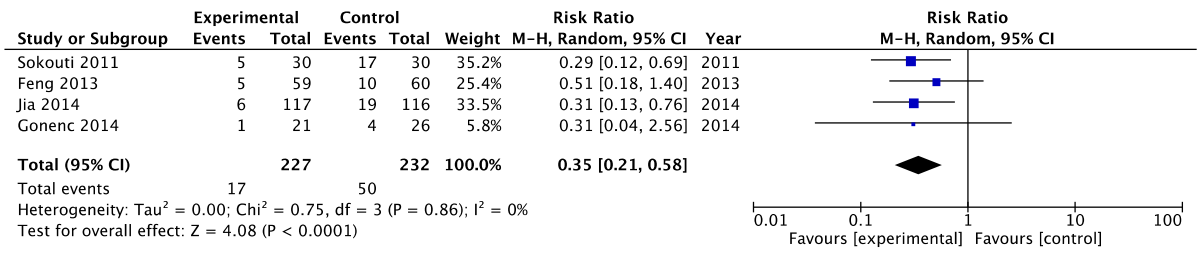

Figure 9.1. Forest plot comparing proportions of patients developing PPCs in RCTs of ERAS against standard post-operative care.

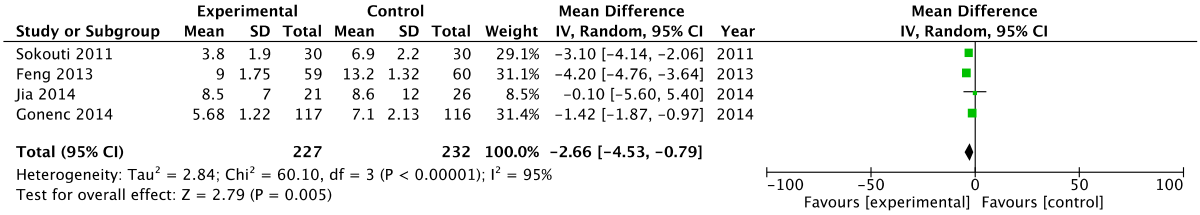

Figure 9.2. Forest plot comparing hospital length of stay in RCTs of ERAS against standard post-operative care.

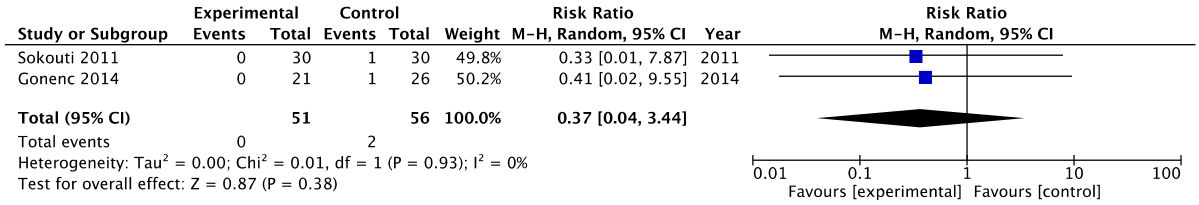

Figure 9.3. Forest plot comparing mortality in RCTs of ERAS against standard post-operative care.

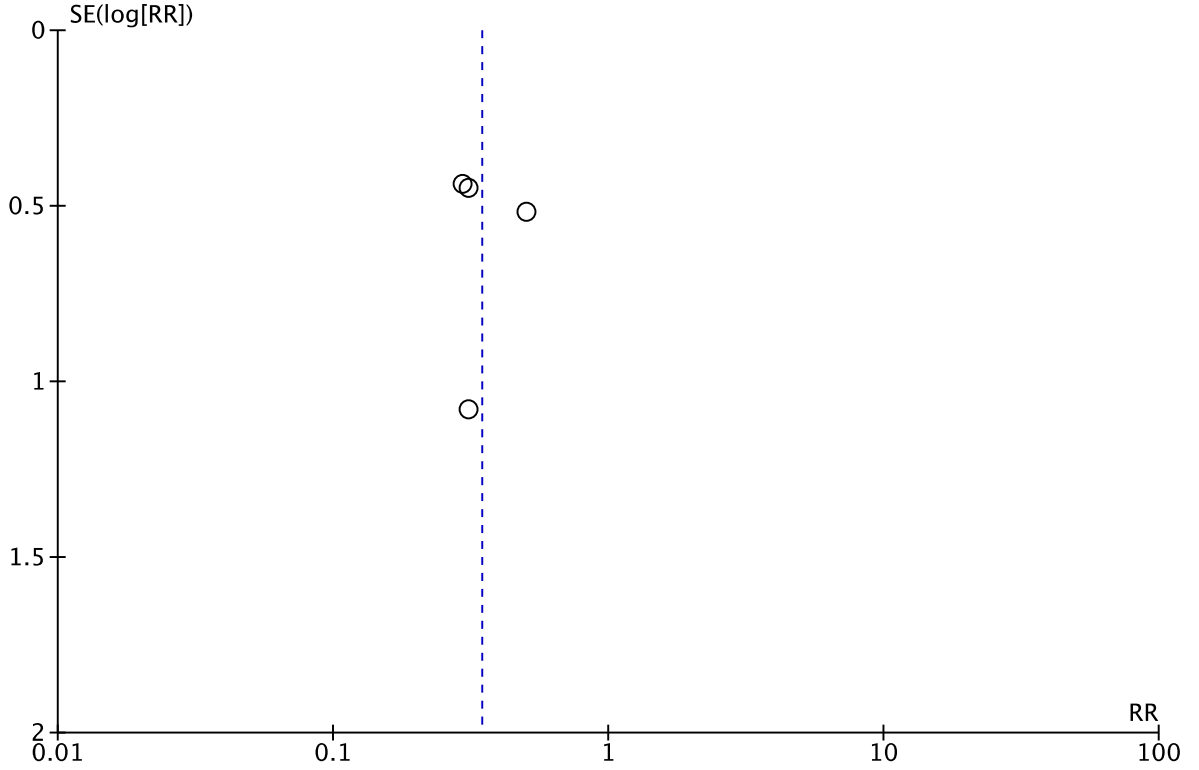

Figure 10.4 Funnel plot for random effects meta-analysis of PPCs outcomes in RCTs of ERAS.

10. Perioperative fluid administration

Study Author and Year	Study Sample and Country	Intervention description	Timing of Intervention Delivery	Pulmonary Outcomes	Risk of bias
Lobo 2002	n=20, UK, single	Restrictive = < or = 2 L water and 77 mmol sodium per day. Liberal = > or = 3 L water and 154 mmol sodium per day	Post-op	Respiratory infection	Some concerns
Brandstrup 2003	n=172, Denmark, multi centre	Restrictive = Volume to volume replacement with HES 6%. Liberal = Pre-operative 0.9% NaCl 500ml + volume to volume replacement + 7ml/kg/h for 1st hour then 5ml/kg/h for 2nd-3rd hours then 3ml/kg/h therafter of 0.9% NaCl	Pre-op, intra-op	Respiratory infection, pulmonary oedema, pneumothorax	Some concerns
Muller 2009	n=156, Switzerland, multicentre	Restrictive = 1 mL/kg/h, nothing by mouth and an intraoperative substitution of 5 mL/kg/h. Liberal = 2 mL and 10 mL/kg/h for preoperative loading and intraoperative substitution, respectively.	Pre-op, intra-op	Respiratory infection	Some concerns
Nisanevich 2005	n=152, Israel, single	Restrictive = Hartman's 4 ml/kg/h. Liberal = 10 ml/kg/h prior to incision, then 12 ml/kg/h maintenance	Intra-op	Respiratory infection	Some concerns
Holte 2007	n=32, Denmark, single	Restrictive = 7 ml/kg/h for 1st hr; 5 ml/kg/h subsequently. Liberal = 18 ml/kg/h	Intra-op, post-op	Respiratory infection, respiratory failure, pulmonary oedema	Low risk
Holte 2007	n=48, Denmark, Single	Restrictive = 10ml/kg/h intraop, 5ml/kg in PACU then 1L oral intake with IV fluids only with clinical evidence of fluid deficit. Liberal = 175ml 6h per-op, 30ml/kg/h intraop, 5ml/kg in PACU then 1L oral intake with IV fluids only with clinical evidence of fluid deficit.	Intra-op, post-op	Respiratory infection	Low risk
McArdle 2009	n=22, UK, single	Restrictive = Hartman's 4 ml/kg/h. Liberal = Hartman's 12 ml/kg/h	Intra-op	Respiratory infection	Some concerns
Futier 2010	n=70, France, single	Restrictive = 6 ml/kg/h. Liberal = 12 ml/kg/h.	Intra-op	Respiratory infection, respiratory failure, pulmonary embolism, pneumothorax	Some concerns
Abraham-Nordling 2012	n=161, Sweden, single	Restrictive = 2 ml/kg/h from start of anaesthesia, then 1 ml/kg/h from early after operation until morning after surgery. Liberal = 500ml-1000ml pre-op, then 1000 ml infused in early postoperative period + 7 ml/kg/h, then then 1 ml/kg/h from early after operation until morning after surgery.	Pre-op, intra-op, post-op	Respiratory infection	Some concerns

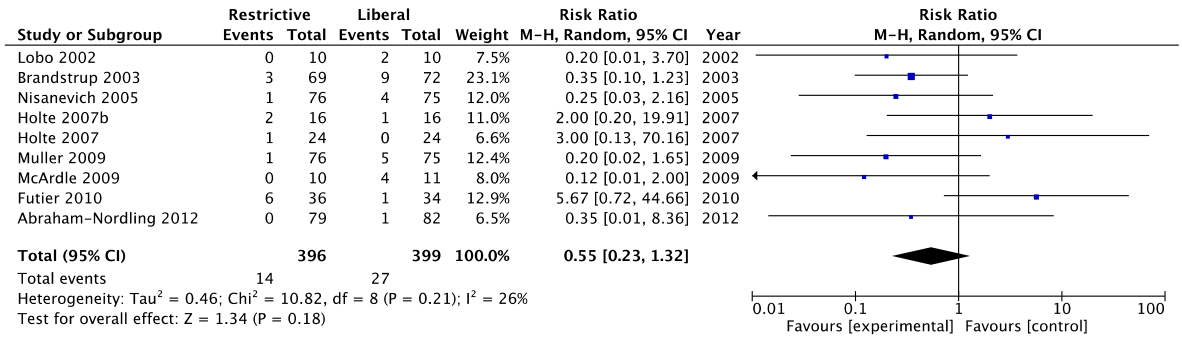

Figure 10.1. Forest plot comparing proportions of patients developing PPCs in RCTs of restrictive versus liberal fluid administration.

