Routine postoperative non-invasive respiratory support and pneumonia after elective surgery: a systematic review and meta-analysis of randomised trials

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SUMMARY

Background

Postoperative pulmonary complications (PPC), including pneumonia, are a substantial cause of morbidity. We hypothesised that routine non-invasive respiratory support was associated with lower incidence of pneumonia after surgery.

Methods

Systematic review and meta-analysis of randomised controlled trials comparing the routine use of Continuous Positive Airway Pressure (CPAP), Non-invasive Ventilation (NIV) or High Flow Nasal Oxygen (HFNO) against standard postoperative care in the adult population. We searched MEDLINE (PubMed), EMBASE, and CENTRAL from start of indexing to 27th July 2021. Articles were reviewed and data extracted in duplicate, with discrepancies resolved by a senior investigator. The primary outcome was pneumonia and the secondary outcome was PPC. We calculated risk difference (RD) with 95% confidence intervals using DerSimonion and Laird random effects models. We assessed risk of bias using the Cochrane risk of bias tool. (PROSPERO: CRD42019156741).

Results

From 18,513 records, we included 38 trials consisting of 9782 patients. Pneumonia occurred in 214/4403 (4.9%) patients receiving non-invasive respiratory support compared to 216/3937 (5.5%) receiving standard care (RD -0.01 [95%CI: -0.02 – 0.00]; I^2= 8%; p = 0.23). PPC occurred in 393/1379 (28%) patients receiving non-invasive respiratory support compared to 280/902 (31%) receiving standard care (RD -0.11 [-0.23 – 0.01]; I^2=79%; p = 0.07). Sub-group analyses did not identify benefit of CPAP, NIV or HFNO in preventing pneumonia. Tests for publication bias suggest six unreported trials.

Conclusion

The results of this evidence synthesis do not support the routine use of postoperative CPAP, NIV or HFNO to prevent pneumonia after surgery in adults.

INTRODUCTION

More than five million patients undergo surgery in the United Kingdom in a typical year (1). This population of patients is increasingly older and at greater risk of complications (2). Some of the most frequent and serious complications affect the respiratory system, including pneumonia, atelectasis, acute respiratory distress syndrome (ARDS) and respiratory failure requiring mechanical ventilation (3, 4). Patients undergoing major abdominal surgery are particularly susceptible to postoperative pulmonary complications, which in turn increases the length of hospital stay, the cost of treatment and reduces long-term survival (5, 6). In patients with SARS-CoV-2 infection, the risk of postoperative mortality is substantially higher, which is further increased among patients with postoperative pulmonary complications (7, 8). The prevention of respiratory complications after surgery is topical and relevant to anaesthetists, surgeons and patients.

The aetiology of postoperative pulmonary complications is unclear. They are likely to arise due to a combination of anaesthesia and the surgical procedure itself, particularly following intra-thoracic or intra-abdominal surgery. General anaesthesia can cause atelectasis and pulmonary collapse, mismatch of ventilation with pulmonary perfusion can lead to hypoxia, while opioid analgesia and incomplete reversal of neuromuscular blockade can reduce respiratory drive (3). Surgery can cause tissue injury, inflammation and pain, which can impair respiratory function and the ability to cough effectively. A combination of these factors increase the risk of pulmonary complications after surgery.

There is growing interest in interventions to reduce postoperative pulmonary complications, bolstered by widespread use of non-invasive respiratory support to treat respiratory failure

during the COVID-19 pandemic (9). Continuous positive airway pressure (CPAP), non-invasive ventilation (NIV) and high-flow nasal oxygen (HFNO) have all been used to treat hypoxic respiratory failure in critical care environments and there is evidence from small trials that some of these interventions may prevent postoperative pulmonary complications when applied to all patients after surgery (10). However, emerging evidence from a large multi-centre clinical effectiveness trial conflicts with the most comprehensive evidence synthesis on this topic, which is now over ten years old (11). Here, we present an updated evidence synthesis of whether preventative postoperative non-invasive respiratory support, including CPAP, NIV and HFNO, can reduce the incidence of pneumonia after elective surgery.

METHODS

This was a systematic review and meta-analysis of randomised clinical trials. The protocol was prospectively registered (PROSPERO CRD42019156741) and we report our findings in accordance with the PRISMA guidelines (12).

