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The effects of high perioperative inspiratory oxygen fraction for adult surgical patients (Review)

Wetterslev J, Meyhoff CS, Jørgensen LN, Gluud C, Lindschou J, Rasmussen LS

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[Intervention Review]

The effects of high perioperative inspiratory oxygen fraction for adult surgical patients

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ABSTRACT

Background

Available evidence on the effects of a high fraction of inspired oxygen (FIO₂) of 60% to 90% compared with a routine fraction of inspired oxygen of 30% to 40%, during anaesthesia and surgery, on mortality and surgical site infection has been inconclusive. Previous trials and meta-analyses have led to different conclusions on whether a high fraction of supplemental inspired oxygen during anaesthesia may decrease or increase mortality and surgical site infections in surgical patients.

Objectives

To assess the benefits and harms of an FIO₂ equal to or greater than 60% compared with a control FIO₂ at or below 40% in the perioperative setting in terms of mortality, surgical site infection, respiratory insufficiency, serious adverse events and length of stay during the index admission for adult surgical patients.

We looked at various outcomes, conducted subgroup and sensitivity analyses, examined the role of bias and applied trial sequential analysis (TSA) to examine the level of evidence supporting or refuting a high FIO₂ during surgery, anaesthesia and recovery.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, BIOSIS, International Web of Science, the Latin American and Caribbean Health Science Information Database (LILACS), advanced Google and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) up to February 2014. We checked the references of included trials and reviews for unidentified relevant trials and reran the searches in March 2015. We will consider two studies of interest when we update the review.

Selection criteria

We included randomized clinical trials that compared a high fraction of inspired oxygen with a routine fraction of inspired oxygen during anaesthesia, surgery and recovery in individuals 18 years of age or older.

Data collection and analysis

Two review authors extracted data independently. We conducted random-effects and fixed-effect meta-analyses, and for dichotomous outcomes, we calculated risk ratios (RRs). We used published data and data obtained by contacting trial authors.

To minimize the risk of systematic error, we assessed the risk of bias of the included trials. To reduce the risk of random errors caused by sparse data and repetitive updating of cumulative meta-analyses, we applied trial sequential analyses. We used Grades of Recommendation, Assessment, Development and Evaluation (GRADE) to assess the quality of the evidence.

Main results

We included 28 randomized clinical trials (9330 participants); in the 21 trials reporting relevant outcomes for this review, 7597 participants were randomly assigned to a high fraction of inspired oxygen versus a routine fraction of inspired oxygen.

In trials with an overall low risk of bias, a high fraction of inspired oxygen compared with a routine fraction of inspired oxygen was not associated with all-cause mortality (random-effects model: RR 1.12, 95% confidence interval (CI) 0.93 to 1.36; GRADE: low quality) within the longest follow-up and within 30 days of follow-up (Peto odds ratio (OR) 0.99, 95% CI 0.61 to 1.60; GRADE: low quality). In a trial sequential analysis, the required information size was not reached and the analysis could not refute a 20% increase in mortality. Similarly, when all trials were included, a high fraction of inspired oxygen was not associated with all-cause mortality to the longest follow-up (RR 1.07, 95% CI 0.87 to 1.33) or within 30 days of follow-up (Peto OR 0.83, 95% CI 0.54 to 1.29), both of very low quality according to GRADE. Neither was a high fraction of inspired oxygen associated with the risk of surgical site infection in trials with low risk of bias (RR 0.86, 95% CI 0.63 to 1.17; GRADE: low quality) or in all trials (RR 0.87, 95% CI 0.71 to 1.07; GRADE: low quality). A high fraction of inspired oxygen was not associated with respiratory insufficiency (RR 1.25, 95% CI 0.79 to 1.99), serious adverse events (RR 0.96, 95% CI 0.65 to 1.43) or length of stay (mean difference -0.06 days, 95% CI -0.44 to 0.32 days).

In subgroup analyses of nine trials using preoperative antibiotics, a high fraction of inspired oxygen was associated with a decrease in surgical site infections (RR 0.76, 95% CI 0.60 to 0.97; GRADE: very low quality); a similar effect was noted in the five trials adequately blinded for the outcome assessment (RR 0.79, 95% CI 0.66 to 0.96; GRADE: very low quality). We did not observe an effect of a high fraction of inspired oxygen on surgical site infections in any other subgroup analyses.

Authors' conclusions

As the risk of adverse events, including mortality, may be increased by a fraction of inspired oxygen of 60% or higher, and as robust evidence is lacking for a beneficial effect of a fraction of inspired oxygen of 60% or higher on surgical site infection, our overall results suggest that evidence is insufficient to support the routine use of a high fraction of inspired oxygen during anaesthesia and surgery. Given the risk of attrition and outcome reporting bias, as well as other weaknesses in the available evidence, further randomized clinical trials with low risk of bias in all bias domains, including a large sample size and long-term follow-up, are warranted.

PLAIN LANGUAGE SUMMARY

The effects of giving adult patients a high inspiratory oxygen fraction around the time of surgery

Review question

The normal air that we breathe contains 21% oxygen. This systematic review assesses the beneficial and harmful effects of a percentage of inspired oxygen of 60% to 90% compared with a routine percentage of 30% to 40% given during anaesthesia, during surgery and in the immediate recovery period on the numbers of deaths and surgical site infections reported in adult surgical patients.

Background

Reduced lung and circulatory function during surgery can lead to reduced levels of oxygen (hypoxia). Also, oxygen levels are often low in wounds at the end of surgery. This may impair bacterial killing and wound healing. Trials and previous meta-analyses have led to different conclusions as to whether a high percentage of inspired oxygen during anaesthesia may decrease or increase the risk of death or surgical site infections. This systematic review used improved Cochrane methodology for carrying out systematic reviews to reassess available evidence derived from randomized clinical trials.

Study characteristics

We identified 28 randomized clinical trials. Eight trials with 4918 participants reported on risk of death, and 15 trials with 7219 participants reported on surgical site infections within 14 to 30 days of surgery. Four trials reported serious adverse events, three trials respiratory insufficiency, nine trials length of stay during the associated hospital admission and one trial quality of life. All trials were conducted without direct industry funding.

The number of participants in each trial ranged from 38 to 1012. The mean age of participants was 50 years (range 15 to 92 years) and 63% were women. Types of surgery included abdominal surgery (eight trials), caesarean section (four trials), breast surgery (one trial), orthopaedic surgery (two trials) and various other surgical procedures (four trials).

Key results

A high percentage of inspired oxygen was not statistically associated with increased risk of death, or with a decrease in surgical site infections, in all trials that measured these outcomes, in trials of highest quality and in those with longest follow-up.

An increased risk of adverse events could not be proved right or wrong for a high percentage of inspired oxygen during anaesthesia and surgery.

Quality and quantity of the evidence

Only five of the included trials had low risk of bias. The trials randomly assigned 9330 participants, of whom only 7537 participants provided data for this review. The number of participants required to detect or reject a 20% relative risk reduction in deaths was not reached; therefore the observed results were uncertain.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Summary of findings in randomized clinical trials with overall low risk of bias and in all trials

Fraction of inspired oxygen of 60% to 90% compared with 30% to 40% oxygen during anaesthesia, surgery and recovery

Patient or population: surgical patients with need for abdominal, caesarean section, orthopaedic or breast surgery

Settings: perioperative and postoperative

Intervention: high fraction of inspired oxygen of 60% to 90% during and after surgery and anaesthesia

Comparison: fraction of inspired oxygen of 30% to 40% during and after anaesthesia and surgery

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk*	Corresponding risk#				
	Inspired fraction of oxygen (30% to 40%)	Inspired fraction of oxygen (60% to 90%)				
Mortality within the longest follow-up in trials with overall low risk of bias (follow-up: 30 days to a median of 3.9 years)	High-risk population		RR 1.12 (0.93 to 1.36)	4758 (3)	⊕⊕⊕⊕ Low^a	TSA (Figure 1) shows that the required information size of 10,736 for a 20% RRI has not been achieved, and that no trial sequential monitoring boundaries have been crossed. The TSA adjusted CI for the RR is 0.73 to 1.60. The required information size is even greater for a lower effect on mortality than a 20% RRI. We therefore downgraded by 1 level for imprecision and by 1 level for attrition bias (Analysis 1.2; Analysis 1.3)
	185 per 1000 (168 to 203)	208 per 1000 (190 to 226)				
Mortality within the longest follow-up, irrespective of risk of bias (14 days to median of 3.9 years)	164 per 1000 (150 to 180)	175 per 1000 (143 to 218)	RR 1.07 (0.87 to 1.33)	4525 (6)	⊕⊕⊕⊕ Very low^b	TSA (Figure 2) shows that the required information size for a 20% RRI has not been achieved, and that no trial sequential monitoring boundaries have been crossed. The required information size for a lower excess mortality than a 20% RRI is even greater. We therefore downgraded by 1 level for imprecision, by 1 level for high risk of attrition bias (Analysis 1.2; Analysis 1.3) and by 1 level for overall risk of bias