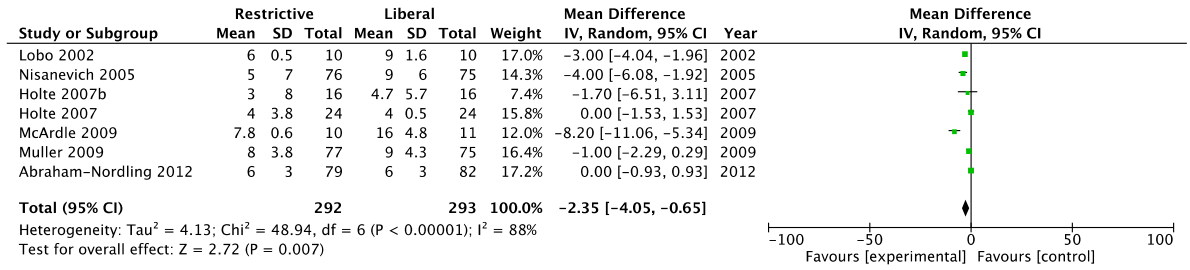

Figure 10.2. Forest plot comparing hospital length of stay in RCTs of restrictive versus liberal fluid administration.

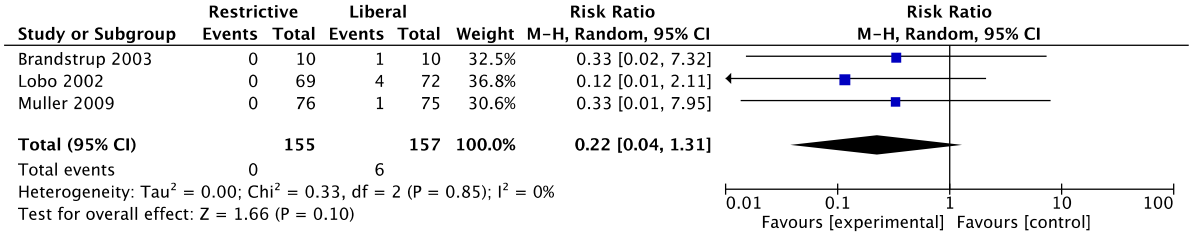

Figure 10.3. Forest plot comparing mortality in RCTs of restrictive versus liberal fluid administration.

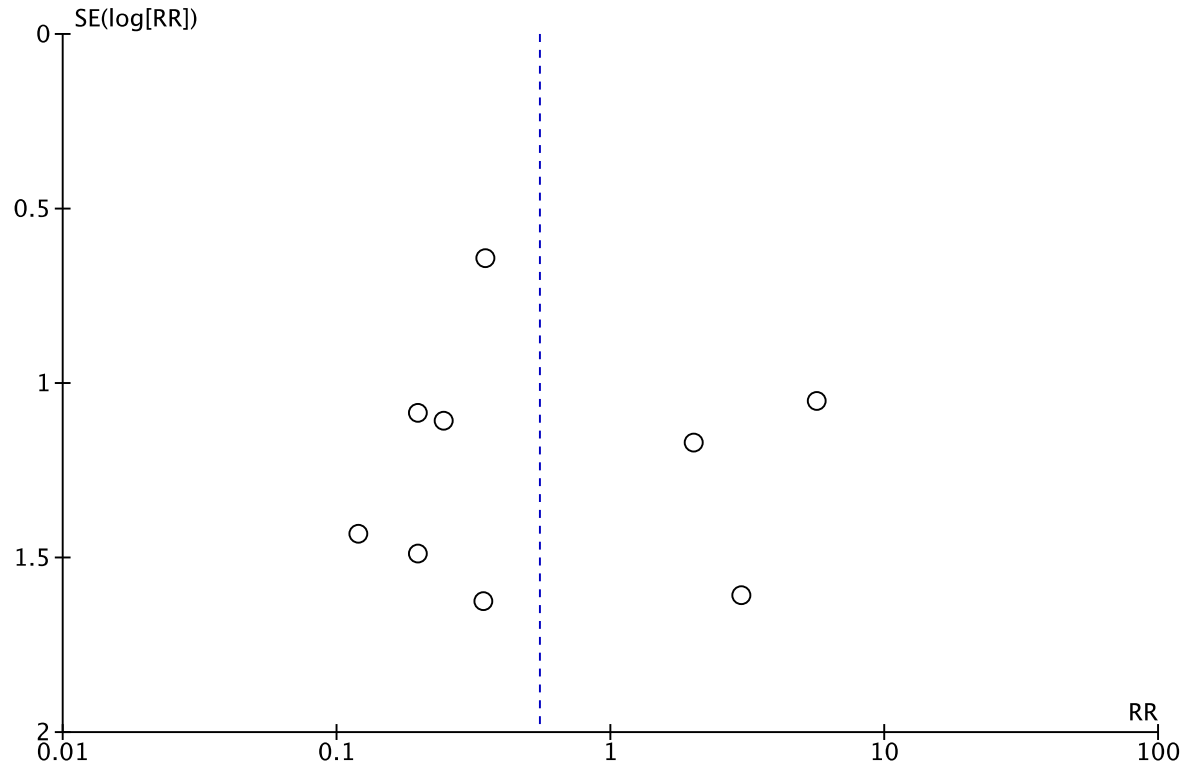

Figure 10.4 Funnel plot for random effects meta-analysis of PPCs outcomes in RCTs of restrictive versus liberal fluid administration.

Study Author and Year	Study Sample and Country	Intervention description	Timing of Intervention Delivery	Pulmonary Outcomes	Risk of bias
Boyd 1993	n=107, single	Pulmonary artery catheter	Intra-op	Respiratory infection	High risk
Wilson 1999	n=138, UK, single	Pulmonary artery catheter. 1 litre of Hartmann's solution + Human albumin solution 4.5% until a pulmonary artery occlusion pressure of 12 mm Hg. 0.025 µg/kg/min for adrenaline and 0.125 µg/kg/min for dopexamine.	Intra-op, post-op	Respiratory infection, ventilatory support for >24h, pulmonary oedema	Low risk
Valentine 1998	n=120, single	Pulmonary artery catheter. Fluid challenges for PAC patients with PCWP less than 15 mm Hg consisted of 9 ml/kg Ringer's lactate solution rapidly instilled through the central venous pressure port. Additional fluid boluses were given until the PCWP was greater than 12 mm Hg or the subject received 3000 ml of fluid.	Intra-op, post-op	Respiratory infection, ventilatory support for >24h, pulmonary oedema	Some concerns
Gan 2002	n=100, USA, single	Oesophageal Doppler. Fluid admistration guided by FTc and stroke volume algorithm.		Respiratory infection, ventilatory support for >24h	Some concerns
Venn 2002	n=90, UK, single	Colloid fluid challenges guided by central venous pressure or oesophageal doppler (2 intervention groups)	Intra-op	Respiratory infection	Low risk
Sandham 2003	n=1994, Canada, multi-centre	Pulmonary artery catheter. Fluid loading, inotropic therapy, vasodilator therapy, vasopressors for hypotension, and blood transfusion for a hematocrit of <27 %, in order to achieve oxygen-delivery index of 550 to 600 ml per minute per square meter of body-surface area, a cardiac index of 3.5 to 4.5 liters per minute per square meter, a mean arterial pressure of 70 mm Hg, a pulmonary-capillary wedge pressure of 18 mm Hg, a heart rate of less than 120 beats per minute	Intra-op	Respiratory infection, pneumothorax	Some concerns
Pearse 2005	n=122, UK, single	250ml fluid bolus until sustained rise in stroke volume of >10% achieved for 20 mins. Dopexamine up to a maximum of 1µg/kg/min if oxygen delivery index (DO2I) did not reach 600 ml/min/m2 with intravenous fluid alone	Post-op	Respiratory infection, ARDS, pulmonary oedema, pulmonary embolism	Low risk
Lopes 2007	n=33, Brazil, Single	Change in pulse pressure variation. HES fluid bolus to maintain $\Delta PP \leq 10\%$	Intra-op	PPC, Respiratory infection, ventilatory support for >24h, Acute lung injury, pulmonary embolism, pulmonary oedema	Some concerns
Benes 2010	n=120, Czech Republic, single	Pulse contour analysis. Maintain the stroke volume variation below 10% using colloid boluses of 3 ml/kg	Intra-op	Respiratory infection, ventilatory support	Some concerns
Mayer 2010	n=60, Germany, single	Pulse contour analysis (FloTrac). Fluid bolus to maintain cardiac index ≥ 2.5	Intra-op, post-op	PPC, Respiratory infection, ventilatory support for >24h, pulmonary oedema	Some concerns
Wenkui 2010	n=299, China, single	Serum lactate level was monitored closely inatra- and post-operatively to maintain a normal pre-operative serum lactate level, with fluid adminstered to maintain serum lactate <1.6 mmol/L	Intra-op, post-op	Respiratory infection, pneumothorax, pulmonary oedema, pulmonary emboli	Some concerns
Cecconi 2011	n=40, UK, Italy, single	Pulse contour analysis (FloTrac). SV was first maximised with fluid challenges. Boluses of 250 mL of HES were administered until the SV	Intra-op, post-op	Respiratory infection	Low risk

		failed to increase by a factor of 10%. If 25 mL/kg HES had been given before SV maximisation was achieved, fluid challenges were then performed with 250 mL boluses of Ringer's lactate solution. If at this stage the DO2I was not greater than 600 mL/m2, then dobutamine was started at a dose of 3 µg/kg/minute and increased by the same increment every 20 minutes to reach the described target.			
Pearse 2014	n=734, UK, multicentre	Pulse contour analysis (LiDCO rapid). Intravenous colloid solution administered in 250mL boluses to achieve and maintain a maximal value of stroke volume; no attempt was made to standardize choice of colloid. Dopexamine was administered at a fixed low dose of 0.5 µg/kg/min	Intra-op, post-op	Respiratory infection, ARDS, pulmonary oedema	Low risk
Ackland 2015	n=204, UK, multi-centre	Pulse contour analysis. 1ml/kg Hartmann's + gelatin colloid until SV <10%. Dobutamine 1-20mcg/kg/min if oxygen delivery < per-op value	Intra-op, post-op	PPC	Low risk