Search strategy and selection criteria

We searched MEDLINE (PubMed), EMBASE, and CENTRAL from database conception (MEDLINE: 1879, EMBASE: 1974, CENTRAL: 1996) to 27th July 2021 using the Health Database Advanced Search platform. The full search strategies can be found in supplementary file. We conducted hand searches within citations of all identified articles and prior systematic reviews and we searched Grey Net (www.greynet.org) for relevant conference proceedings. Studies were considered for inclusion if they were randomised controlled trials describing routine postoperative non-invasive respiratory support; in adult patients (≥16 years of age) undergoing major surgery, including thoracic and abdominal surgery; and reported either postoperative pulmonary complications or mortality as part of their outcomes. We excluded studies with paediatric patients (<16 years old); where patients did not undergo surgery according to a standardised definition; or if an intervention was used to treat existing respiratory failure (13). We did not apply a language restriction. Initial record screening, full text assessment, and data extraction were all conducted independently by two investigators (different combinations between authors MW, VL, SB, TF, and JS). Records were screened (title and abstract) using Mendeley Reference Manager (Elsevier, Amsterdam, Netherlands). Where full texts were not available online we contacted the authors directly. Non-English studies were translated by an expert, fluent speaker where possible. Full text assessment and data extraction were performed using a

standardised, piloted web-based form (Google Form, Google, Alphabet Inc, California, USA). All discrepancies between investigators were resolved through discussion with a third investigator (one of authors SH, TA, or AF).

Data analysis

Data were extracted for each trial arm individually. Trials with multiple eligible arms were treated as separate studies with two arms. Study characteristics are reported on a study level, whereas patient-level outcomes are reported on an arm level, to account for multiple eligible arms from one study. Risk of bias was assessed using the Cochrane Risk of Bias Tool for Randomised Trials (RoB2) (14) by two independent assessors (JYN, NC) and any discrepancies were reviewed by a third assessor (SH). We extracted data including number of centres, level of randomisation, geographical location, country income status according to The World Bank (October 2020) (15), urgency of surgery, type of surgery, intervention and control settings, participant age, participant body mass index, proportion of obese patients, length of surgical procedure, proportion of patients with existing respiratory disease, and smoking status.

The intervention was postoperative non-invasive respiratory support, considered as three separate interventions consisting of either: continuous positive airways pressure (CPAP), non-invasive ventilation (NIV) or high-flow nasal oxygen (HFNO). This did not include non-invasive respiratory support used to treat respiratory failure or hypoxia. The primary outcome measure was postoperative pneumonia, defined according to individual study definitions, but ideally using the CDC criteria (16). Secondary outcomes were acute respiratory distress syndrome (ARDS), re-intubation, all-cause mortality and postoperative

pulmonary complications (PPC), ideally using the STEP-COMPAC criteria (4). Process and safety outcomes were incidence of anastomotic leak, pulmonary aspiration, unplanned admission to critical care, and length of hospital stay. Data preparation was performed by a third independent author (SH). Continuous variables were converted into mean (standard deviation) using the methods described by Wan, et al (17).

The primary analysis compared the risk of the primary outcome between patients that received either CPAP, NIV or HFNO against standard postoperative care. We calculated the risk difference (RD) using the DerSimonion and Laird random effects model and uncertainty was measured by 95% confidence interval [95% CI]. Consistency was measured with I^2, Chi^2, and Tau^2 tests. Between-study variability or agreement was presented using Forest plots. Publication bias was assessed visually using funnel plots and associated Egger tests. The secondary analysis repeated the methodology of the primary analysis for the secondary outcome measures. All statistical analyses were performed using R (version 3.6.1, R Core Team, Vienna, Austria) and the “meta”, “metafor”, and “robvis” packages.

Role of the funding source

There was no funding to report for this study.

RESULTS

Our search yielded 18,513 records and we identified 15 records from other sources. We selected 261 for full text assessment and 38 were included in the analysis. 32 of the 38 studies had direct comparison of one control and one intervention arm. Six studies had more than one intervention arm, of which two studies had a shared control group and we combined their intervention arms (18, 19); one study had two separate intervention and control arms (20), which we included separately (21-23). We selected a single intervention and control arm from three studies. In total, 39 pairs of arms were analysed from 38 studies (Figure 1), representing 9782 patients. A summary of included trials is provided in Table 1, with characteristics listed in supplementary table 1 and important risk factors for pulmonary complications in supplementary table 3. 18 of 39 (46%) arms examined CPAP. Most trials were single-centre (30 of 38 (81%)), and the median number of participants per trial was 66 (IQR: 41-158).

Primary analysis

23 of 38 trials reported our pre-specified primary outcome (pneumonia) and were included in the primary analysis; seven used the Centre for Diseases Control definition for pneumonia; seven provided no definition, and eight were independently defined. In the 23 studies that reported pneumonia, 4403 of 8340 patients were randomised to non-invasive respiratory support of whom 214 (4.9%) developed pneumonia. 3937/8340 were randomised to standard postoperative care of whom 216 (5.5%) developed pneumonia. Compared to standard care, the use of CPAP, NIV or HFNO did not reduce the incidence of pneumonia (RD -0.01 [95%CI: -0.02 – 0.00]; I^2= 8%; p = 0.23) (Figure 2).