Mortality with-in 30 days of follow-up with over-all low risk of bias (14 days to 30 days)	18 per 1000 (13 to 25)	18 per 1000 (13 to 25)	POR 0.99 (0.61 to 1.60)	4758 (3)	⊕⊕⊕⊕ Moderate^c	The required information size for a 20% RRI has not been reached, and no trial sequential monitoring boundaries have been crossed
Mortality with-in 30 days of follow-up, irrespective of risk of bias (14 days to 30 days)	20 per 1000 (15 to 27)	17 per 1000 (11 to 26)	POR 0.83 (0.54 to 1.29)	4525 (6)	⊕⊕⊕⊕ Low^d	TSA shows that the required information size for a 20% RRI has not been achieved, and that no trial sequential monitoring boundaries have been crossed. The required information size for a lower excess mortality than a 20% RRI is even greater. We therefore downgraded by 1 level for imprecision and by 1 level for overall risk of bias
Surgical site infection within 30 days in trials with low risk of bias (14 days to 30 days)	140 per 1000 (126 to 155)	119 per 1000 (106 to 134)	RR 0.86 (0.63 to 1.17)	4201 (5)	⊕⊕⊕⊕ Low^a	TSA (Figure 3) shows that the required information size of 13,189 participants for a 20% RRR has not been achieved, and that no trial sequential monitoring boundaries have been crossed. The required information size is even greater for a lower effect on mortality than a 20% RRR. Best/worst and worst/best case scenarios indicate possible attrition bias. Therefore we downgraded by 1 level for imprecision and by 1 level for attrition bias
Surgical site infection within 30 days, irrespective of risk of bias (14 days to 30 days)	129 per 1000 (118 to 140)	112 per 1000 (92 to 138)	RR 0.87 (0.71 to 1.07)	7229 (15)	⊕⊕⊕⊕ Low^e	TSA (Figure 3) shows that the required information size of 13,189 participants for a 20% RRR of surgical site infection has not been reached, and that no trial sequential monitoring boundaries have been crossed. The required information size for a lower effect on surgical site infection than a 20% RRR is even greater. As the result of overall risk of bias and imprecision, we downgraded by 2 levels
Respiratory insufficiency	44 per 1000 (31 to 62)	55 per 1000 (35 to 88)	RR 1.25 (0.79 to 1.99)	1386 (1)	⊕⊕⊕⊕ Moderate^c	Information size is too small to be conclusive. We downgraded by 1 level for imprecision

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **LCL**: Lower confidence limit; **MD**: Mean difference; **POR**: Peto odds ratio; **RR**: Risk ratio; **RRR**: relative risk reduction; **RRI**: relative risk increase; **TSA**: trial sequential analysis; **UCL**: Upper confidence limit.

GRADE Working Group grades of evidence.

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

- *Mean of mortality in groups of included trials with 30% to 40% inspiratory fraction of oxygen.
#Calculated from: $RR \times \text{assumed risk}$ (95% CL: LCL of $RR \times \text{assumed risk}$ to UCL of $RR \times \text{assumed risk}$).
^aDowngraded by 2 levels because of risk of attrition bias and imprecision.
^bDowngraded by 3 levels because of risk of attrition bias, imprecision and overall risk of bias.
^cDowngraded by 1 level because of imprecision.
^dDowngraded by 2 levels because of overall risk of bias and imprecision.
^eDowngraded by 2 levels because of overall risk of bias and imprecision.

Figure 1. Funnel plot of comparison: 1 60% to 90% oxygen vs 30% to 40% oxygen perioperatively, outcome: 1.5 Surgical site infection stratified according to overall risk of bias in a random-effects model.

Figure 2. Trial sequential analysis of the effect on mortality within the longest follow-up in trials with overall low risk of bias. With an anticipated relative risk increase (RRI) of 20%, mortality in the control group of 15.7% with a type 1 error of 5% and a type 2 error of 20%, and diversity (D^2) of 57%, the required information size is 10,736 participants. The cumulative Z-curve does not cross the conventional boundary nor the trial sequential monitoring boundary for harm. The cumulative Z-curve does not reach the futility area. Therefore evidence of an effect on all-cause mortality based on trials with low risk of bias is lacking, and we cannot exclude a 20% RRI due to lack of data.

Figure 3. Trial sequential analysis of all trials reporting all-cause mortality. With an anticipated relative risk increase (RRI) of 20%, mortality in the control group of 15.7% with a type 1 error of 5% and a type 2 error of 20% and diversity (D^2) of 65%, the required information size is 13,264 participants. The cumulative Z-curve does not cross the conventional boundaries nor the boundaries for benefit or harm. The cumulative Z-curve does not reach the futility area. Therefore evidence of both beneficial and harmful effects on all-cause mortality is lacking for all trials regardless of risk of bias and with varying time to follow-up. We cannot exclude a 20% RRI or RRR due to lack of data.

BACKGROUND

Trials by Greif et al (Greif 2000) and by Belda et al (Belda 2005) have suggested a significant reduction in the frequency of surgical wound infections within 30 days when 80% rather than 30% oxygen was given for inspiration during surgery and the first postoperative hours. On the other hand, the PROXI trial (Meyhoff 2009) found no significant differences and the trial of Mayzler et al (Mayzler 2005) was inconclusive because these studies had very low power. The trial by Gardella et al (Gardella 2008) was stopped early, as it was unlikely that investigators were going to show the anticipated difference if continued, and the trial by Pryor et al (Pryor 2004) was stopped prematurely because the frequency of wound infection was more than doubled in the high oxygen fraction group. High inspiratory oxygen concentrations have been associated with adverse outcomes in a variety of emergency medical conditions, including exacerbation of chronic obstructive pulmonary disease (Austin 2010), myocardial infarction (Cabello 2013), resuscitation after cardiac arrest (Kilgannon 2010) and traumatic brain injury (Brenner 2012).

The ENIGMA trial provided long-term follow-up data for 83% of participants (Leslie 2011) with an unadjusted hazard ratio (HR) for death with 80% oxygen compared with 30% oxygen of 1.09 (95% confidence interval (CI) 0.90 to 1.35). Recently Meyhoff et al (Meyhoff 2014) reported long-term follow-up (median 3.9 years) from the PROXI trial with similar rates of new and recurrent cancer with 80% versus 30% oxygen during anaesthesia and surgery within the observation time. However, the HR for death, new cancer or recurrent cancer was increased with a high fraction of inspired oxygen (HR 1.19, 95% CI 1.01 to 1.42), indicating a median of 99 days shorter time to death or new or recurrent cancer. Accordingly evidence suggests that a high fraction of inspired oxygen during anaesthesia and surgery may be associated with an increased number of adverse events, as well as beneficial effects on surgical site infection (Hovaguimian 2013).

At least one large trial (Myles 2007) reported a lower rate of major complications with nitrous oxide-free anaesthesia. However, recent data indicate that the presence of adjuvant nitrous oxide in the inhaled gas mixture during anaesthesia does not affect clinically important outcomes after surgery (Fleischmann 2005; Imberger 2014; Myles 2014; Myles 2014b).

We undertook this review to investigate all available evidence on benefits and harms for mortality and surgical site infection with an inspiratory fraction of oxygen of 60% to 90% compared with a routine fraction of 30% to 40% oxygen during anaesthesia, surgery and recovery.

Description of the condition

According to the criteria of the Centers for Disease Control and Prevention (CDC), surgical site infection may consist of superficial or deep wound infection or intra-abdominal organ or space infection (Mangram 1999). The condition may or may not be accompanied by a positive bacterial culture. The CDC criteria (CDC 2009) for diagnosing surgical site infection are listed in Appendix 1. Surgical site infection is a common and serious complication following surgery, especially after abdominal surgery (Coello 2005). Surgical site infection may or may not be defined according to the criteria developed by the CDC (CDC 2009). We evaluated the

investigators' definitions of surgical site infection with respect to CDC criteria.

Description of the intervention

After induction of anaesthesia and tracheal intubation, participants randomly assigned to a high fraction of inspired oxygen (FIO₂) were given an FIO₂ equal to or above 60% until the end of surgery. Additionally, in the first two hours following extubation, these participants might have breathed an FIO₂ equal to or above 60% as administered by means of a face mask with a reservoir and a high flow mixture of oxygen and air (around 16 L/min). Participants randomly assigned to the control FIO₂ were given an FIO₂ at or below 40% after tracheal intubation; after extubation, they received a high flow (around 16 L/min) mixture of oxygen and air through an identical face mask.

How the intervention might work

To prevent surgical site infection, it is essential to optimize perioperative conditions, as the first hours following bacterial contamination are pivotal for avoiding an established infection (Hopf 2008; Miles 1957). Oxygen tension is often low in wounds and in colorectal anastomoses at the end of surgery. This may reduce bacterial eradication, the body's defences against bacteria and tissue healing. Possible mechanisms occur via diminished oxidative killing by neutrophils and impaired tissue healing caused by reduced collagen formation, neovascularization and epithelialization (Allen 1997; Babior 1978; Hopf 1997; Hopf 2008; Niinikoski 1977). Perioperative arterial and wound oxygen tension may be increased by a higher inspiratory oxygen fraction (Greif 2000; Hopf 1997). However, wound oxygen tension is low in hypoperfused patients and may not increase much with a high fraction of inspiratory oxygen (Gottrup 1987; Jonsson 1987). Further, many of the antibiotics used perioperatively are oxygen-dependent in their effect; it is therefore possible that patients receiving a high FIO₂ will benefit more from these antibiotics than patients receiving antibiotics without an elevated oxygen fraction. Beneficial effects have also been reported for other outcomes such as improved healing of colorectal anastomoses (García-Botello 2006) and reduced postoperative nausea and vomiting (Greif 1999; Turan 2006).