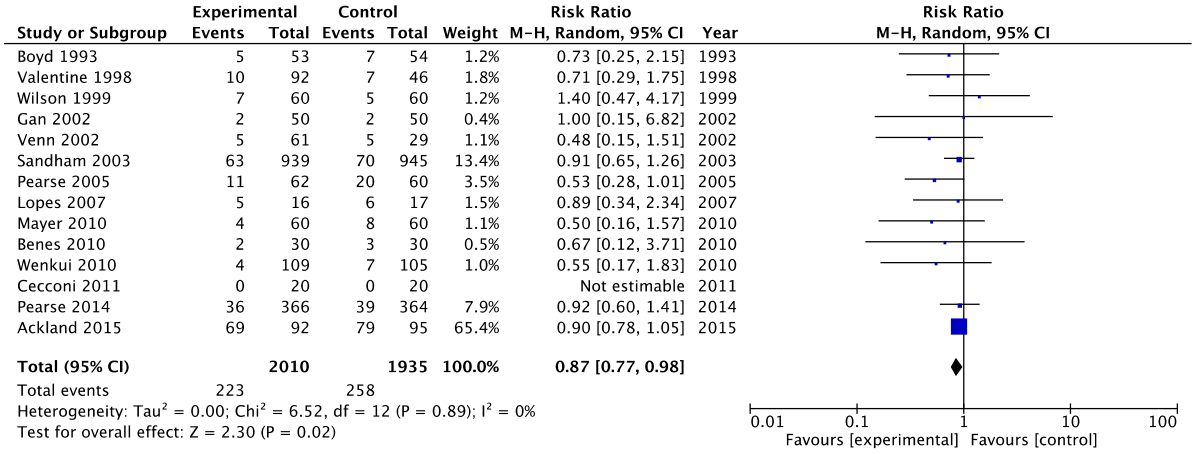

Figure 10.5. Forest plot comparing proportions of patients developing PPCs in RCTs goal directed haemodynamic therapy.

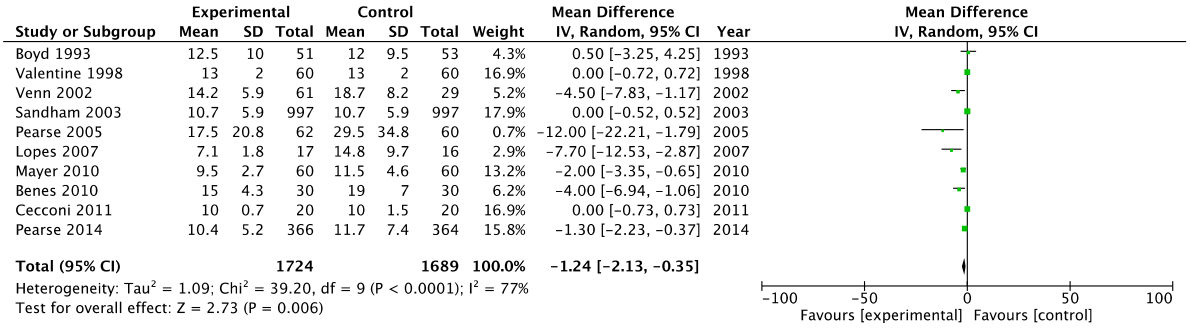

Figure 10.6. Forest plot comparing hospital length of stay in RCTs of goal directed haemodynamic therapy.

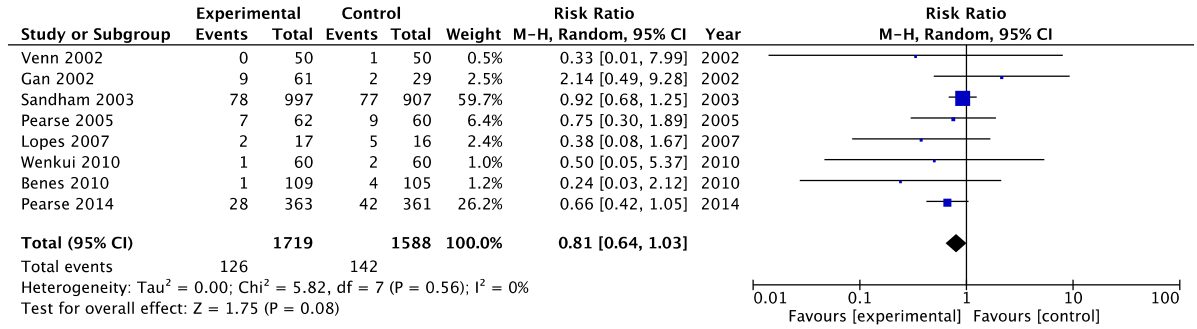

Figure 10.7. Forest plot comparing mortality in RCTs of goal directed haemodynamic therapy.

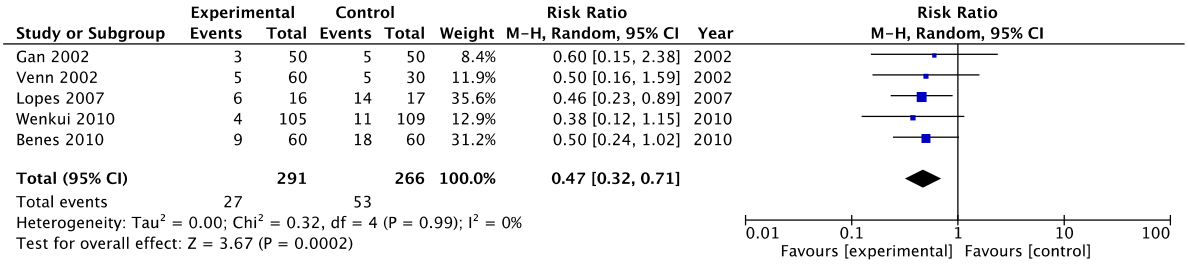

Figure 10.8. Subgroup analysis of proportions of patients developing PPCs in RCTs of goal directed fluid therapy (i.e. vasopressor and inotropic intervention trials excluded).

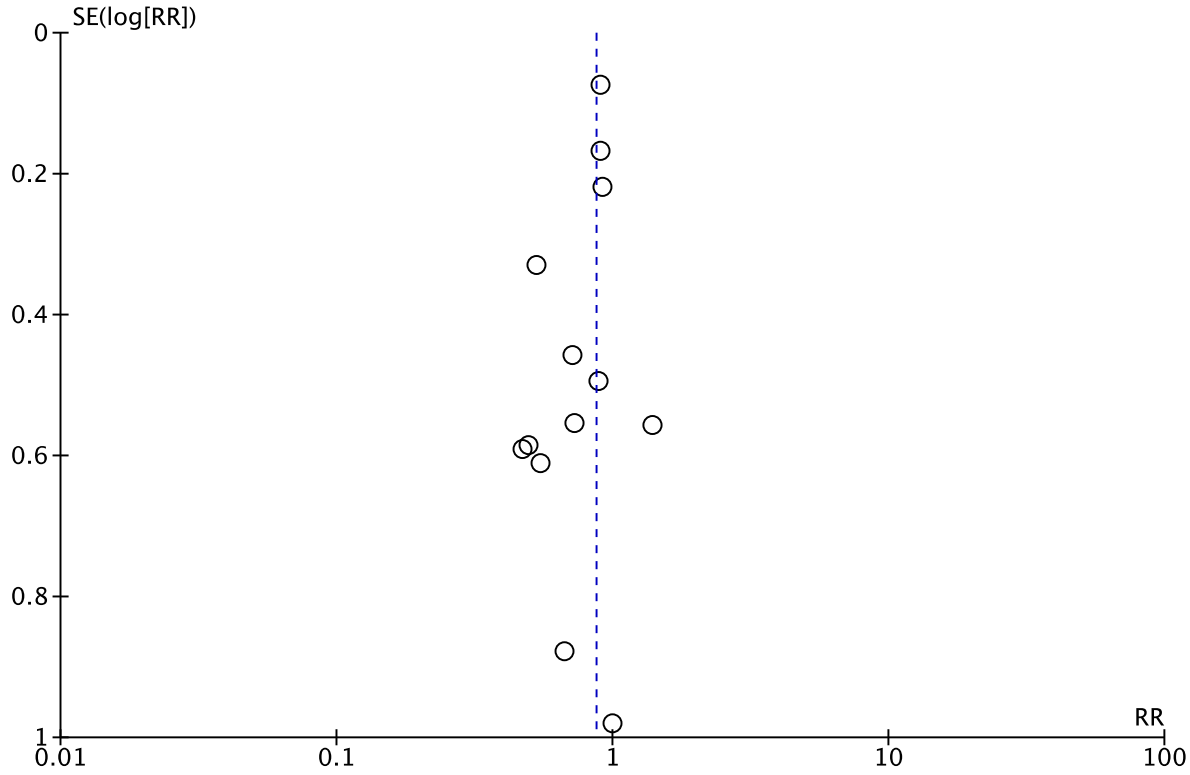

Figure 10.8 Funnel plot for random effects meta-analysis of PPCs outcomes in RCTs of goal directed haemodynamic therapy.