Secondary analyses

Postoperative pulmonary complications (PPC) were reported in 11 of 38 (29%) trials (13 arms). None met all four components of the STEP-COMPAC definition of postoperative pulmonary complications (4) and all were author-defined with significant heterogeneity in its criteria. We found no differences in the incidence of PPC (Figure 3), ARDS, re-intubation or mortality (supplementary figures 2-4) for patients that received non-invasive respiratory support compared to usual postoperative care.

Subgroup analyses

Compared to standard postoperative care care, the risk of pneumonia and mortality were not different between patients exposed to CPAP compared with NIV or HFNO (Figure 4 and supplementary table 2). Risk of pneumonia did not differ between patients who underwent abdominal surgery vs cardiothoracic surgery or mixed; and risk of mortality did not differ between patients exposed to different modalities of non-invasive respiratory support (supplementary figures 9-10 and supplementary table 2).

Safety and process outcomes

There was a statistically significant reduction in length of stay in patients who received postoperative non-invasive respiratory support (SMD -0.31 [95%CI: -0.62 – -0.00]; I^2= 93%, p= 0.05). There was no significant difference in re-admission to critical care, pulmonary aspiration, or anastomotic leak (supplementary figures 5-8).

Certainty and quality of evidence

Most studies were considered at low risk of bias (21 of 38 (55%)). 11 of 38 had cause for some concern, and six were considered at high risk of bias (supplementary figure 1). The domain most frequently at high-risk or of some concern of bias was measurement of outcome. The funnel plot for the primary analysis was asymmetrical on visual inspection (Figure 5) and Eggers test confirmed asymmetry ($p = 0.03$). A trim and fill analysis identified six potentially missing studies (24), however our findings were unchanged after accounting for these (supplementary figure 11).

DISCUSSION

The principal finding of this evidence synthesis is that routine postoperative non-invasive respiratory support was not associated with a reduction in the incidence of postoperative pneumonia or pulmonary complications. We did not identify a difference between modality of non-invasive respiratory support or an effect of the intervention on any of the secondary outcomes aside from length of stay. The reduction in length of stay should be interpreted with caution as it was minimal (one third of a day), there was evidence of high between study heterogeneity and much of the included data was skewed. Although the majority of the constituent trials were comparatively small (the median number of participants per trial was 54), the risk of bias assessment suggested that there was low risk of bias. The results of this evidence synthesis do not support the routine use of postoperative non-invasive respiratory support to prevent pneumonia or pulmonary complications after surgery.

The majority of trials in this field have examined the use of postoperative CPAP and the findings of our meta-analysis are consistent with the most recent evidence from randomised controlled trials in this area (25). However, our results are at odds with the results of a

previous Cochrane Review, which suggested there may be a benefit of postoperative CPAP in preventing postoperative pulmonary complications (10). This narrative tension can be largely explained by the increasing size of the body of evidence surrounding perioperative non-invasive respiratory support during the time period between reviews and the development of the methodology of randomised trials that these reviews are based on. Initial evidence of potential benefit of CPAP to prevent postoperative respiratory failure and pulmonary complications was largely derived from several small efficacy trials, where the intervention could be tightly controlled by senior clinicians among a highly selected group of patients (10, 26-28). However, as more trials have been conducted, including several large clinical effectiveness trials, the initial promise of potential clinical benefit does not appear to persist when these interventions are tested in 'real world' settings (18, 25, 29). The largest of these trials is the PRISM trial, a pragmatic multi-centre randomised clinical trial in ~70 hospitals across five countries. The investigators found no evidence of benefit of routine postoperative CPAP to prevent pneumonia, endotracheal re-intubation or death after major abdominal surgery among just under five thousand participants. Due to the large size, it is likely that the results of our meta-analyses that included CPAP were substantially influenced by the PRISM trial (25). However, the risk of bias from this trial is low.

There has been renewed interest in the use of non-invasive respiratory support in critical care and perioperative settings as a treatment for acute hypoxic respiratory failure, principally in response to COVID-19 pulmonary disease (8, 30). The pandemic has seen the expansion of capacity for both invasive and non-invasive ventilation in many hospitals worldwide (31). As such, these non-invasive methods of respiratory support have become much more familiar to many healthcare workers, both inside and outside of the critical care

unit. CPAP, NIV and HFNO have been used, primarily, as rescue therapies to mitigate or delay the need for invasive mechanical ventilation. Consequently, there may be enthusiasm to use non-invasive respiratory support in the perioperative setting as an intervention to prevent or reduce postoperative respiratory failure when the disruption to surgery caused by the pandemic eases (3, 9, 25, 32). While there is some evidence to support the use of HFNO or NIV to prevent or delay endotracheal intubation and invasive mechanical ventilation in patients with hypoxic respiratory failure, the results of this systematic review do not support the routine use of non-invasive respiratory support in the postoperative period in order to prevent respiratory complications (33-37). The safety and efficacy of non-invasive respiratory support to prevent postoperative respiratory failure among patients with SARS-CoV-2 infection remains unknown.