Hyperoxia throughout the perioperative period may result in pulmonary complications, but this important aspect or oxygenation has been studied in only 30 patients (Akca 1999b). In a subgroup of participants from the trial by Greif et al (Greif 2000), a statistically non-significant trend towards larger areas of atelectasis (collapsed areas of the lung) in the 80% oxygen group was observed on computed tomography scans (Akca 1999b). The PROXI trial by Meyhoff et al (Meyhoff 2009) found no significant differences in proportions of atelectasis, pneumonia or respiratory failure, but a trend towards higher mortality was found in the 80% oxygen group. More specifically, a high inspiratory oxygen fraction has been associated with detrimental effects such as increased airway inflammation (Carpagno 2004); poor regulation of blood glucose, which may affect healing (Bandali 2003); and decreased cardiac output/index (Harten 2003).

Why it is important to do this review

Complications after surgery are numerous and range from minor problems to fatalities, especially after emergency and upper

abdominal procedures. The proportion of patients developing surgical site infections varies across types of surgery and reaches 10% to 20% for open abdominal surgery (Meyhoff 2009; Pryor 2004). Surgical site infection is a significant complication for all surgical patients and increases the risk of sepsis, admission to an intensive care unit (ICU), incisional hernia and hospital stay (Gotzsche 2000). Moreover, surgical site infection causes a heavy workload and an economic burden for hospitals as well as society. A high FIO₂ administered to surgical patients, equal to or greater than 60% oxygen, is an easily applied and inexpensive intervention with few known/unknown contraindications or adverse events. However, several trials have reported contradictory results, and the benefits and harms of an FIO₂ equal to or greater than 60%, as compared with a control FIO₂ at or below 40%, are presently uncertain. Although several meta-analyses and reviews have been published (Al-Niaimi 2009; Chura 2007) they have not included recent trials, they have emphasized the fixed-effect model and they have not assessed bias control according to the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Recently, several trials (Duggal 2013; Schietroma 2013; Scifres 2011; Stall 2013; Thibon 2012) that tested the effects of an FIO₂ of 80% compared with 30% on the occurrence of surgical site infection have been published. Likewise, three meta-analyses (Hovaguimian 2013; Klingel 2013; Patel 2012) have been published within the past two years, and none of these have used stringent Cochrane methodology to assess risk of bias or to perform Grades of Recommendation, Assessment, Development and Evaluation (GRADE) of the overall quality of the evidence. Further, these meta-analyses have not determined the information size required to detect or reject a 20% relative risk reduction (RRR) or increase (RRI), and they have not used trial sequential analysis (TSA) to assess whether sufficient evidence was obtained before the required information size was reached (Wetterslev 2008; Wetterslev 2009). These meta-analyses therefore are prone to increased risk of random error due to sparse data and repetitive testing because of multiple updating, as new trials are included in the cumulative meta-analyses.

OBJECTIVES

To assess the benefits and harms of an FIO₂ equal to or greater than 60% compared with a control FIO₂ at or below 40% in the perioperative setting in terms of mortality, surgical site infection, respiratory insufficiency, serious adverse events and length of stay during the index admission for adult surgical patients.

We looked at various outcomes, conducted subgroup and sensitivity analyses, examined the role of bias and applied TSA (Brok 2008; Brok 2009; Thorlund 2009; Wetterslev 2008; Wetterslev 2009) to examine the level of evidence supporting or refuting a high FIO₂ during surgery, anaesthesia and recovery.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized clinical trials (RCTs) without consideration of publication status, blinding status or language. We contacted investigators and study authors to retrieve relevant data.

We included unpublished trials only if trial data and methodological descriptions were provided in written form or by direct contact with study authors.

We excluded trials using quasi-randomization and observational studies for the study of benefits. However, we were not able to establish an appendix enumerating the findings from observational studies regarding adverse events, as we did not find any. We excluded cross-over trials even if they compared high FIO₂ with routine FIO₂ during the perioperative period.

Types of participants

We included surgical patients 18 years of age or older who were undergoing elective or emergency surgery.

Types of interventions

We compared a high FIO₂ of 60% or above with a control FIO₂ of 40% or below during surgery or both during surgery and during time spent in the postanaesthetic care unit.

Types of outcome measures

Primary outcomes

1. All-cause mortality: assessed according to the longest follow-up period for each trial.
2. Surgical site infection within 30 days of follow-up after surgery: defined by investigators of involved trials or according to the criteria of the CDC (Appendix 1) as superficial or deep wound infection or intra-abdominal organ or space infection (Mangram 1999).

Secondary outcomes

1. All-cause mortality within 30 days of follow-up.
2. Respiratory insufficiency: defined as the need for respiratory assistance provided as ventilator therapy or non-invasive ventilation within the longest follow-up period.
3. Serious Adverse events: with a serious adverse event defined, according to the International Conference on Harmonisation Guidelines and the European Directive (Directive 2001), as "any event that leads to death, was life-threatening, required in-patient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability, and any important medical event, which may have jeopardised the patient or required intervention to prevent it". All other adverse events were considered to be non-serious events.
4. Duration of postoperative hospitalizations.
5. Quality of life as measured by the included trials.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (2014, Issue 2); SilverPlatter MEDLINE (WebSPIRS) (1950 to February 2014); SilverPlatter EMBASE (WebSPIRS) (1980 to February 2014); SilverPlatter BIOSIS (WebSPIRS) (1993 to February 2014); International Web of Science (1964 to February 2014); Latin American Caribbean Health Sciences Literature (LILACS via BIREME) (1982 to February 2014); the Chinese Biomedical Literature Database; advanced Google and the Cumulative Index to Nursing and Allied Health Literature (CINAHL via EBSCO host) (1980 to

February 2014). We reran the searches in March 2015. We will consider studies of interest when we update the review.

We performed systematic and sensitive searches to identify relevant RCTs without language or date restrictions. These searches were conducted within six months of the date the draft review was emailed to the editorial office. For specific information regarding our search strategies, please see the Appendices ([Appendix 2](#), MEDLINE; [Appendix 3](#), EMBASE; [Appendix 4](#), CENTRAL; [Appendix 5](#), Web of Science; [Appendix 6](#), CINAHL).

We searched for ongoing clinical trials and unpublished studies on the following Internet sites.

1. [Current Controlled Trials](#).
2. [ClinicalTrials.gov](#).
3. [www.centerwatch.com](#).

Searching other resources

We handsearched the reference lists of reviews, randomized and non-randomized studies and editorials to look for additional studies. Moreover, we contacted the main authors of studies and experts in this field to ask about missed, unreported or ongoing trials.

Data collection and analysis

Selection of studies

Two review authors (JW and CSM) independently evaluated all relevant trials and provided a detailed description of included and excluded articles under the sections [Characteristics of included studies](#) and [Characteristics of excluded studies](#), respectively. We also provided a detailed description of our search results.

Data extraction and management

We screened titles and abstracts to identify studies for eligibility. JW and CSM independently extracted and collected data on a standardized paper form ([Appendix 7](#)). We were not blinded to the study author, institution or publication source of trials. We resolved disagreements by discussion. We approached all corresponding authors of included trials to ask for additional information relevant to the review's outcomes measures and risk of bias domains. For more specific information, please see the section [Contributions of authors](#).

Assessment of risk of bias in included studies

We evaluated the validity and design characteristics of each trial. To draw conclusions about the overall risk of bias for an outcome, it is necessary to evaluate the trials for major sources of bias, also defined as domains (random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other sources of bias). The tool recommended by The Cochrane Collaboration for assessing risk of bias is neither a scale nor a checklist but rather a domain-based evaluation. Any assessment of the overall risk of bias involves consideration of the relative importance of the different domains ([Higgins 2011](#)).

Even the most realistic assessment of the validity of a trial may involve subjectivity, as it is impossible to know the extent of bias (or even the true risk of bias) in a given trial. Some domains affect

the risk of bias across outcomes in a trial, for example, sequence generation and allocation sequence concealment; others such as blinding and incomplete outcome data may present different risks of bias for different outcomes within a trial. Thus, the risk of bias is not the same for all outcomes in a trial. We performed separate sensitivity analyses for patient-reported outcomes (subjective outcomes) and for mortality ([Higgins 2011](#)).

We defined trials as having low risk of bias only if they adequately fulfilled the criteria listed in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)) and reproduced in [Appendix 8](#); we performed summary assessments of the risk of bias for each important outcome (across domains) within and across studies and prepared a 'Risk of bias graph' and a 'Risk of bias summary figure' ([Higgins 2011](#)).

We presented results for all outcomes including adverse events in [Summary of findings for the main comparison](#) ([Higgins 2011](#)).

As no sufficiently well-designed formal statistical method was available by which to combine the results of trials with high and low risk of bias, the principal approach to incorporating risk of bias assessments into Cochrane reviews is to restrict meta-analyses to trials with low (or lower) risk of bias ([Higgins 2011](#)). We used the risk of bias (ROB) table described in the *Cochrane Handbook for Systematic Reviews of Interventions*, section 8.5 ([Higgins 2011](#)), as a tool for assessing risk of bias in included trials. We assessed risk of bias in the different domains as described in [Appendix 8](#).

Measures of treatment effect

We reported length of stay in hospital after surgery, in days, as a continuous outcome, and the intervention effect as the mean difference with 95% confidence interval. All other outcomes are dichotomous and were reported as risk ratios (RRs) with 95% confidence limits. For mortality, we calculated the Peto odds ratio (POR). We also calculated the risk difference (RD) with 95% confidence interval and subsequently numbers needed to treat for an additional beneficial outcome, when possible.

Unit of analysis issues

Numbers of events in all binary meta-analyses and days in the meta-analysis of length of stay in hospital after surgery.

Dealing with missing data

We contacted all first study authors and contact persons for trials with missing data to retrieve the relevant data. We performed a modified intention-to-treat (ITT) analysis, including, if possible, all randomly assigned participants who underwent surgery, or who did not withdraw their consent before surgery.