11. Miscellaneous

Study Author and Year	Study Sample and Country	Intervention description	Timing of Intervention Delivery	Pulmonary Outcomes	Risk of bias
Amar 2015	n=137, USA, single centre	Atorvastatin 40mg daily, 1 week before and one week after surgery	Pre-operative	Respiratory infection, respiratory failure	High risk
Berg 1997	n=691, Denmark, multi-centre	Atracurium (0.4-0.5mg/kg with 5-10mg boluses) and vecuronium (0.08-0.1 mg/kg with 1-2mg boluses)	Intra-operative, postoperative	Composite PPC	High risk
de la Gala 2017	n=174, Spain, single centre	Propofol total intravenous anaesthesia. Dose titrated to achieve BIS 40-60	Intra-operative	Composite PPC, respiratory infection, respiratory failure, atelectasis	Low risk
Parker 2015	n=322, UK, single centre	Spinal anaesthesia. Exact technique and doses of drugs used for the different types of anaesthesia was the choice of the anaesthetist.	Intra-operative	Respiratory infection	High risk
Tyagi 2010	n=100, India, single centre	Filter aseptically connected between ETT and breathing system	Intra-operative	Respiratory infection	High risk
Gaitini 2004	n=150, Israel, single centre	Proseal laryngeal mask airway or Laryngeal Tube Suction device placed after GA and neuromuscular blocking drug administration	Intra-operative	Respiratory infection (Aspiration)	Some concerns
Lai 2017	n=40, Taiwan, single centre	Igel vs ETT for laparoscopic surgery with Trendelenburg position	Intra-operative	Respiratory infection (Aspiration)	Low risk
Wong 2007	n=103, UK, single centre	Both groups were warmed during surgery, but patients in the warming group were additionally warmed 2 h before and after surgery using a conductive carbon polymer mattress	Intra-operative	Respiratory infection	Low risk
Monsel 2016	n=109, France, single centre	Spherical vs tapered shape cuffs on endotracheal tubes	Intra-operative	Respiratory infection	Low risk
Brueckmann 2015	n=150, USA, single centre	Reversal of neuromuscular blockade with Sugammadex (2 or 4 mg/kg) or usual care (neostigmine/glycopyrrolate)	Intra-operative	Respiratory infection	Low risk

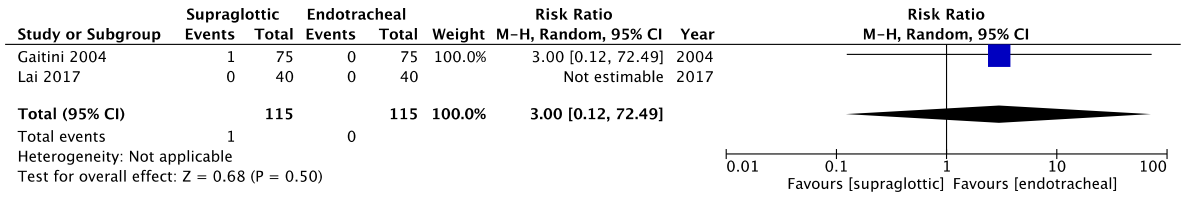

Figure 11.1. Forest plot comparing proportions of patients developing PPCs in RCTs supraglottic airway devices vs. endotracheal tube intubation.

Appendix 3. Subgroup analysis by surgical type

Incentive spirometry

Type of surgery	Number of RCTs	Number of patients	Risk ratio of PPC (95% CI)
Thoracic	2	247	0.87 (0.46 to 1.67; p = 0.68; I^2 = 0%)
Upper GI	2	361	1.19 (0.48 to 2.97; p = 0.71; I^2 = 30%)
Lower GI	2	1332	1.09 (0.84 to 1.40; p = 0.53; I^2 = 0%)

Table 1. PPC risk ratios for incentive spirometry, stratified by subgroup of surgery received by all or largest proportion of patients in RCTs.

Supervised physiotherapy

Type of surgery	Number of RCTs	Number of patients	Risk ratio of PPC (95% CI)
Thoracic	3	279	0.91 (0.34 to 2.41; p = 0.85; I^2 = 60%)
Upper GI	4	581	0.43 (0.17 to 1.08; p = 0.07; I^2 = 65%)
Lower GI	3	426	0.53 (0.21 to 1.34; p = 0.18; I^2 = 25%)

Table 2. PPC risk ratios for physiotherapy, stratified by subgroup of surgery received by all or largest proportion of patients in RCTs.

Drug therapies to improve pulmonary function

Type of surgery	Number of	Number of	Risk ratio of PPC (95% CI)

	RCTs	patients	
Thoracic	2	200	0.30 (0.11 to 0.77; p = 0.01; I^2 = 0%)
Upper GI	1	252	0.45 (0.24 to 0.85; p = 0.01; I^2 = N/A)
Lower GI	0	0	N/A

Table 3. PPC risk ratios for of prophylactic mucolytics, stratified by subgroup of surgery received by all or largest proportion of patients in RCTs.

Intraoperative anaesthetic gas composition

Type of surgery	Number of RCTs	Number of patients	Risk ratio of PPC (95% CI)
Thoracic	0	0	N/A
Upper GI	0	0	N/A
Lower GI	2	1416	1.12 (0.80 to 1.58; p = 51; I^2 = 0%)

Table 4. PPC risk ratios for of FiO2 0.8 versus 0.3, stratified by subgroup of surgery received by all or largest proportion of patients in RCTs.

Intraoperative ventilation strategies

Type of surgery	Number of RCTs	Number of patients	Risk ratio of PPC (95% CI)
Thoracic	1	100	0.18 (0.04 to 0.78; p = 0.02; I^2 = N/A)
Upper GI	0	0	N/A
Lower GI	3	1347	0.61 (0.32 to 1.18; p = 0.14; I^2 = 89%)

Table 5. PPC risk ratios for of lung protective ventilation, stratified by subgroup of surgery received by all or largest proportion of patients in RCTs.

Prophylactic non-invasive ventilation

Type of surgery	Number of RCTs	Number of patients	Risk ratio of PPC (95% CI)
Thoracic	3	442	1.00 (0.70 to 1.43; p = 1.00; I^2 = 14%)
Upper GI	3	147	0.35 (0.16 to 0.79; p = 0.01; I^2 = 0%)
Lower GI	0	0	N/A

Table 6. PPC risk ratios for prophylactic non-invasive ventilation (bilevel and CPAP), stratified by subgroup of surgery received by all or largest proportion of patients in RCTs.

Analgesia

Type of surgery	Number of RCTs	Number of patients	Risk ratio of PPC (95% CI)
Thoracic	1	50	0.75 (0.19 to 3.01; p = 0.69; I^2 = N/A)
Upper GI	0	0	N/A
Lower GI	7	2216	0.74 (0.62 to 0.89; p = 0.001; I^2 = 0%)

Table 7. PPC risk ratios for epidural, stratified by subgroup of surgery received by all or largest proportion of patients in RCTs.

Lifestyle modifications

Type of surgery	Number of RCTs	Number of patients	Risk ratio of PPC (95% CI)
Thoracic	0	0	N/A
Upper GI	0	0	N/A
Lower GI	3	463	0.89 (0.27 to 2.93; p = 0.85; I^2 = 0%)

Table 8. PPC risk ratios for incentive spirometry, stratified by subgroup of surgery received by all or largest proportion of patients in RCTs.

Enhanced post-operative recovery pathways

Type of surgery	Number of RCTs	Number of patients	Risk ratio of PPC (95% CI)
Thoracic	1	60	0.29 (0.12 to 0.69; p = 0.005; I^2 = N/A)
Upper GI	0	0	N/A
Lower GI	3	399	0.38 (0.20 to 0.71; p = 0.003; I^2 = 0%)

Table 9. PPC risk ratios for enhanced recovery after surgery, stratified by subgroup of surgery received by all or largest proportion of patients in RCTs.

Goal directed haemodynamic and fluid therapy

Type of surgery	Number of RCTs	Number of patients	Risk ratio of PPC (95% CI)
Thoracic	0	0	N/A

Upper GI	0	0	N/A
Lower GI	7	726	0.56 (0.21 to 1.46; p = 0.23; I^2 = 30%)

Table 10. PPC risk ratios for restrictive vs. liberal fluid administration, stratified by subgroup of surgery received by all or largest proportion of patients in RCTs.

Type of surgery	**Number of RCTs**	**Number of patients**	**Risk ratio of PPC (95% CI)**
Thoracic	0	0	N/A
Upper GI	0	0	N/A
Lower GI	10	3555	0.89 (0.79 to 1.01; p = 0.08; I^2 = 0%)

Table 11. PPC risk ratios for perioperative goal directed haemodynamic therapy, stratified by subgroup of surgery received by all or largest proportion of patients in RCTs.