This study has several strengths. It is the most up-to-date and comprehensive systematic review of postoperative non-invasive respiratory support (including CPAP, NIV and HFNO) of which we are aware. All searches, abstract reviews, full text reviews and data extractions were completed in duplicate, with discrepancies resolved by a third investigator, which we hope has reduced bias between reviewers. We used standardised methodology to conduct both the systematic review and meta-analysis, and we registered the protocol before starting the project. Our analysis also has several limitations. We were only able to include papers for which we had access to the full text of the manuscript. We were careful to contact the author of papers that were not readily available. However, it was not always possible to locate the full text version, which may introduce a selection bias. We searched all the main indexing systems, the grey literature and performed hand searches of references of included papers. However, it is possible, although unlikely, that our search

missed some eligible trials. We included trials based on pre-specified criteria relating to the population of interest, the intervention and outcome. It is possible that we did not include some trials in this area because they did not meet our inclusion criteria. Our pre-specified aim was to examine postoperative non-invasive respiratory support as a strategy to prevent pulmonary complications, rather than as a treatment for established postoperative hypoxaemia or respiratory failure. There may be evidence to support the latter, but this was outside the scope of this review. The majority of the included trials examined CPAP, with comparatively smaller numbers examining NIV or HFNO. We conducted a sensitivity analysis that examined each treatment modality individually and found no signal to support any intervention. However, further larger randomised trials may be required to confirm this finding.

Conclusion

The results of this systematic review and meta-analysis do not support the use of routine postoperative non-invasive respiratory support to prevent pneumonia or pulmonary complications in adults post-operatively. This finding is consistent with the results of recent large randomised clinical trials. Further research could address non-invasive respiratory support to treat postoperative pulmonary complications, including respiratory failure, or to prevent respiratory complications in surgical patients with COVID-19.

Authors' contributions

SH: design, analysis and interpretation of data, writing first draft of manuscript

AJF: concept, design, analysis and interpretation of data

RC: design

TF: data acquisition

JS: data acquisition

SB: data acquisition

VL: data acquisition

MW: data acquisition

MK: data acquisition

JN: data acquisition

NC: data acquisition

RP: interpretation of data, revision of final draft

TA: concept, design, analysis and interpretation of data, writing first draft of manuscript, study guarantor

All authors: critical revision of manuscript for important intellectual content, and approval of the final version of manuscript

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Declaration of interests

Dr. Abbott reports grants from Barts Charity, the British Journal of Anaesthesia and the Royal College of Anaesthetists, during the conduct of the study; has performed consultancy work for MSD, outside the submitted work; and is a member of the editorial board of the British Journal of Anaesthesia. Dr Fowler reports grants from the NIHR, during the conduct of the study. Professor Pearse reports grants from NIHR, grants and non-financial support from Intersurgical UK, during the conduct of the study; grants and personal fees from

Edwards Life Sciences, outside the submitted work; and has given lectures and/ or performed consultancy work for GlaxoSmithKline and Edwards Lifesciences, and holds editorial roles with the British Journal of Anaesthesia, and the British Journal of Surgery. All other members of the writing committee report no relevant interests.

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Data sharing

The authors will consider requests for access to study data by *bona fide* researchers, according to a prespecified statistical analysis plan and with a data sharing agreement. Data will be available at the time of publication. Data access requests should be made to the corresponding author.