Intention-to-treat analysis is recommended to minimize bias in the design, follow-up and analysis of efficacy of RCTs. It yields a pragmatic estimate of the benefit of a change in treatment policy rather than a measure of the potential benefit in patients who receive treatment exactly as planned ([Hollis 1999](#)). Full application of ITT is possible only when complete outcome data are available for all randomly assigned participants. Despite the fact that about half of all published reports of RCTs state that ITT analysis was used, handling of deviations from randomized allocation varies widely, and in many trials data for the primary outcome variable are missing. Methods used to deal with this are generally inadequate, potentially leading to bias ([Hollis 1999](#)).

Performing an ITT analysis in a systematic review is not straightforward, as review authors must decide how to handle outcome data that are missing from contributing trials (Gamble 2005). No consensus has been reached regarding how missing data should be handled in ITT analyses, and different approaches may be appropriate in different situations (Higgins 2011; Hollis 1999).

In cases of missing data, for our primary outcomes we used a 'complete-case analysis' by simply excluding all participants for whom the outcome was missing from the analysis. Additionally, we conducted sensitivity analyses for our primary outcomes by applying best/worst and worst/best case scenarios.

Best case scenarios included the following: All participants lost to follow-up in the high FIO₂ group survived, and all participants lost to follow-up in the FIO₂ below 40% group died; all participants lost to follow-up in the high FIO₂ group did not have a surgical site infection, and all participants lost to follow-up in the FIO₂ below 40% group did have a surgical site infection. Worst case scenarios included these: All participants lost to follow-up in the high FIO₂ group died, and all participants lost to follow-up in the FIO₂ below 40% group survived; all participants lost to follow-up in the high FIO₂ group had a surgical site infection, and all participants lost to follow-up in the FIO₂ below 40% group did not have a surgical site infection.

Selective outcome reporting occurs when non-significant results are selectively withheld from publication (Chan 2004). It is defined as selection, on the basis of results, of a subset of the original recorded variables for inclusion in the publication of a trial. The most important types of selective outcome reporting are selective omission of outcomes from reports; selective choice of data for an outcome; selective reporting of analyses using the same data; selective reporting of subsets of data and selective underreporting of data (Higgins 2011b). Statistical methods developed to detect within-study selective reporting are still in their infancy stage. We explored selective outcome reporting by comparing publications with their protocols, when the latter were available.

Assessment of heterogeneity

We quantified the degree of heterogeneity observed in the results by using diversity (D²) (Wetterslev 2009) and inconsistency factor (I²) statistics, which can be interpreted as the proportion of the total variation observed between trials that is attributable to differences between trials rather than to sampling error (chance) (Higgins 2002). P value ≤ 0.10 indicates significant heterogeneity, and suggested I² statistic thresholds for low, moderate and high heterogeneity are 25% to 49%, 50% to 74% and ≥ 75%, respectively (Higgins 2003). If I² = 0, we reported results using the random-effects model only. In the case of I² > 0, we reported results using both random-effects and fixed-effect models. However, we believed that using a fixed-effect model offered little value in cases of substantial heterogeneity, which may be present in this review because of inclusion of various patient types, as well as variable adjuvant gases, definitions of surgical site infection and outcome reporting. So we emphasized the results from the random-effects model analysis unless a few trials dominated the meta-analysis (e.g. > 50% of the accumulated fixed weight percentage). Additionally, in cases of I² > 0 (for mortality and surgical site infection outcomes), we sought to determine the cause

of heterogeneity by performing meta-regression analyses and relevant subgroup and sensitivity analyses. We aimed to combine trial results in a meta-analysis only when clinical heterogeneity was low to moderate.

Assessment of reporting biases

Publication bias occurs when publication of research results depends on their nature and direction (Dickersin 1990). We examined this by providing funnel plots to detect publication bias or differences between smaller and larger studies (small study effects), expressed as asymmetry of the funnel plot (Egger 1997). In cases of asymmetry, we applied the Arcsine-Thompson test as proposed by Rücker (Rücker 2008).

Funding bias is defined as bias in the design, outcome and reporting of industry-sponsored research showing that a drug has a favourable outcome (Bekelman 2003). Relationships between industry, scientific investigators and academic institutions are widespread and often result in conflicts of interest (Bekelman 2003). We conducted a sensitivity analysis to examine the role of funding bias when relevant (see Sensitivity analysis).

Data synthesis

We used Review Manager software (RevMan 5.3.3) for statistical analysis. We calculated risk ratios (RRs) with 95% confidence intervals (CIs) for dichotomous variables (binary outcomes). We also calculated risk differences (RDs) (Keus 2009); if results were similar, we reported only RRs. Additionally, we calculated mean differences (MDs) as measures of absolute change with 95% CIs for continuous outcomes. We used D² (Wetterslev 2009) and I² statistics (Higgins 2002) to describe heterogeneity among the included trials. We explored causes of substantial heterogeneity by performing meta-regression using Comprehensive Meta-Analysis (CMA, version one) and Stata, version 13. We used the Chi² test to provide an indication of heterogeneity between studies, with P value ≤ 0.10 considered significant.

Adverse events may be rare but serious, and hence important (Sutton 2002), when meta-analysis is applied to combined results from several trials reporting binary outcomes (i.e. event or no event). First, we applied the Peto odds ratio (POR) in cases of small event proportions. Most meta-analytical software packages do not include options for analyses to calculate RRs when included trials have 'zero events' in both arms (intervention vs control). Exempting these trials from calculations of RRs and CIs may lead to overestimation of a treatment effect, as the control event proportion may be overestimated. Thus we performed a sensitivity analysis by applying empirical continuity corrections to our zero event trials, as proposed by Sweeting et al (Keus 2009; Sweeting 2004), by applying an imaginary small mortality in both arms (Higgins 2011). We used trial sequential analysis (TSA) (Thorlund 2011).

Meta-analyses may result in type 1 errors as the result of sparse data and repeated significance testing following updates with new trials (Brok 2008; Brok 2009; Thorlund 2009; Wetterslev 2008; Wetterslev 2009). Systematic errors from trials with high risk of bias, outcome reporting bias, publication bias, early stopping for benefit and small trial bias may result in spurious P values.

In a single trial, interim analysis increases the risk of type 1 errors. To avoid type 1 errors, group sequential monitoring boundaries

(Lan 1983) are applied to show whether a trial could be terminated early because of a sufficiently small P value, that is, when the cumulative Z-curve crosses the monitoring boundary. Sequential monitoring boundaries can be applied to meta-analyses as well and are called trial sequential monitoring boundaries (TSMB). In TSA, the addition of each trial to a cumulative meta-analysis is regarded as an interim meta-analysis and reveals whether additional trials are needed (Higgins 2011; Thorlund 2011; Wetterslev 2008). So far several meta-analyses and reviews have been published, providing an increasing quantity of trial results as new trials have been published (Al-Niaimi 2009; Chura 2007; Qadan 2009). Therefore adjusting new meta-analyses for multiple testing on accumulating data seems appropriate for controlling the overall type 1 error risk in cumulative meta-analysis (Pogue 1997; Pogue 1998; Thorlund 2009; Wetterslev 2008).

In TSA if the cumulative Z-curve crosses the boundary, a sufficient level of evidence is reached and no further trials may be needed. However, evidence is insufficient to allow a conclusion if the Z-curve does not cross the boundary or does not surpass the required information size. To construct the TSMB, the required information size is needed and will be calculated as the least number of participants needed in a well-powered single trial (Brok 2008; Pogue 1998; Thorlund 2011; Wetterslev 2008). We adjusted the required information size for heterogeneity by using the diversity adjustment factor (Wetterslev 2009). We applied TSA, as it prevents an increase in the risk of type 1 errors (< 5%) due to potential multiple updating and testing on accumulating data whenever new trial results are included in a cumulative meta-analysis (Pogue 1997; Pogue 1998). This provided important information to permit estimation of the level of evidence on the experimental intervention (Pogue 1997; Pogue 1998; Thorlund 2009), and to determine the need for additional trials and their required sample sizes (Wetterslev 2008; Wetterslev 2009; Wetterslev 2010; Wetterslev 2012; Wetterslev 2012b). We applied TSMB according to an information size suggested by trials with low risk of bias (Wetterslev 2008; Wetterslev 2009) and an a priori 20% relative risk reduction (RRR) of surgical site infection, using a control event proportion suggested by large observational studies and by the pooled estimate of event proportions in the control groups of included trials. As mortality seemed low in trials conducted when the protocol was finished, and hence the ability to detect small intervention effects was lacking, we also performed a TSA using an information size estimated for an a priori 35% RRR of mortality (Wetterslev 2008; Wetterslev 2009).

Subgroup analysis and investigation of heterogeneity

We conducted the following subgroup analyses by assessing the benefits and harms of a high FIO₂ for surgical site infection.

1. Trials using inspiratory oxygen with or without nitrous oxide.
2. Trials using inspiratory oxygen with an FIO₂ of 80% or higher compared with trials using an FIO₂ equal to or greater than 60% but lower than 80%.
3. Trials using a high FIO₂ only during surgery or during both surgery and postoperative care.
4. Participants undergoing abdominal surgery according to type of surgery, that is, all kinds of abdominal surgery, procedures requiring laparotomy, upper laparotomy if possible, lower laparotomy if possible or laparoscopic procedures.

5. Type of surgery (abdominal, orthopaedic, other).
6. Whether follow-up for surgical site infection lasted 14 or fewer days or more than 14 days.