Appendix 4. Trial sequential analysis

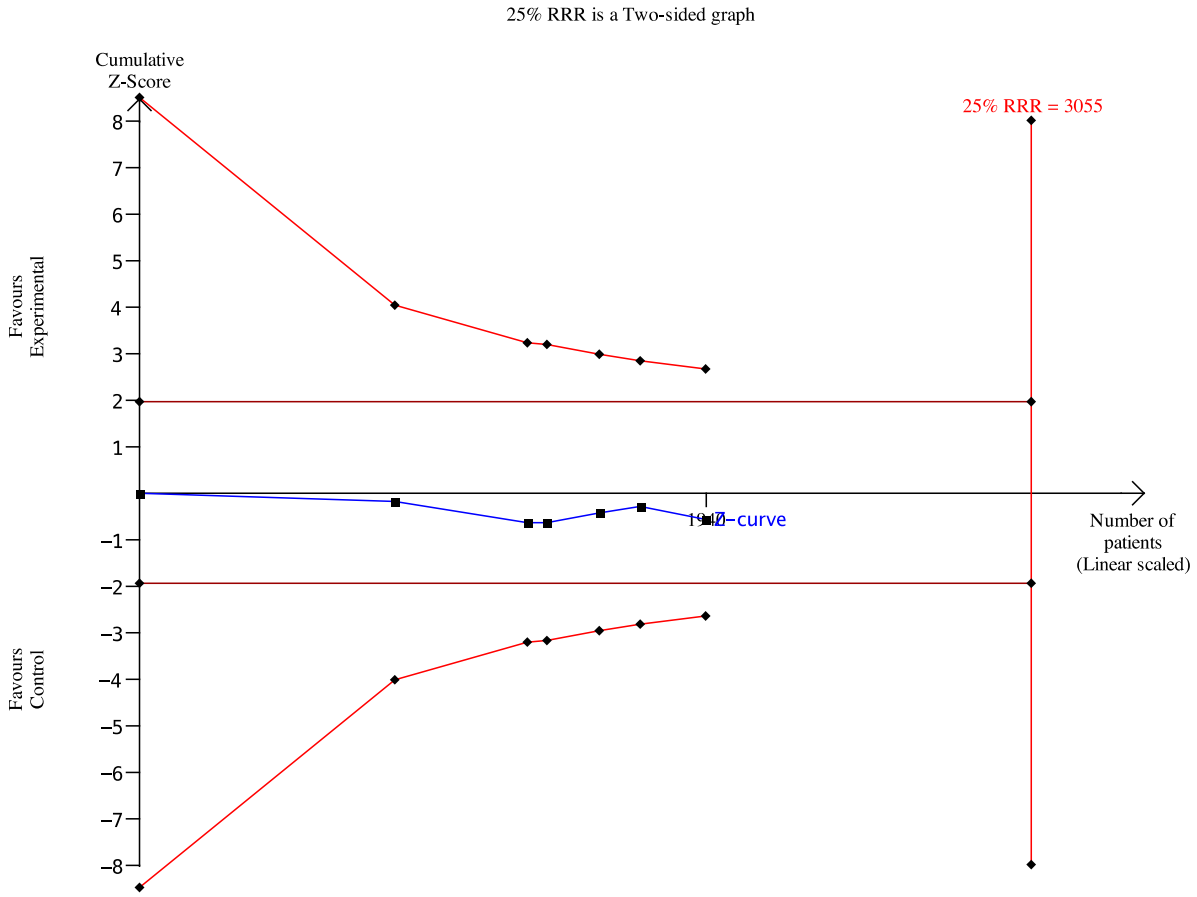

Figure 1. Trial sequential analysis (TSA) for incidence of PPCs in trials comparing incentive spirometry (IS) to control. The upper half of the graph above the zero axis represents the area of advantage with IS and the lower half represents the advantage area with control. The green lines at +1.96 and −1.96 on the Y-axis represent the conventional model boundaries for TSA with an α of 5%. The vertical red line shows the calculated minimum required information size (IS) for the conventional boundary model for making conclusions is 3055. The symmetrical red curves represent the calculated trial sequential monitoring boundaries (TSMBs). The blue line represents the cumulative z-value, with each consecutive trial marked by a filled square. Firm evidence has been reached when the cumulative z-curve crosses the calculated boundaries before the calculated IS. Spurious significant differences between treatments are found when the cumulative z-curve crosses the traditional z = −1.96 or z = 1.96, but not the calculated TSMBs. The cumulative z-score line (blue) does not crosses the conventional boundaries (green lines) indicating there is no conclusive evidence of superiority for the IS or control groups based upon a 25% relative risk reduction.

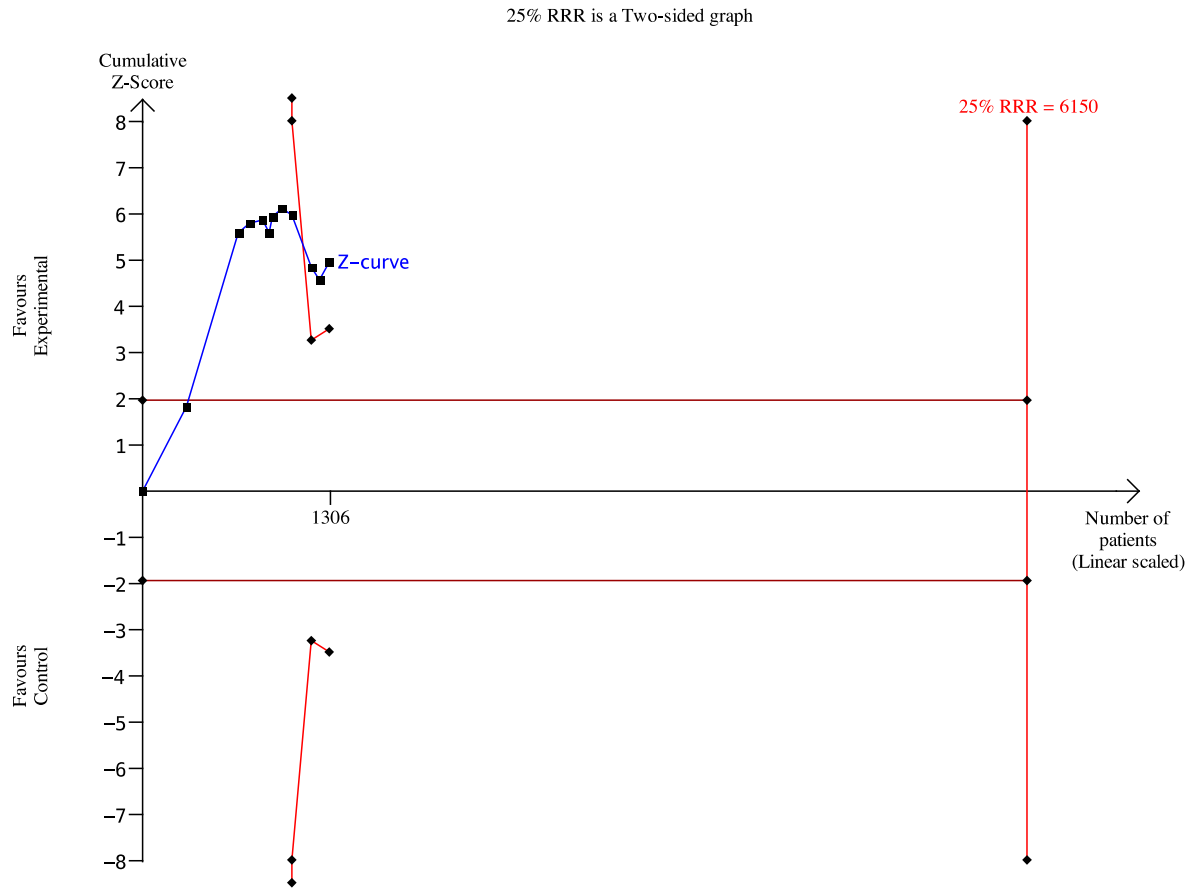

Figure 2. Trial sequential analysis (TSA) for incidence of PPCs in trials comparing supervised physiotherapy to control. The cumulative z-curve crosses both the conventional boundaries and calculated trial sequential monitoring boundaries (TSMBs). This result indicates there is firm evidence of superiority for the supervised physiotherapy (based on a 25% relative risk reduction). Although the calculated IS needed (6,150 participants) has not been reached yet (1,306 participants so far), no more additional participants are needed because the cumulative z-curve crosses the TSMB.

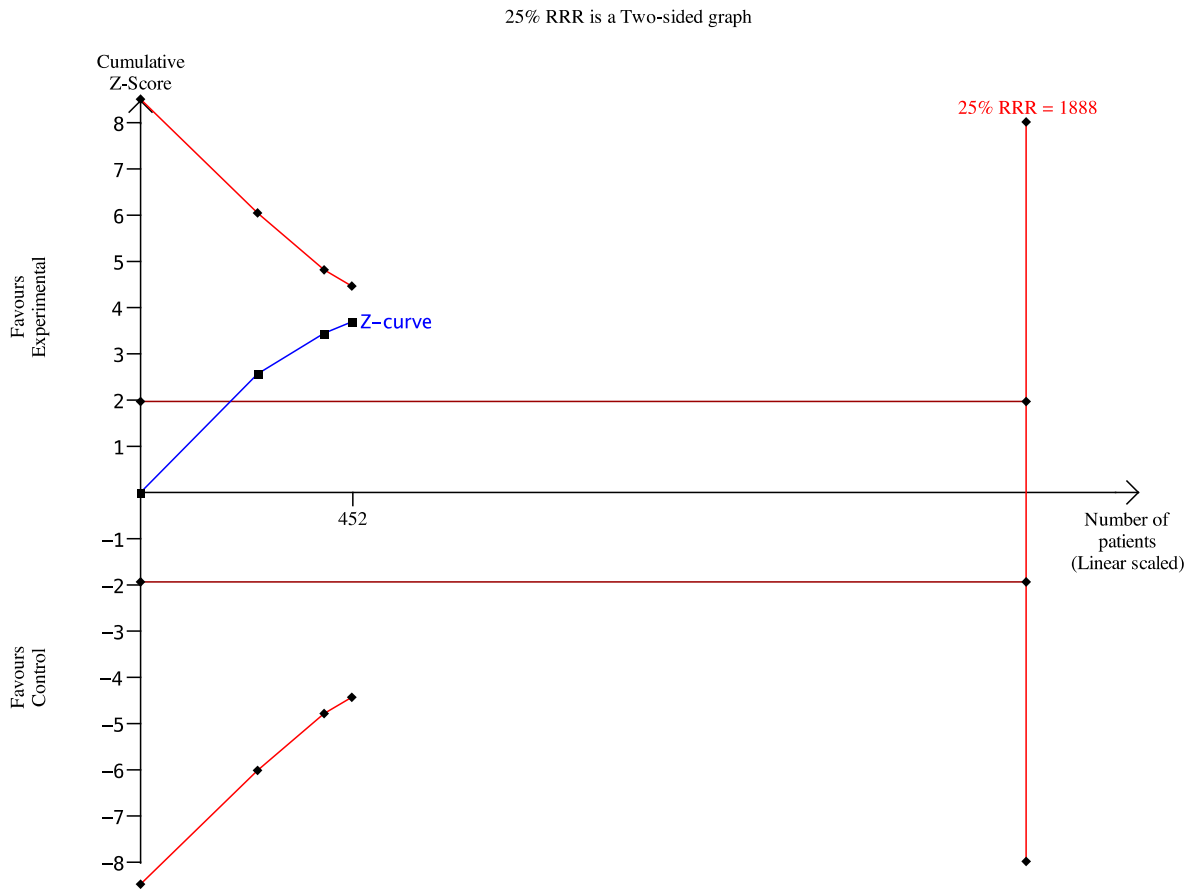

Figure 3. Trial sequential analysis (TSA) for incidence of PPCs in trials comparing Ambroxol to control. The cumulative z-curve crosses the conventional boundaries but not the calculated trial sequential monitoring boundaries (TSMBs). Nor has the calculated IS needed been reached. This result indicates that conventional meta-analysis may have produced a potential spurious positive result (type 1 error) for Ambroxol (based on a 25% relative risk reduction).