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TABLES

Name	Surgical category	Intervention mode	Centres	Patients randomised	Individual outcomes reported					
					Pneumonia	ARDS	Re-intubation	Pulmonary aspiration	PPC	Mortality
Abrard et al., 2021 (38)	Gynaecological, Upper GI, Lower GI, HPB, Urology and kidney, Cardiac, Thoracic, Vascular	NIV	>1	266	Y	Y	Y	Y	N	Y
Alexandropoulou et al., 2019 (39)	Upper GI, Bariatric	NIV	1	47	Y	N	Y	N	Y	Y
Baltieri et al., 2014 (21)	Upper GI, Bariatric	NIV	1	40	N	N	N	N	N	N
Barbagallo et al., 2012 (40)	Thoracic	CPAP	1	52	Y	N	Y	N	Y	Y
Bohner et al., 2002 (41)	Vascular	CPAP	1	237	Y	N	Y	N	N	Y
Brainard et al., 2017 (42)	Thoracic	HFNO	1	51	N	N	N	N	Y	N
Carlsson et al., 1981 (43)	Upper GI, HPB	CPAP	1	24	N	N	N	N	N	N
Cavalcanti et al., 2018 (44)	Upper GI, Bariatric	NIV	1	54	Y	N	N	N	N	N
Celebi et al., 2008 (22)	Cardiac	NIV	1	100	N	N	Y	N	N	Y
Danner et al., 2012 (45)	Thoracic	NIV	1	21	Y	N	Y	N	Y	Y
Ferrando et al., 2018 (18) (A): "OLA-iCPAP" vs "STD-O2" (B): “OLA-CPAP" vs "STD-O2" (C): "STD-CPAP" vs "STD-O2"	Upper GI, Lower GI, HPB, Vascular	CPAP	>1	1012	Y	Y	Y	Y	Y	Y
Ferrando et al., 2019 (29)	Upper GI, Bariatric	HFNO	1	64	Y	Y	Y	N	N	N
Futier et al., 2019 (46)	Upper GI, Lower GI, HPB, Thoracic	HFNO	>1	220	Y	Y	Y	N	N	Y
Garutti et al., 2014 (47)	Thoracic	CPAP	1	110	Y	Y	N	N	N	Y
Hewidy et al., 2016 (48)	Upper GI	CPAP	1	46	Y	N	Y	N	N	Y
Jaaly et al., 2013 (49)	Cardiac	NIV	1	129	Y	N	Y	N	N	Y
Jousela et al., 1994 (50)	Cardiac, Thoracic	CPAP	1	30	Y	N	N	N	N	N
Kilic et al., 2017 (19) (A): CPAP vs control (B): NIV vs control	Upper GI, Lower GI, HPB	CPAP	1	45	N	N	N	N	N	N
Kindgen-Milles et al., 2005 (51)	Vascular	CPAP	1	50	Y	Y	Y	N	Y	Y
Liao et al., 2010 (52)	Thoracic	NIV	1	50	Y	Y	N	N	Y	N
Lindner et al., 1987 (53)	Upper GI, HPB	CPAP	1	34	Y	N	N	N	Y	N

Lorut et al., 2014 (54)	Thoracic	NIV	>1	360	Y	Y	Y	N	N	Y
Mamo et al., 2018 (55)	Vascular	NIV	1	40	Y	Y	Y	N	N	Y
Neligan et al., 2009 (56)	Upper GI	CPAP	1	40	N	N	Y	N	N	Y
Olsen et al., 2002 (57)	Thoracic, Upper GI, Lower GI	CPAP	1	70	N	N	Y	N	N	Y
Palleschi et al., 2018 (58)	Thoracic	CPAP	>1	167	Y	N	Y	N	N	Y
Parke et al., 2013 (59)	Cardiac	HFNO	1	341	N	N	Y	N	N	Y
Pearse et al., 2021 (25)	Upper GI, Lower GI, HPB, Vascular, Intra-peritoneal surgery	CPAP	>1	4806	Y	Y	Y	Y	N	Y
Pennisi et al., 2019 (60)	Thoracic	HFNO	1	96	N	N	Y	N	Y	Y
Perrin et al., 2007 (61)	Thoracic	NIV	1	39	N	N	N	Y	N	Y
Pessoa et al., 2010 (62)	Upper GI	NIV	1	18	N	N	N	N	N	N
Pibul et al., 2021 (63)	Cardiac	HFNO	1	67	N	N	Y	N	N	N
Puente-Maestu et al., 2021 (64)	Thoracic	CPAP	>1	426	N	N	N	N	Y	Y
Sahin et al., 2018 (65)	Cardiac	HFNO	1	100	Y	N	Y	N	N	Y
Stock et al., 1984 (23)	Cardiac, Thoracic	CPAP	1	38	N	N	N	N	N	N
Wong et al., 2011 (66)	Bariatric, Upper GI	CPAP	1	90	N	N	Y	N	N	Y
Yu et al., 2017 (67)	Thoracic	HFNO	>1	110	Y	N	Y	N	N	Y
Zarbock et al., 2009 (20) (A): late extubation (B): early extubation	Cardiac	CPAP	1	292	Y	N	Y	N	Y	N

Table 1. Summary of included studies. Characteristics described include surgical categories, intervention mode, single/ multi-centre, total number of patients randomised. Individual outcome components are recorded as either “Y” for recorded or “N” for not recorded.