We made inferences from subgroup analyses in terms of implications for clinical practice only if the overall analysis of one of the co-primary outcomes became statistically significant. When analyses of co-primary outcomes did not become statistically significant, we referenced them in [Implications for research](#) to provide hypotheses for future research.

We compared intervention effects in subgroups using a test of interaction (Altman 2003). P value < 0.05 was considered indicative of a significant interaction between the high FIO₂ effect on surgical site infection and the subgroup category (Higgins 2011; Chapters 9.6.1 and 9.7).

We explored causes of moderate to high heterogeneity using meta-regression, including mean age of the trial population at baseline. We planned to explore causes of moderate to high heterogeneity using meta-regression with the following co-variables: mean body mass index (BMI) of the trial population at baseline; fraction of participants with diabetes in the trial population at baseline; fraction of smokers in the trial population at baseline; and fraction of participants with a contaminated or dirty infected surgical field during surgery; however, because data were lacking in the included trials, this was not possible.

Sensitivity analysis

1. We compared estimates of the pooled intervention effect in trials with low risk of bias versus estimates from trials with high risk of bias (i.e. trials with at least one unclear or high risk of bias component).
2. We compared estimates of the pooled intervention effect in trials based on different components of risk of bias (random sequence generation, allocation concealment, blinding, follow-up, intention to treat).
3. We assessed benefits and harms of high FIO₂ by conducting a continuity correction of trials with zero events.
4. We assessed benefits and harms of high FIO₂ by conducting sensitivity analyses excluding the smallest or the largest trial.
5. We assessed benefits and harms of high FIO₂ by excluding data from trials published only as abstracts.
6. We assessed benefits and harms of high FIO₂ by excluding data from trials with commercial funding.

We calculated RRs with 95% CIs and applied a complete case analysis, when possible, to sensitivity and subgroup analyses based on the co-primary outcomes of mortality and surgical site infection.

RESULTS

Description of studies

Results of the search

We identified a total of 2148 references of possible interest by searching the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Chinese Database of Randomized Trials and reference lists. We identified two additional ongoing trials by searching databases of ongoing trials ([Osvaldo](#)

2011; Santa Clara Valley Health). We will include data from these two trials in future updates of this review. We excluded 403 duplicates and 1701 clearly irrelevant references upon reading the abstracts. Accordingly, we retrieved 59 references for further assessment. Of these, we excluded 26 references describing 26 studies because they were not randomized trials or did not fulfil the inclusion criteria of our review. We listed reasons for exclusion in the [Characteristics of excluded studies](#) table. We reran the search

in March 2015 and found 40 citations, one of which was a duplicate from a previous search; we excluded 37 trials. We will consider two studies of interest when we update the review.

In total, 28 RCTs described in 33 references fulfilled our inclusion criteria ([Figure 4](#)). The included trials consisted of a total of 9330 participants; 7537 participants provided data for the outcomes analysed in this review.

Figure 4. Trial flow diagram. We reran the search in March 2015. We found two studies of interest, which we will consider when we update the review.

Figure 4. (Continued)

We approached 28 corresponding or first study authors to request missing or unclear information and received answers from 10 of them.

We presented detailed descriptions in the [Characteristics of included studies](#) table and in the appendices. A summary overview follows.

Included studies

Trial characteristics

Eight of the 28 trials, with 4918 participants (Belda 2005; Greif 2000; Meyhoff 2009; Myles 2007; Pryor 2004; Schietroma 2013; Stall 2013; Williams 2013), reported on mortality; 15 trials reported on surgical site infections (Belda 2005; Bickel 2011; Duggal 2013; Gardella 2008; Golfam 2011; Greif 2000; Mayzler 2005; Meyhoff 2009; Myles 2007; Pryor 2004; Schietroma 2013; Scifres 2011; Stall 2013; Thibon 2012; Williams 2013); three reported on serious adverse events (SAEs) (Meyhoff 2009; Myles 2007; Pryor 2004); three on respiratory insufficiency (Kotani 2000; Meyhoff 2009; Zorembo 2010); seven on length of stay during the index admission (LOS) (Belda 2005; Bickel 2011; Gardella 2008; Greif 2000; Meyhoff 2009; Myles 2007; Pryor 2004); one on quality of life (Greif 1999); 10 only on outcomes that were not relevant to this review (Bhatnagar 2005; Goll 2001; Joris 2003; McKeen 2009; Purhonen 2003; Purhonen 2006; Simurina 2010; Turan 2006); eight only on nausea and vomiting (Bhatnagar 2005; Goll 2001; Joris 2003; McKeen 2009; Purhonen 2003; Purhonen 2006; Simurina 2010; Turan 2006; Mackintosh 2012; García-Botello 2006); one on requirements for postoperative supplemental oxygen (Mackintosh 2012); and one on intestinal pH (phi) and carbon dioxide (CO₂) gaps (García-Botello 2006). All 28

trials used a parallel-group design, and the 18 trials that provided data on the outcomes selected for this review used a two-parallel group design. These trials were published from 1999 to 2013. All were conducted without direct funding by industry; however, two trials reported that a company was involved in their design (Belda 2005; Thibon 2012). Seven trials were conducted in Europe (Belda 2005; García-Botello 2006; Greif 2000; Meyhoff 2009; Schietroma 2013; Thibon 2012; Zorembo 2010); seven in North America (Duggal 2013; Gardella 2008; Mackintosh 2012; Pryor 2004; Scifres 2011; Stall 2013; Williams 2013); three in the Middle East (Bickel 2011; Golfam 2011; Mayzler 2005); one in Australia, Hong Kong and the People's Republic of China (Myles 2007); and one in Japan (Kotani 2000). Twenty-six trials were conducted in high-income countries (Belda 2005; Bickel 2011; Duggal 2013; Gardella 2008; Greif 2000; Mayzler 2005; Meyhoff 2009; Myles 2007; Pryor 2004; Schietroma 2013; Scifres 2011; Stall 2013; Thibon 2012; Williams 2013; Kotani 2000; Zorembo 2010; Goll 2001; Joris 2003; McKeen 2009; Purhonen 2003; Purhonen 2006; Simurina 2010; Turan 2006; Mackintosh 2012; García-Botello 2006), and two in a developing country (Golfam 2011; Bhatnagar 2005).

Participants

A total of 7597 participants were randomly assigned to an FIO₂ of 60% or more versus 30% to 40% in the 18 trials reporting on outcomes for this review (Belda 2005; Bickel 2011; Duggal 2013; Gardella 2008; Golfam 2011; Greif 1999; Greif 2000; Kotani 2000; Mayzler 2005; Meyhoff 2009; Myles 2007; Pryor 2004; Schietroma 2013; Scifres 2011; Stall 2013; Thibon 2012; Williams 2013; Zorembo 2010), and three trials described as using an FIO₂ of less than 80% (Duggal 2013; Myles 2007; Williams 2013). The number of

participants in each trial ranged from 38 to 1012 (median 222; interquartile ratio (IQR) 147 to 564). One trial included a minor proportion of participants 15 to 17 years of age (Bickel 2011). The approximate weighted mean age of participants was 50 years (range 15 to 92 years). The approximate mean proportion of women was 63%.

Seven trials included mainly colorectal and abdominal surgical patients (Belda 2005; García-Botello 2006; Greif 2000; Mayzler 2005; Meyhoff 2009; Pryor 2004; Schietroma 2013), and one trial included exclusively patients for appendectomy (Bickel 2011). Four trials included only women for caesarean section (Duggal 2013; Gardella 2008; Scifres 2011; Williams 2013); one trial included only breast surgery patients (Golfam 2011); two trials only patients for orthopaedic surgery (Kotani 2000; Stall 2013); and four trials patients undergoing a variety of surgical procedures (Myles 2007; Mackintosh 2012; Thibon 2012; Zoremba 2010).

Experimental interventions

Of the 28 trials, 25 used an FIO₂ of 80% oxygen or greater in the group with a high FIO₂ during anaesthesia; two of these used more than 90% oxygen (Kotani 2000; Mackintosh 2012), and three used an FIO₂ of 60% to 80% (Duggal 2013; Myles 2007; Williams 2013). Fourteen trials also aimed for an FIO₂ of 80% or more in the high FIO₂ group during the recovery room period, and two trials used a high FIO₂ only during surgery. Thirteen trials used non-rebreathing or tight/sealed masks with high flow, and three trials used ordinary face masks. Two trials used oxygen at the discretion of the attending physicians during the recovery room period.

Comparator interventions

An FIO₂ of 30% to 40% during surgery was applied in all 28 trials in the control group. Of these, 17 trials aimed to achieve an FIO₂ of 30% to 40%, also during recovery room stay, and two trials used only supplemental oxygen during surgery. Fourteen trials used non-rebreathing or tight masks with high flow, and three trials used a nasal catheter or cannula in the 30% to 40% oxygen group. Thirteen trials did not use nitrous oxide during surgery, and four trials used nitrous oxide with an FIO₂ of 30% to 40% during surgery in the control groups (Bickel 2011; Mayzler 2005; Myles 2007; Pryor 2004). Use of nitrous oxide was not described in two trials (García-Botello 2006; Golfam 2011).

Co-interventions used in experimental and comparator intervention groups

An antibiotic was administered before surgical intervention to both intervention groups in 12 trials, whereas four trials with

patients for caesarean section reported on antibiotics used after delivery at cord clamping in both intervention groups (Duggal 2013; Gardella 2008; Scifres 2011; Williams 2013). The different regimens of antibiotic prophylaxis are described in [Characteristics of included studies](#). Bowel preparation on the day before surgery was described in two trials (Belda 2005; Greif 2000).