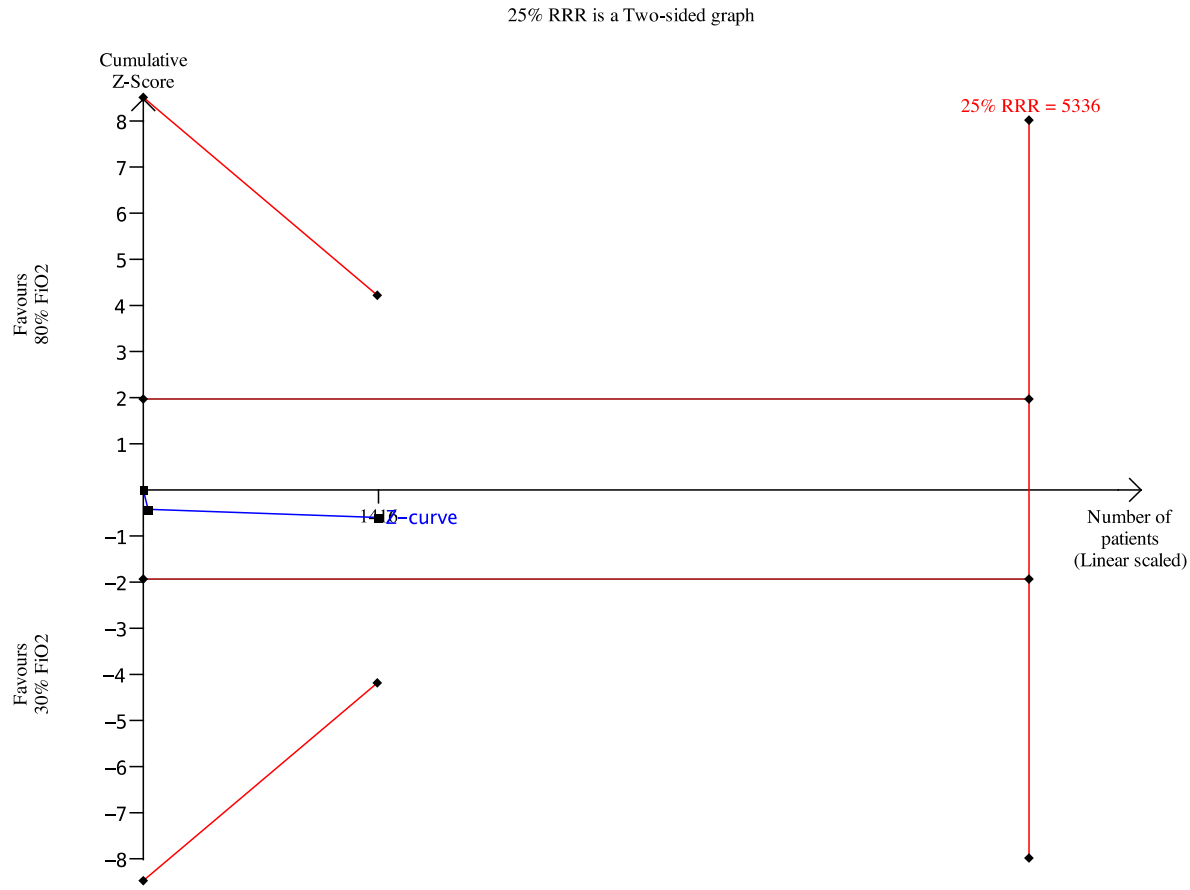

Figure 4. Trial sequential analysis (TSA) for incidence of PPCs in trials comparing FiO2 0.8 to FiO2 0.3. The cumulative z-curve does not cross the conventional or the trial sequential monitoring boundaries (TSMBs). The actual information size (1416) is far short of the calculated IS needed (5336), based on a 25% relative risk reduction. This result is inconclusive for either FiO2 0.3 or 0.8 in preventing PPCs.

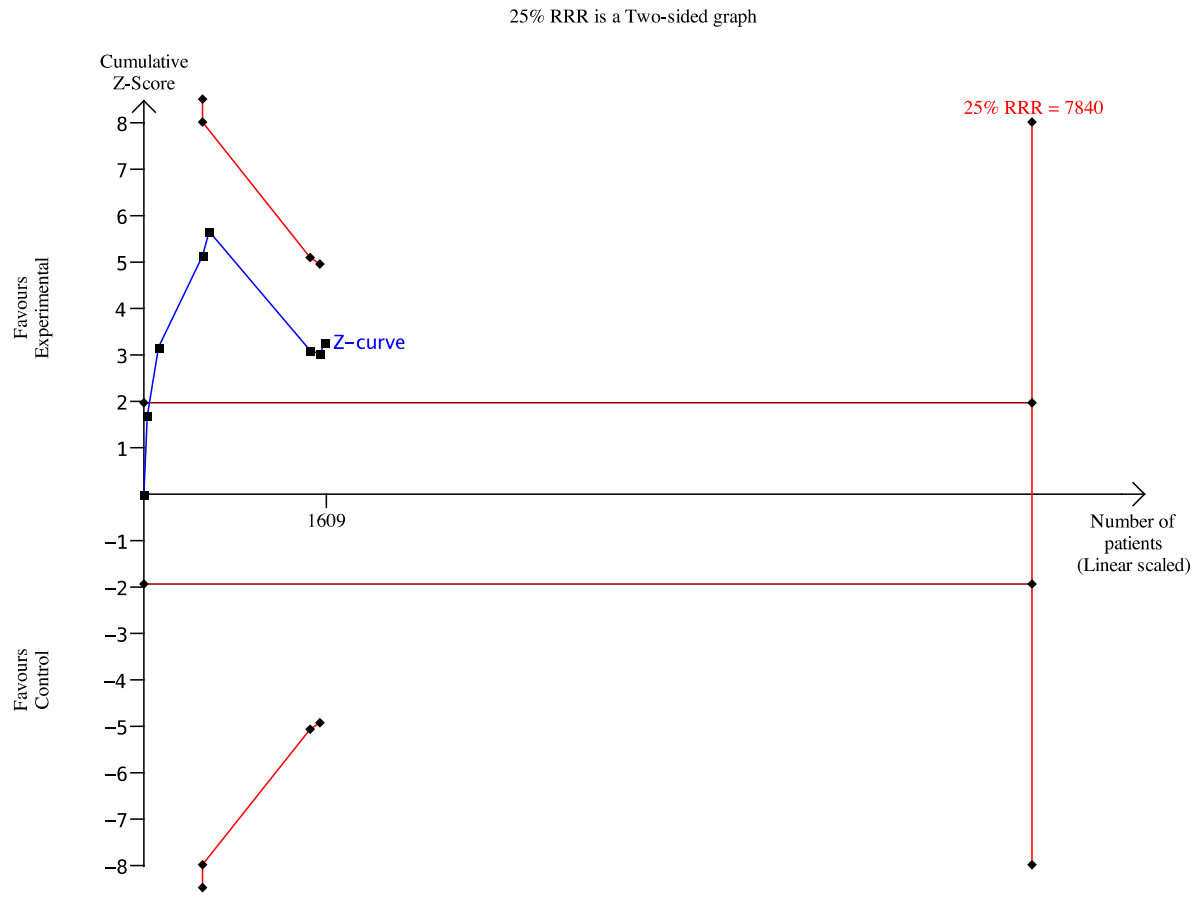

Figure 5. Trial sequential analysis (TSA) for incidence of PPCs in trials comparing lung protective ventilation to control. The cumulative z-curve crosses the conventional boundaries but not the calculated trial sequential monitoring boundaries (TSMBs). Nor has the calculated IS needed been reached. This result indicates that conventional meta-analysis may have produced a potential spurious positive result (type 1 error) for lung protective ventilation (based on a 25% relative risk reduction).