FIGURES

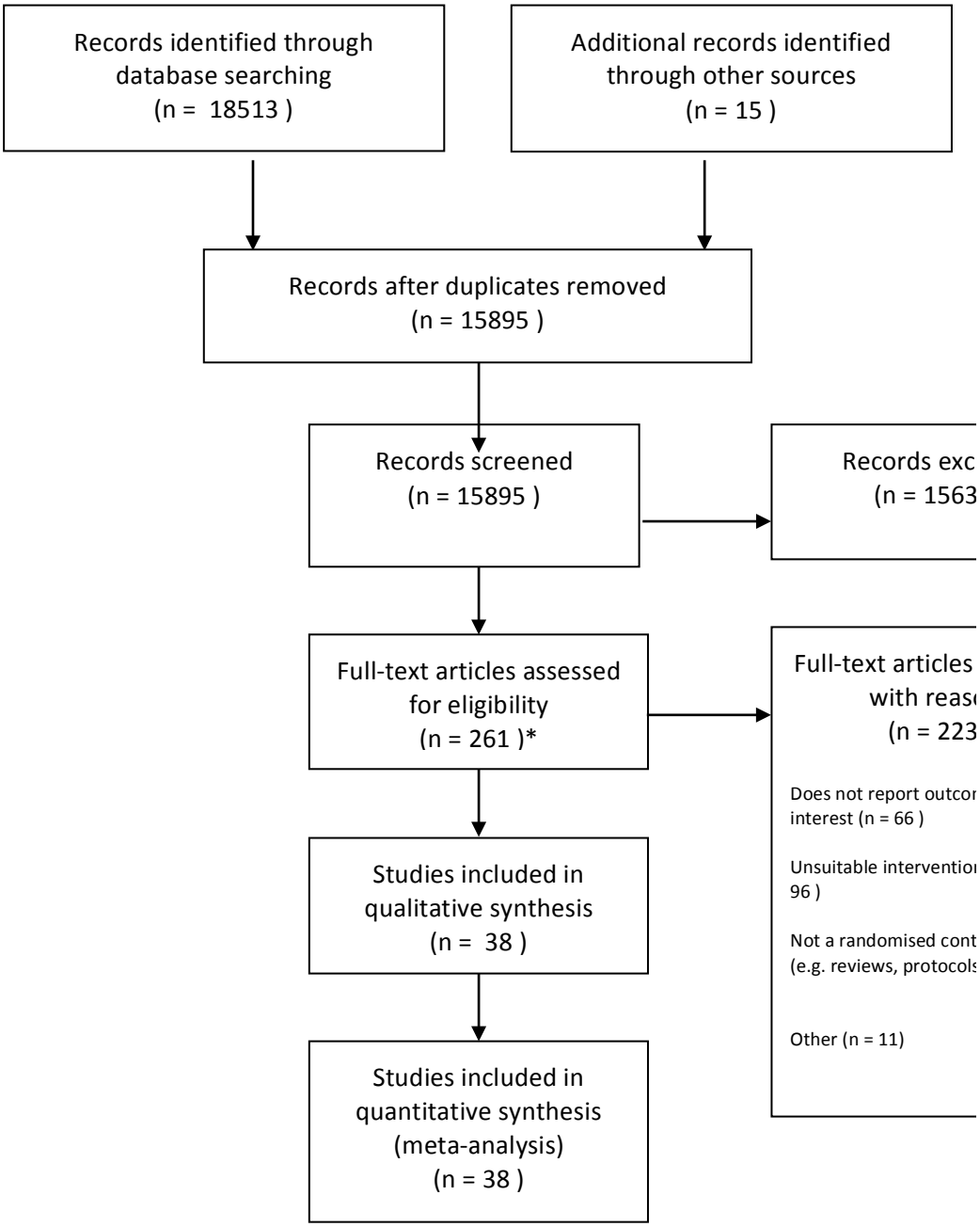

Figure 1. Study selection (PRISMA) diagram. * = unable to locate full texts of 56