Ongoing studies

Two ongoing trials (Osvaldo 2011; Santa Clara Valley Health) identified at www.clinicaltrials.gov are seeking to include women for emergency caesarean section and elective caesarean section, respectively. The trial by Osvaldo 2011 aimed for 382 participants and, according to www.clinicaltrials.gov, planned to start in 2011. The Santa Clara Valley Health trial did not mention the aim for a sample size and, according to www.clinicaltrials.gov, planned to start in 2006. See additional details at [Ongoing studies](#).

Awaiting classification

Two studies are awaiting classification (Gin 2013; Schietroma 2014). Please refer to [Characteristics of studies awaiting classification](#) for further details.

Excluded studies

We presented a detailed description of the characteristics of 24 excluded studies in [Characteristics of excluded studies](#). We excluded seven articles for not reporting a randomized trial but instead a review or a meta-analysis. We excluded seven articles because these trials used interventions outside the scope of this review. We excluded four articles because they were letters to the editor. We excluded three articles because of retractions for fraud and one article because the study included children only.

Risk of bias in included studies

Three trials had low risk of bias in all bias domains, including adequate outcome reporting on mortality (Greif 2000; Meyhoff 2009; Myles 2007). Five trials had low risk of bias in all bias domains, including adequate outcome reporting on surgical site infection (Gardella 2008; Greif 2000; Meyhoff 2009; Myles 2007; Williams 2013). Six trials reported on mortality; three of these had overall low risk of bias (Meyhoff 2009; Myles 2007; Greif 2000), and four had high or unclear risk of bias in one or more bias domains other than outcome reporting bias (Belda 2005; Greif 2000; Pryor 2004; Schietroma 2013) (Figure 5).

Figure 5. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

The funnel plot (Figure 1) of all trials reporting surgical site infection showed slight asymmetry indicating bias; however, Egger's test was not statistically significant (P value = 0.63). As fewer than 10 trials were included in all other analyses, we did not construct a funnel plot for these outcomes.

Allocation

Generation of the allocation sequence

Ten trials reporting on the primary outcome of surgical site infection described adequate generation of the allocation sequence (Belda 2005; Duggal 2013; Gardella 2008; Greif 2000; Meyhoff 2009; Myles 2007; Pryor 2004; Stall 2013; Thibon 2012; Williams 2013); four trials did not describe the method of sequence generation and were considered as having unclear risk of bias (Bickel 2011; Golfam 2011; Schietroma 2013; Scifres 2011). One trial had high risk of bias, as investigators used tossing of envelopes for sequence generation (Mayzler 2005).

Allocation concealment

Twelve trials reporting on the primary outcome of surgical site infection described adequate allocation concealment (Belda 2005; Bickel 2011; Gardella 2008; Greif 2000; Mayzler 2005; Meyhoff 2009; Myles 2007; Pryor 2004; Schietroma 2013; Scifres 2011; Stall 2013; Williams 2013); three trials did not describe whether allocation concealment was adequate and thus were judged as having unclear risk of bias (Duggal 2013; García-Botello 2006; Golfam 2011). One trial did not adequately conceal allocation, as the anaesthesiologist enrolling participants to the trial had access to the allocation list (Thibon 2012).

Blinding

Blinding of participants and personnel

Seven trials reporting on the primary outcome of surgical site infection described adequate blinding of participants and personnel (Belda 2005; Gardella 2008; Greif 2000; Meyhoff 2009; Myles 2007; Schietroma 2013; Williams 2013); five trials reported unclear blinding of participants and personnel (Duggal 2013;

Golfam 2011; Mayzler 2005; Stall 2013; Thibon 2012). Three trials were described as inadequately blinded for participants and personnel and thus were considered at high risk of bias (Bickel 2011; Pryor 2004; Scifres 2011).

Blinding of outcome assessors

Twelve trials reporting on the primary outcome of surgical site infection described adequate blinding of outcome assessors (Belda 2005; Bickel 2011; Duggal 2013; Gardella 2008; Greif 2000; Mayzler 2005; Meyhoff 2009; Myles 2007; Schietroma 2013; Stall 2013; Thibon 2012; Williams 2013); two trials did not describe this bias risk and thus were considered as having unclear risk of bias (Golfam 2011; Scifres 2011). One trial had high risk of bias, as perioperative FIO_2 could be assessed during the postoperative period and at wound evaluation, and as data on FIO_2 or gas flow used during anaesthesia were available in the participant file (Pryor 2004).

Incomplete outcome data

Eleven trials reporting on the primary outcome of surgical site infection provided numbers and reasons for dropouts and withdrawals in the intervention groups, or described no dropouts or withdrawals (Belda 2005; Bickel 2011; Duggal 2013; Gardella 2008; Mayzler 2005; Meyhoff 2009; Myles 2007; Pryor 2004; Schietroma 2013; Thibon 2012; Williams 2013). We judged four trials as having unclear risk of bias, as they did not consistently report on dropouts or withdrawals (Golfam 2011; Greif 2000; Scifres 2011; Stall 2013).

Selective reporting

Fourteen trials reported adequately on surgical site infection, and one trial reported exclusively on anastomosis leakage - not on all types of surgical site infection (García-Botello 2006). Three trials did not report surgical site infection at all (Mackintosh 2012; Mayzler 2005; Zoremba 2010).

Six trials reported on mortality within 14 to 30 days after randomization (Belda 2005; Greif 2000; Meyhoff 2009; Myles 2007; Pryor 2004; Schietroma 2013). Two trials described long-term

mortality within a median of 3.9 years and 3.5 years, respectively (Meyhoff 2009; Myles 2007).

Three trials reported on SAEs (Meyhoff 2009; Myles 2007; Pryor 2004) - two trials on respiratory insufficiency (Meyhoff 2009; Myles 2007) and one trial on postoperative pulse oximetry monitored desaturation (Zoremba 2010).

Nine trials reported on length of stay (LOS) (Belda 2005; Bickel 2011; Gardella 2008; Greif 2000; Mayzler 2005; Meyhoff 2009; Myles 2007; Pryor 2004; Schietroma 2013).

One trial reported on quality of life (Greif 1999).

Therefore we determined that 20 studies had low risk of reporting bias, and eight studies had unclear risk (García-Botello 2006; Gardella 2008; Kotani 2000; Mackintosh 2012; Mayzler 2005; Purhonen 2006; Turan 2006; Zoremba 2010) as they did not present adequate information for assessment of selective reporting.

Other potential sources of bias

Two trials had unclear risk of industry bias, as a company was involved in planning and design of the trials (Belda 2005; Thibon 2012).

Seventeen trials reporting on outcomes included in this review had low risk of financial bias (Bickel 2011; Duggal 2013; García-Botello 2006; Gardella 2008; Golfam 2011; Greif 1999; Greif 2000; Mackintosh 2012; Mayzler 2005; Meyhoff 2009; Myles 2007; Pryor 2004; Scifres 2011; Williams 2013; Zoremba 2010; Schietroma 2013; Stall 2013).

Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings in randomized clinical trials with overall low risk of bias and in all trials

Primary outcomes

1. All-cause mortality in all trials according to the longest follow-up period for each trial.

Eight trials with 4229 participants provided data on all-cause mortality (Belda 2005; Greif 2000; Meyhoff 2012; Myles 2007; Pryor 2004; Schietroma 2013; Stall 2013; Williams 2013). Two trials reported long-term mortality with a median follow-up of 3.9 years in 83% of randomly assigned participants and 3.5 years in 99% of participants, respectively (Myles 2007; Meyhoff 2009). Four trials reported mortality only within 30 days (Belda 2005; Greif 2000; Pryor 2004; Schietroma 2013). Overall, in all trials a high fraction of inspired oxygen with an FIO₂ of 60% to 90% compared with 30% to 40% oxygen used during anaesthesia and surgery was not associated with all-cause mortality within the longest follow-up in a random-effects model (RR 1.07, 95% CI 0.87 to 1.33; participants = 4918; trials = 8; I² = 30%; Analysis 1.1); nor in a fixed-effect model (RR 1.10, 95% CI 0.97 to 1.25; participants = 4918; trials = 8; I² = 30%; Analysis 1.1).

All-cause mortality according to overall risk of bias in the included trials

Within longest follow-up

In trials with overall low risk of bias (Meyhoff 2009; Myles 2007; Greif 2000; Williams 2013), an FIO₂ of 60% to 90% compared with 30% to 40% oxygen used during anaesthesia and surgery was not associated with mortality within the longest follow-up in a random-effects model (RR 1.12, 95% CI 0.93 to 1.36; P value = 0.23; I² = 41; Analysis 1.1). In trials with overall high or unclear risk of bias (Belda 2005; Pryor 2004; Schietroma 2013; Stall 2013), a high fraction of oxygen during anaesthesia and surgery was not associated with all-cause mortality within the longest follow-up in a random-effects model (RR 0.43, 95% CI 0.15 to 1.20; P value = 0.11; I² = 0; Analysis 1.1). The test of interaction for a subgroup difference was not statistically significant (P value = 0.07; I² = 69.5%).

All-cause mortality in best/worst and worst/best case scenarios of participants lost to follow-up

In a best/worst case scenario (Analysis 1.2): Assuming that all participants lost to follow-up in the group randomly assigned to a high fraction of inspired oxygen did survive, and that all participants lost to follow-up in the group randomly assigned to a 30% to 40% fraction of inspired oxygen died, 60% to 90% oxygen was not associated with all-cause mortality in a random-effects model (RR 0.56, 95% CI 0.25 to 1.25).