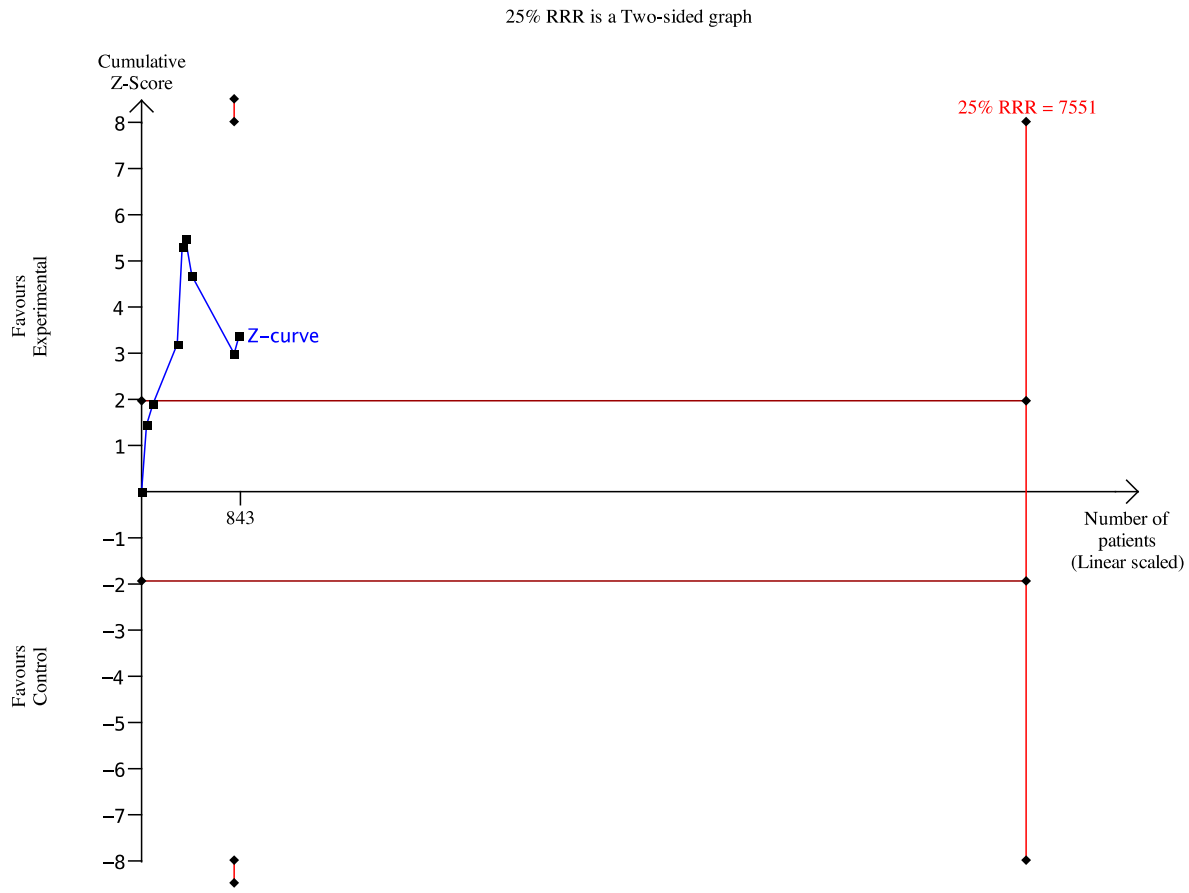

Figure 6. Trial sequential analysis (TSA) for incidence of PPCs in trials comparing continuous positive airway pressure (CPAP) to control. The cumulative z-curve crosses the conventional boundaries but not the calculated trial sequential monitoring boundaries (TSMBs). Nor has the calculated IS needed been reached. This result indicates that conventional meta-analysis may have produced a potential spurious positive result (type 1 error) for CPAP (based on a 25% relative risk reduction).

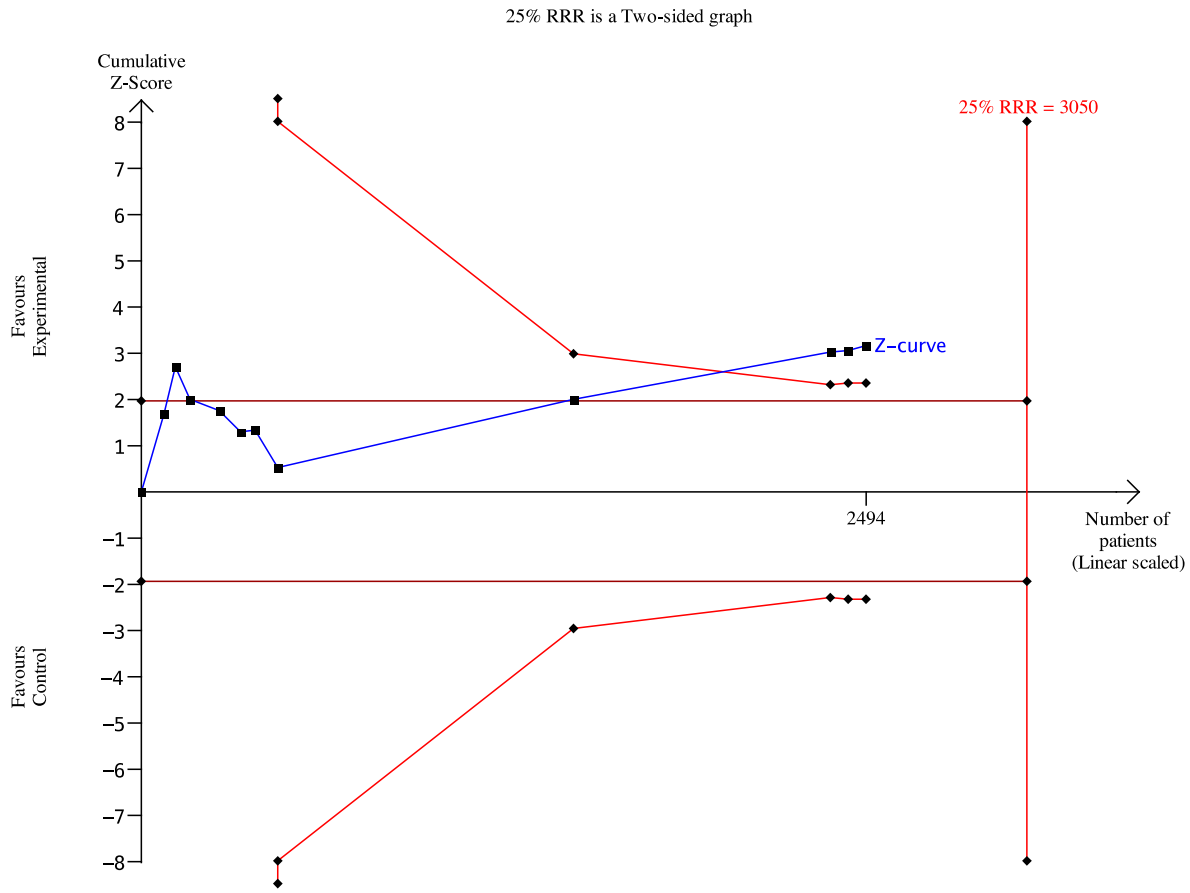

Figure 7. Trial sequential analysis (TSA) for incidence of PPCs in trials comparing epidural analgesia to control. The cumulative z-curve crosses both the conventional boundaries and calculated trial sequential monitoring boundaries (TSMBs). This result indicates there is firm evidence of superiority for epidural analgesia (based on a 25% relative risk reduction). Although the calculated IS needed (3,050 participants) has not quite been reached yet (2,494 participants so far), no more additional participants are needed because the cumulative z-curve crosses the TSMB.

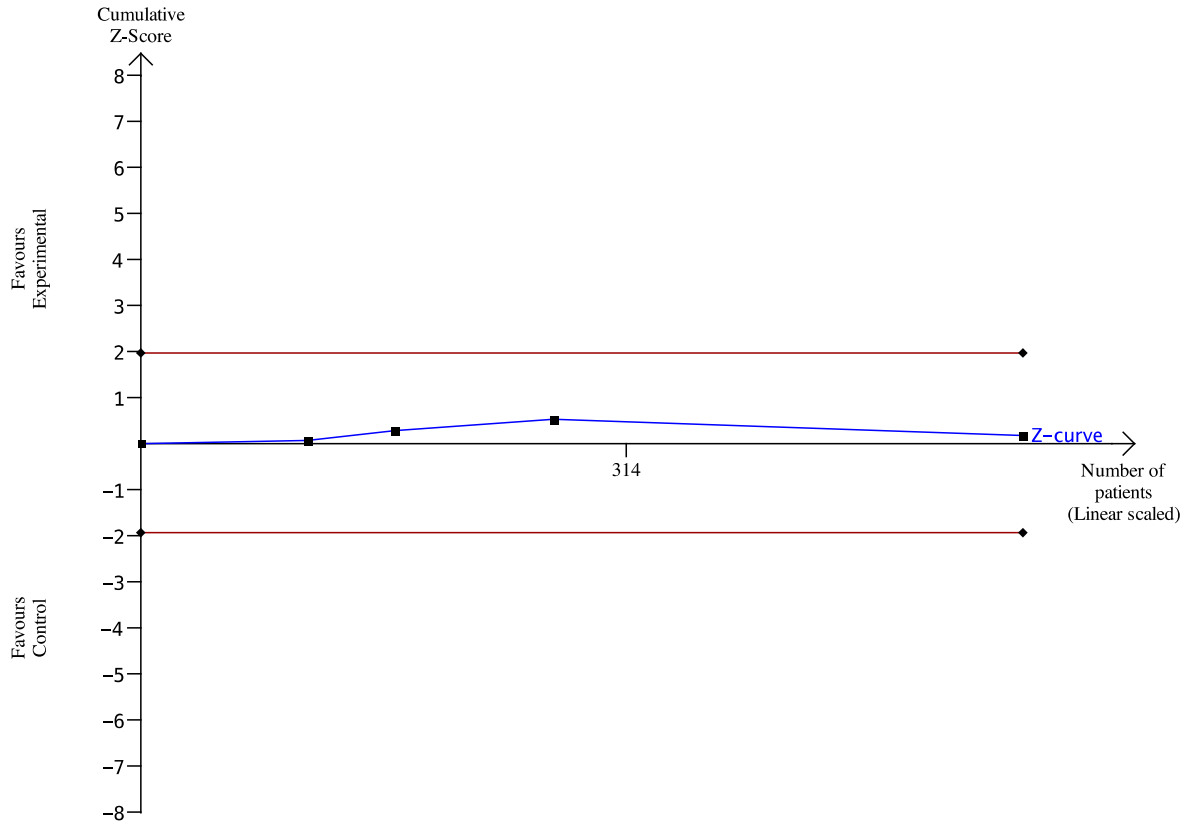

Figure 8. Trial sequential analysis (TSA) for incidence of PPCs in trials comparing smoking cessation therapies to control. This result is inconclusive for whether smoking cessation therapies prevent PPCs.