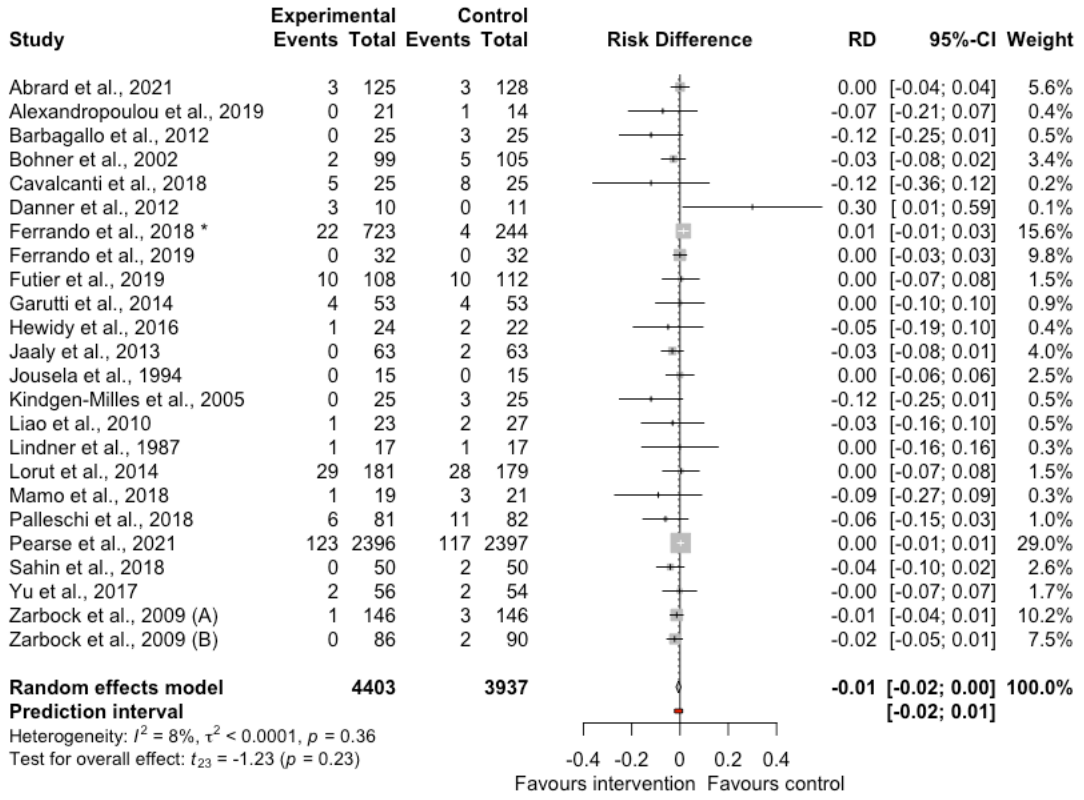

Figure 2. Forest plot of the effect of routine postoperative non-invasive respiratory support on postoperative development of pneumonia. A random effects model was used to calculate the risk difference and is presented along with its associated 95% confidence interval. *Ferrando et al., 2018: this study had three intervention arms and one control arm; to avoid unit-of-analysis error, the outcomes for the three intervention groups were merged for this analysis.

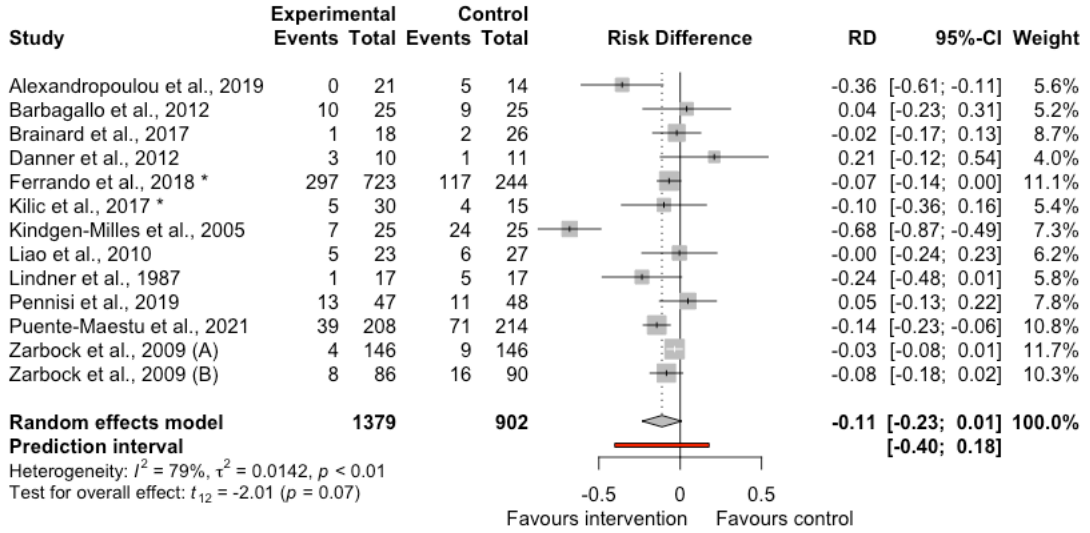

Figure 3. Forest plot of the effect of routine postoperative non-invasive respiratory support on postoperative pulmonary complications. A random effects model was used to calculate the risk difference and is presented along with its associated 95% confidence interval. *Ferrando et al., 2018 and Kilic et al., 2017: these studies had more than two or more intervention arms and one control arm; to avoid unit-of-analysis error, the outcomes for the intervention groups were merged for this analysis.