In a worst/best case scenario (Analysis 1.3): Assuming that all participants lost to follow-up in the group randomly assigned to a high fraction of inspired oxygen died, and that all participants lost to follow-up in the group randomly assigned to 30% to 40% inspiratory oxygen survived, 60% to 90% oxygen was associated with an increase in all-cause mortality in a random-effects model (RR 1.50, 95% CI 1.04 to 2.15; P value = 0.03; I² = 66%).

Trial sequential analysis on all-cause mortality

TSA (Figure 2) of the four trials (Greif 2000; Meyhoff 2009; Myles 2007; Williams 2013) with overall low risk of bias reporting all-cause mortality showed that with an anticipated RRI of 20%, mortality in the control group of 15.7% and a type 1 error of 5% and a type 2 error of 20%, and diversity (D²) of 57%, the required information size was 10,736 participants. The cumulative Z-curve did not cross any boundaries for benefit and harm nor TSMB for futility, indicating that evidence was insufficient to refute a 20% RRI or a 20% RRR for benefit or harm of a high fraction of inspired oxygen of 60% to 90%, in the light of sparse data and repetitive testing. The TSA adjusted confidence interval for the intervention effect measured in the three trials with low risk of bias was RR 1.12 with TSA adjusted CI 0.80 to 1.59.

TSA (Figure 3) of all eight trials (Belda 2005; Greif 1999; Meyhoff 2009; Myles 2007; Pryor 2004; Schietroma 2013; Stall 2013; Williams 2013) of the effect of a high fraction of inspired oxygen on all-cause mortality within the longest follow-up showed that with an anticipated RRI of 20%, mortality in the control group of 15.7% and a type 1 error of 5% and a type 2 error of 20%, and diversity (D²) of 67%, the required information size was 13,264 participants. The cumulative Z-curve did not cross the conventional boundary (P value < 0.05) nor the TSMB for harm. Neither did the cumulative Z-curve reach the futility area. Therefore evidence was insufficient for an effect on all-cause mortality based on all trials disregarding risk

of bias and time to follow-up. We could not exclude a 20% RRI nor a 20% RRR for lack of data. The TSA adjusted

confidence interval for the intervention effect measured in all trials was RR 1.07, with TSA adjusted CI 0.73 to 1.60.

Using a fixed-effect model for all trials reporting all-cause mortality did not change the results noticeably, as the cumulative Z-curve did not enter the futility area for a 20% RRI or RRR.

2. Surgical site infection within 14 to 30 days of follow-up after surgery

Fifteen trials with 7219 participants provided data on surgical site infection. Overall, in all trials a high fraction of inspired oxygen of 60% to 90% compared with 30% to 40% oxygen used during anaesthesia and surgery was not associated with a change in the risk of surgical site infection in a random-effects model (RR 0.87, 95% CI 0.71 to 1.07; P value = 0.18; I^2 = 48%; [Analysis 1.5](#)). However, in the fixed-effect model, an FIO₂ of 60% to 90% compared with 30% to 40% oxygen used during anaesthesia and surgery was associated with a reduction in the risk of surgical site infection (RR 0.87, 95% CI 0.77 to 0.99; [Analysis 1.6](#)).

Surgical site infection according to overall risk of bias

In trials with overall low risk of bias ([Gardella 2008](#); [Greif 2000](#); [Meyhoff 2009](#); [Myles 2007](#); [Williams 2013](#)), an FIO₂ of 60% to 90% compared with 30% to 40% oxygen used during anaesthesia and surgery was not associated with risk of surgical site infection in a random-effects model (RR 0.86, 95% CI 0.63 to 1.17; participants = 4201; studies = 5; I^2 = 60%; [Analysis 1.5](#)) and in the fixed-effect model (RR 0.86, 95% CI 0.73 to 1.00; participants = 4201; studies = 5; I^2 = 60%; [Analysis 1.6](#)). In trials with overall high or unclear risk of bias ([Belda 2005](#); [Bickel 2011](#); [Duggal 2013](#); [Golfam 2011](#); [Mayzler 2005](#); [Pryor 2004](#); [Schietroma 2013](#); [Scifres 2011](#); [Stall 2013](#); [Thibon 2012](#)) in one or more bias domains, a high fraction of inspired oxygen during anaesthesia and surgery was not associated with risk of surgical site infection in a random-effects model (RR 0.87, 95% CI

0.64 to 1.18; participants = 3018; studies = 10; I^2 = 47%; [Analysis 1.5](#)) and in the fixed-effect model (RR 0.91, 95% CI 0.74 to 1.11; [Analysis 1.6](#)). The test of interaction for a subgroup difference in effect between trials with low risk of bias and those with unclear or high risk of bias was not significant (P value = 0.96; [Analysis 1.5](#)).

Trial sequential analysis on surgical site infection

In the TSA of a high fraction of inspired oxygen of 60% to 90% versus 30% to 40% on surgical site infection within 14 to 30 days of follow-up in trials with low risk of bias (RR 0.86, 95% CI 0.63 to 1.17; participants = 4201; studies = 5; I^2 = 60%; [Analysis 1.5](#)), the required information size to detect or reject an a priori anticipated intervention effect of 20% RRR in a random-effects model was estimated to be 18,399 participants using a control event proportion of 12.9% and the diversity of 74% found among included trials (I^2 = 60%; 95% CI 34% to 75%; P value = 0.04). Five trials with 4211 participants provided data on surgical site infection. The conventional boundary for statistical significance was not crossed (P value = 0.33), and the TSMB for benefit was not crossed (RR 0.86, TSA adjusted CI 0.42 to 1.75), suggesting that a high fraction of inspired oxygen was not associated with risk of surgical site infection.

TSA ([Figure 6](#)) of a high fraction of inspired oxygen of 60% to 90% versus 30% to 40% oxygen on surgical site infection in all trials of surgical patients within 14 to 30 days of follow-up shows that the required information size to detect or reject a 20% RRR in a random-effects model was 13,189 participants using a control event proportion of 12.9% and the 63% diversity found among the included trials (I^2 = 48%; 95% CI 30% to 62%; P value = 0.02). The conventional boundary for statistical significance was not crossed (P value = 0.18), nor was the TSMB for benefit (RR 0.87, 95% CI 0.65 to 1.17). However, in a fixed-effect model (RR 0.87, TSA adjusted CI 0.77 to 0.998; P value = 0.033), the TSMB for benefit was crossed, suggesting that a high fraction of inspired oxygen may be associated with surgical site infection.

Figure 6. Trial sequential analysis (TSA) of high inspiratory supplemental oxygen fraction 60% to 90% vs 30% to 40% in surgical site infection for all trials of surgical participants within 14 to 30 days of follow-up. The required information size to detect or reject a 20% relative risk reduction in a random-effects model was estimated at 13,189 participants, using a control event proportion of 12.9% and diversity of 63% among included trials ($I^2 = 48\%$; 95% CI 30% to 62%; P value = 0.02). Fifteen trials with 7219 participants provided data on surgical site infection. The conventional boundary for statistical significance was not crossed (P value = 0.18) and the trial sequential monitoring boundary for benefit was not crossed, as the TSA adjusted CI for the risk ratio was as follows: RR 0.87, 95% CI 0.65 to 1.17).

The information size required to detect or reject an intervention effect suggested by the point estimate of 13% RRR in the random-effects model of all trials was 34,890. No boundaries were crossed.

In the fixed-effect model (RR 0.87, 95% CI 0.77 to 0.99), assuming absence of heterogeneity, the required information size of 4840 was surpassed and the high inspired oxygen fraction may be associated with a reduction in surgical site infection (RR 0.87, TSA adjusted CI 0.77 to 1.00; participants = 7219; studies = 15; $D^2 = 63\%$).

Surgical site infection according to use or no use of nitrous oxide in the control group

In trials with no use of nitrous oxide in the control group, a high fraction of inspired oxygen of 60% to 90% compared with 30% to 40% oxygen used during anaesthesia and surgery was not associated with a change in the risk of surgical site infection (RR 0.88, 95% CI 0.71 to 1.11; [Analysis 1.7](#)); in trials with use of nitrous oxide in the control group, supplemental oxygen during anaesthesia and surgery was not associated with a change in the risk of surgical site infection (RR 0.85, 95% CI 0.45 to 1.61; [Analysis 1.7](#)) and the test of interaction was not significant (P value = 0.91). Results when a fixed-effect model was used were not noticeably different.

Surgical site infection according to FiO_2 of 80% or higher in the experimental intervention

In trials that used an FiO_2 of 80% or higher in the experimental group compared with 30% to 40% oxygen during anaesthesia and surgery, a high fraction of inspired oxygen was not associated with risk of surgical site infection in a random-effects model (RR 0.87, 95% CI 0.66 to 1.15; [Analysis 1.8](#)). Likewise, in trials that used an FiO_2 between 60% and 80% in the experimental intervention during anaesthesia and surgery, the high fraction of inspired oxygen was not associated with risk of surgical site infection in a random-effects model (RR 0.81, 95% CI 0.65 to 1.02; [Analysis 1.8](#)), and the test of interaction was not significant (P value = 0.71). Results when a fixed-effect model was used were not noticeably different.

Surgical site infection according to use of high FiO_2 during the postoperative recovery period in the experimental intervention group

In trials that used a high FiO_2 during postoperative recovery compared with 30% to 40% oxygen during anaesthesia, surgery and recovery, a high fraction of inspired oxygen was not associated with risk of surgical site infection in a random-effects model (RR 0.87, 95% CI 0.70 to 1.09; [Analysis 1.9](#)). However, in a fixed-effect model, a high fraction of inspired oxygen during both surgery and

postoperative recovery was associated with lower risk of surgical site infection (RR 0.87, 95% CI 0.77 to 0.99). In trials reporting use of a high fraction of inspired oxygen only during surgery, the high fraction of inspired oxygen was not associated with risk of surgical site infection in a random-effects model (RR 0.88, 95% CI 0.45 to 1.73; [Analysis 1.9](#)) nor in a fixed-effect model (RR 0.87, 95% CI 0.44 to 1.70). However, the test for subgroup differences was not statistically significant (P value = 0.91).