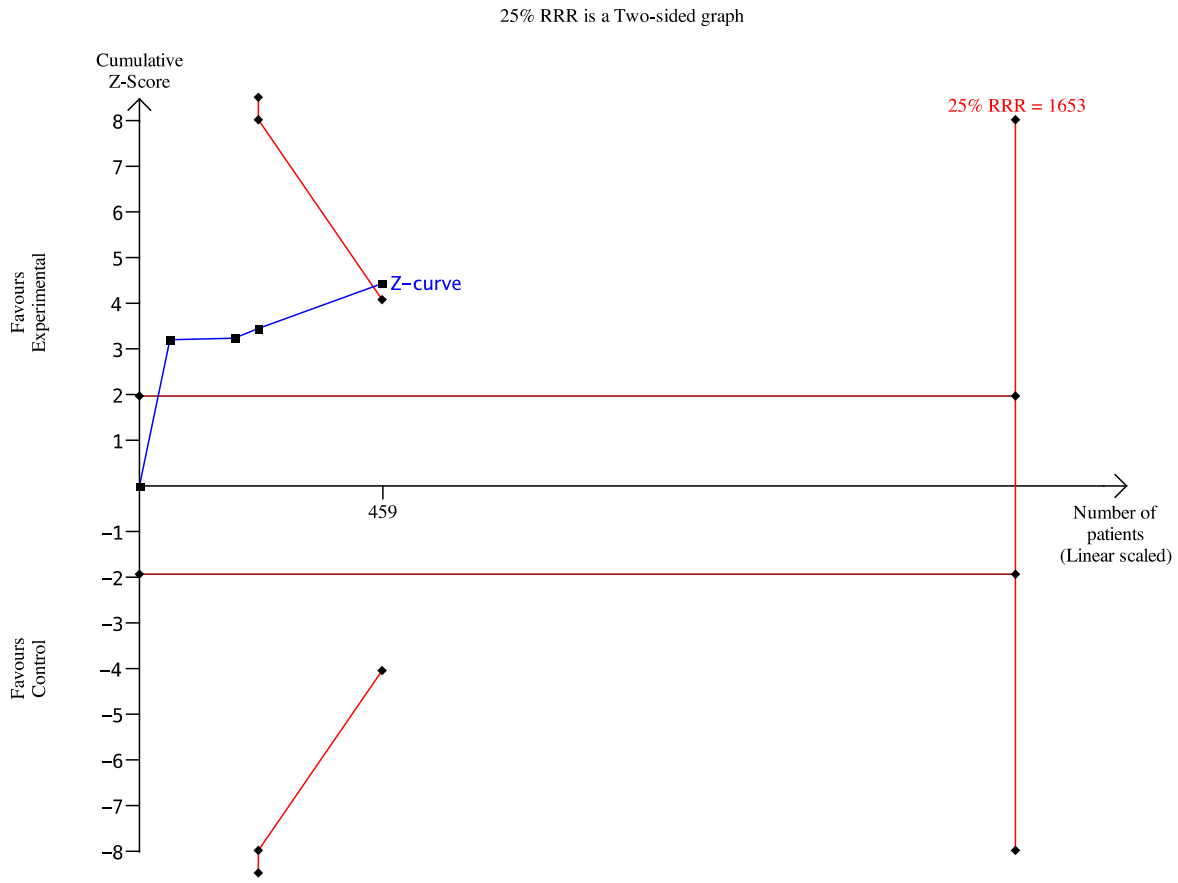

Figure 9. Trial sequential analysis (TSA) for incidence of PPCs in trials comparing enhanced recovery after surgery (ERAS) protocols to control. This result indicates there is firm evidence of superiority for ERAS (based on a 25% relative risk reduction).

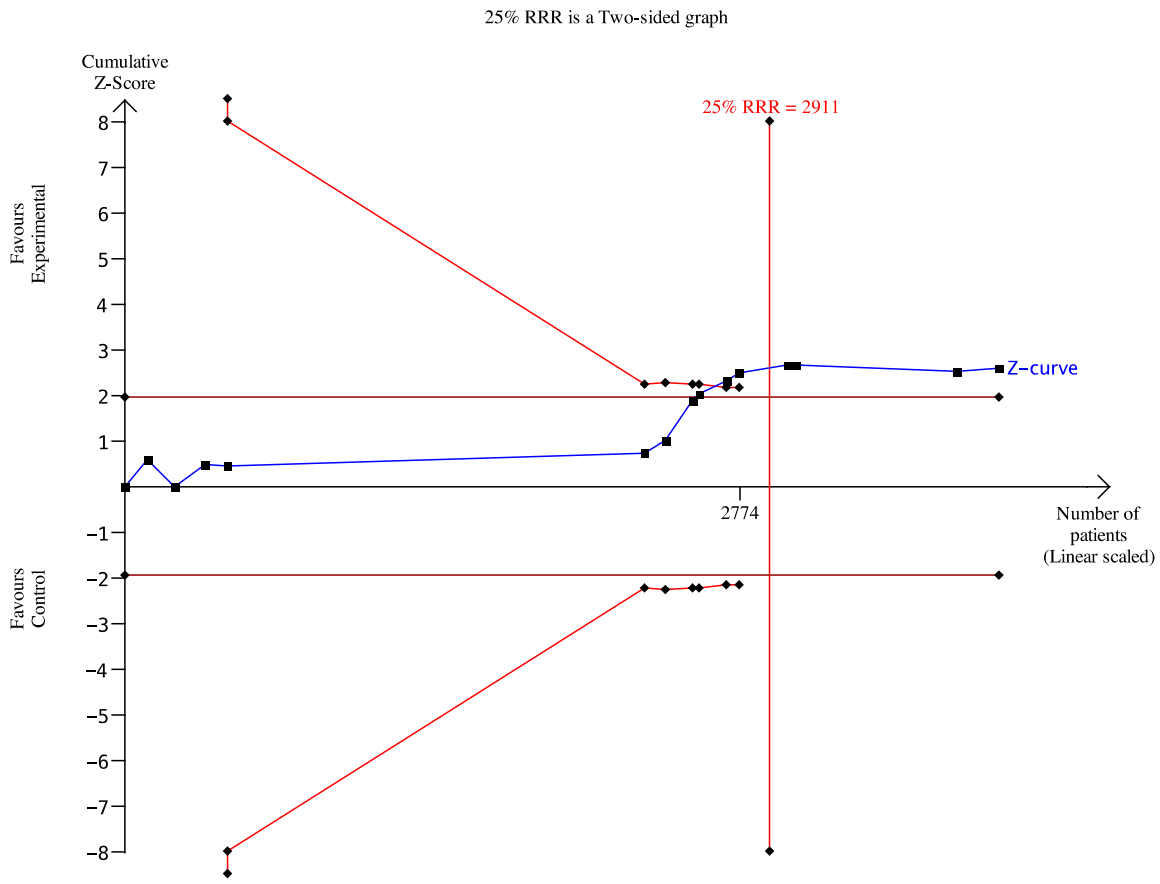

Figure 10. Trial sequential analysis (TSA) for incidence of PPCs in trials comparing goal directed haemodynamic therapies to control. The cumulative z-curve crosses both the conventional boundaries and calculated trial sequential monitoring boundaries (TSMBs). This result indicates there is conclusive evidence of superiority for the goal directed haemodynamic therapies (based on a 25% relative risk reduction). The required information size was exceeded, hence minimising the chance of both type I and II errors.

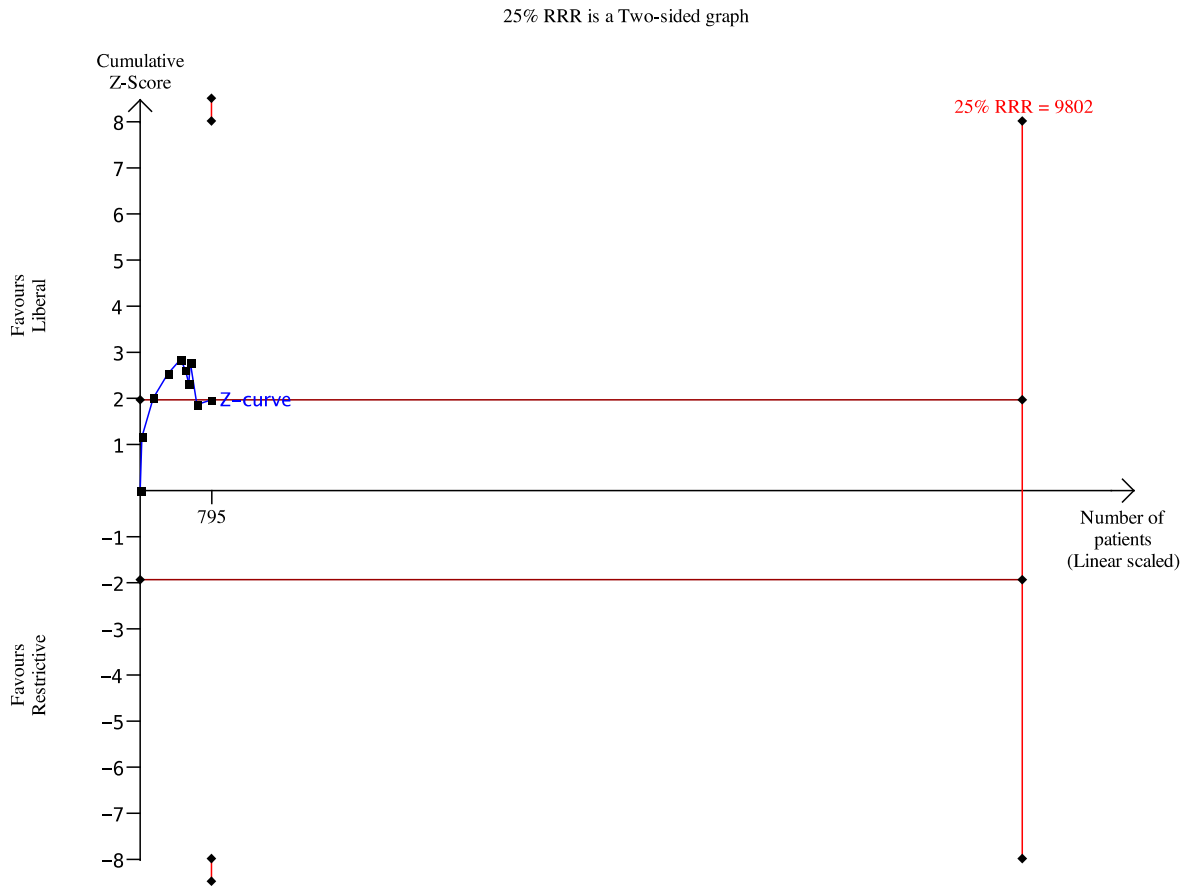

Figure 11. Trial sequential analysis (TSA) for incidence of PPCs in trials comparing restrictive (intervention) fluid therapies to liberal (control) fluid therapy. The cumulative z-curve is on the margins of the conventional boundaries but is far from the calculated trial sequential monitoring boundaries (TSMBs). The actual IS is far from the calculated IS needed to demonstrate a 25% relative risk reduction. This result indicates that far more trials are needed to produce firm evidence, although a smaller number of trials with a similar outcome may result in the conventional boundaries being crossed and a potentially spurious positive result produced by conventional meta-analysis.