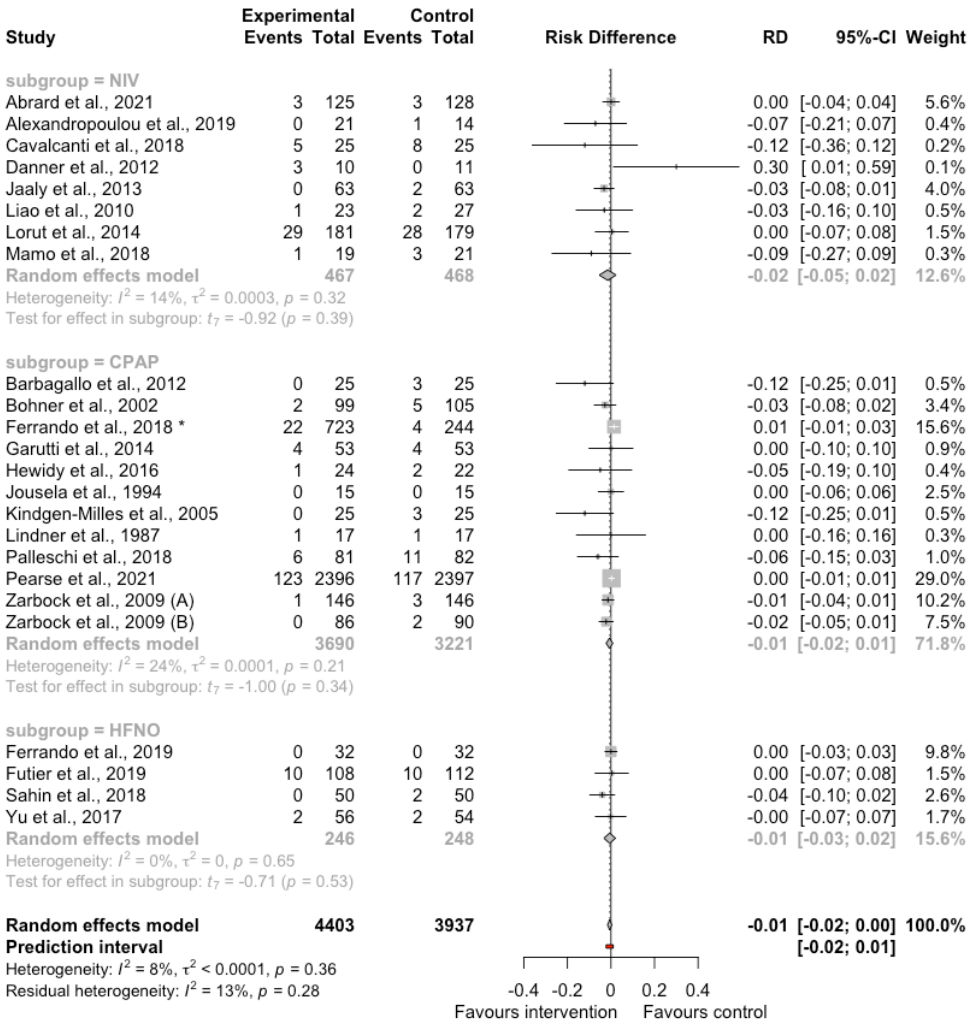

Figure 4. Subgroup analysis: forest plot of the effects of the different non-invasive respiratory support modalities on postoperative development of pneumonia. A random effects model was used to calculate the risk difference and is presented along with its associated 95% confidence interval. *Ferrando et al., 2018: this study had three intervention arms and one control arm; to avoid unit-of-analysis error, the outcomes for the three intervention groups were merged for this analysis.

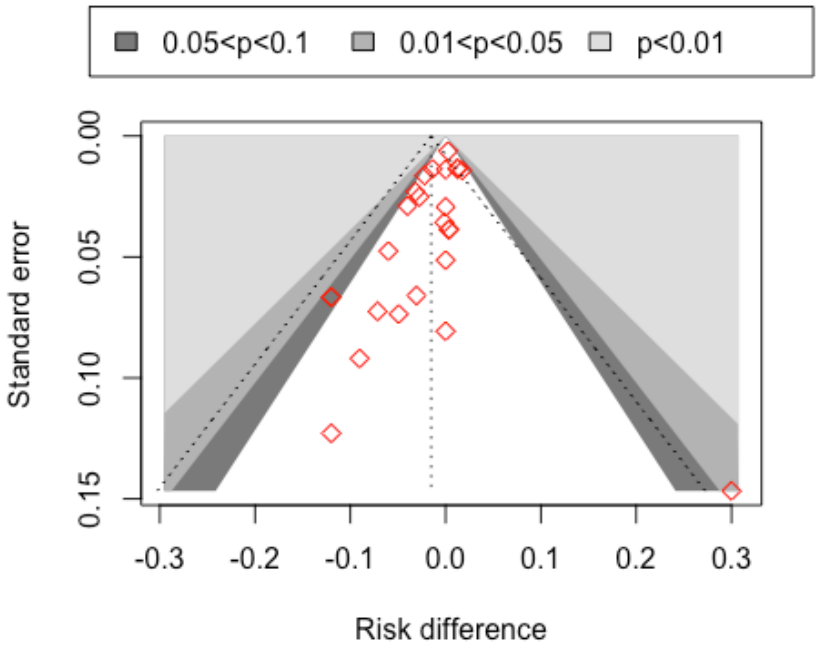

Figure 5. Funnel plot for the primary outcome of routine postoperative non-invasive respiratory support versus standard postoeprative care. Eggers test confirmed asymmetry in the plot (t = -0.7; p=0.03).