Surgical site infection according to type of surgery

In trials including colorectal and abdominal surgical patients, a high FIO₂ compared with 30% to 40% oxygen during anaesthesia and surgery was not associated with risk of surgical site infection (RR 0.74, 95% CI 0.50 to 1.09; [Analysis 1.10](#)), but in the fixed-effect model, a high fraction of inspired oxygen was associated with lower risk of surgical site infection (RR 0.84, 95% CI 0.70 to 0.99). In trials including only patients for caesarean section, a high FIO₂ during anaesthesia and surgery was not associated with risk of surgical site infection in a random-effects model (RR 1.21, 95% CI 0.91 to 1.60; [Analysis 1.10](#)), and the result did not change noticeably in the fixed-effect model. In trials including only patients for orthopaedic surgery, a high FIO₂ during anaesthesia and surgery was not associated with risk of surgical site infection (RR 0.71, 95% CI 0.37 to 1.34; [Analysis 1.10](#)), and the result did not change noticeably in a fixed-effect model. In the trial including only patients for breast surgery, a high FIO₂ during anaesthesia and surgery was not associated with a change in the risk of surgical site infection (RR 0.33, 95% CI 0.01 to 7.87; [Analysis 1.10](#)). Among patients undergoing various types of surgical procedures, use of a high FIO₂ during anaesthesia and surgery was associated with a decrease in the risk of surgical site infection (RR 0.76, 95% CI 0.59 to 0.99; [Analysis 1.10](#)), but the test of interaction for a subgroup difference in effect was not statistically significant (P value = 0.10).

Surgical site infection according to follow-up longer or shorter than 14 days

In trials with follow-up longer than 14 days, a high FIO₂ during postoperative recovery compared with 30% to 40% oxygen used during anaesthesia and surgery was not associated with risk of surgical site infection (RR 0.87, 95% CI 0.72 to 1.05; [Analysis 1.11](#)); this association also was not seen in trials with follow-up of 14 or fewer days (RR 0.84, 95% CI 0.48 to 1.47; [Analysis 1.11](#)). The test for a subgroup difference was not statistically significant (P value = 0.91). Use of a fixed-effect model did not change the results noticeably.

Surgical site infection according to preoperative use of antibiotics

In trials with preoperative use of antibiotics, a high FIO₂ compared with 30% to 40% oxygen used during anaesthesia and surgery was associated with risk of surgical site infection in a random-effects model (RR 0.76, 95% CI 0.60 to 0.97; P value = 0.04; I² = 49%; [Analysis 1.12](#)), but this association was lacking in trials not reporting or not using preoperative antibiotics (RR 1.20, 95% CI 0.91 to 1.58; P value = 0.21; I² = 0; [Analysis 1.12](#)). The test for a subgroup difference was statistically significant (P value = 0.02; I² = 82.6%). Use of a fixed-effect model did not change the results noticeably.

Surgical site infection according to low risk of bias compared with unclear or high risk of bias of specific bias components

Surgical site infection according to adequate allocation sequence generation

In trials with adequate allocation sequence generation, an FIO₂ of 60% to 90% compared with 30% to 40% oxygen used during anaesthesia and surgery was not associated with surgical site infection in a random-effects model (RR 0.89, 95% CI 0.71 to 1.11; [Analysis 1.13](#)) nor in trials with unclear or inadequate allocation sequence generation (RR 0.69, 95% CI 0.36 to 1.31; [Analysis 1.13](#)). The test for a subgroup difference was not statistically significant (P value = 0.46; I² = 0).

Surgical site infection according to adequate allocation concealment

In trials with adequate allocation concealment, an FIO₂ of 60% to 90% compared with 30% to 40% oxygen used during anaesthesia and surgery was not associated with risk of surgical site infection in a random-effects model (RR 0.85, 95% CI 0.67 to 1.08; [Analysis 1.14](#)) nor in trials with unclear or inadequate allocation concealment (RR 0.96, 95% CI 0.66 to 1.40; [Analysis 1.14](#)). The test for a subgroup difference was not statistically significant (P value = 0.60; I² = 45%).

Surgical site infection according to blinding of participants and personnel

In trials with adequate blinding of participants and personnel, an FIO₂ of 60% to 90% compared with 30% to 40% oxygen used during anaesthesia and surgery was not associated with risk of surgical site infection in a random-effects model (RR 0.79, 95% CI 0.61 to 1.03; [Analysis 1.15](#)) nor in trials with unclear or inadequate blinding of participants and personnel (RR 0.98, 95% CI 0.70 to 1.37; [Analysis 1.15](#)). The test for a subgroup difference was not statistically significant (P value = 0.33; I² = 0).

Surgical site infection according to blinding of outcome assessors

In trials with adequate blinding of outcome assessors, an FIO₂ of 60% to 90% compared with 30% to 40% oxygen used during anaesthesia and surgery was associated with a decrease in risk of surgical site infection in a random-effects model (RR 0.79, 95% CI 0.66 to 0.96; [Analysis 1.16](#)), but in trials with unclear or inadequate blinding of outcome assessors, a high oxygen fraction was associated with an increase in the risk of surgical site infection (RR 1.57, 95% CI 1.04 to 2.37; [Analysis 1.16](#)). The test for a subgroup difference was statistically significant (P value = 0.003; I² = 48%).

Surgical site infection according to completeness of outcome data

In trials with adequate completeness of outcome data, an FIO₂ of 60% to 90% compared with 30% to 40% oxygen used during anaesthesia and surgery was not associated with risk of surgical site infection in a random-effects model (RR 0.89, 95% CI 0.71 to 1.11; [Analysis 1.17](#)) nor in trials with unclear or inadequate completeness of outcome data (RR 0.77, 95% CI 0.41 to 1.43; [Analysis 1.17](#)). The test for subgroup differences was not statistically significant (P value = 0.67; I² = 0).

Surgical site infection according to adequate outcome reporting

Six trials ([Belda 2005](#); [Greif 2000](#); [Meyhoff 2009](#); [Myles 2007](#); [Pryor 2004](#); [Schietroma 2013](#)) reported adequately on all-cause mortality within a follow-up ranging from 14 days to a median of 3.9 years. Sixteen trials reported adequately on their predefined outcome of

surgical site infection (RR 0.87, 95% CI 0.71 to 1.07; participants = 7264; studies = 16; $I^2 = 48\%$; [Analysis 1.18](#)), whereas one trial ([García-Botello 2006](#)) reported only on pH_i, CO₂ and anastomotic dehiscence within seven days - not on surgical site infections. Nine trials ([Bhatnagar 2005](#); [Joris 2003](#); [Kotani 2000](#); [Mackintosh 2012](#); [McKeen 2009](#); [Purhonen 2003](#); [Purhonen 2006](#); [Simurina 2010](#); [Zorembo 2010](#)) did not report any of the outcomes chosen for this review.

Surgical site infection according to the presence of other bias

In trials with no presence of other bias risk, an FIO₂ of 60% to 90% compared with 30 to 40% oxygen used during anaesthesia and surgery was not associated with risk of surgical site infection in a random-effects model (RR 0.89, 95% CI 0.71 to 1.13; [Analysis 1.19](#)), nor in trials with the presence of unclear or other bias (RR 0.72, 95% CI 0.48 to 1.07; [Analysis 1.19](#)). The test for subgroup differences was not statistically significant (P value = 0.36; $I^2 = 48\%$).

Surgical site infection in best/worst compared with worst/best case scenarios of participants lost to follow-up

The best/worst case scenario ([Analysis 1.20](#)): Assuming that all participants lost to follow-up in the group randomly assigned to a high fraction of inspired oxygen did not develop a surgical site infection, and that all participants lost to follow-up in the group randomly assigned to 30% to 40% inspired oxygen developed a surgical site infection, the intervention effect was as follows: RR 0.71, 95% CI 0.54 to 0.93.

The worst/best case scenario ([Analysis 1.21](#)): Assuming that all participants lost to follow-up in the group randomly assigned to a high fraction of inspired oxygen developed a surgical site infection, and that all participants lost to follow-up in the group randomly assigned to 30% to 40% oxygen did not develop a surgical site infection, the intervention effect was as follows: RR 1.05, 95% CI 0.78 to 1.42.

Sensitivity analyses

Assessment of the benefits and harms of high FIO₂ performed by conducting a continuity adjustment of trials with zero events did not change the results, as very few of the trials included in meta-analyses had a zero event.

Excluding the largest trial did change the point estimate of all-cause mortality (RR 0.61, 95% CI 0.26 to 1.41) but was not associated with a statistically significant intervention effect and did not change the effect on surgical site infection (RR 0.89, 95% CI 0.70 to 1.12).

Excluding the smallest trial did not change our results substantially regarding all-cause mortality (RR 1.07, 95% CI 0.86 to 1.35) nor surgical site infection (RR 0.88, 95% CI 0.71 to 1.08).

Excluding data from trials published only as abstracts and from trials with commercial involvement did not change the results for all-cause mortality (RR 1.07, 95% CI 0.87, 1.33) and surgical site infection (RR 0.89, 95% CI 0.71 to 1.13).

Secondary outcomes

1. All-cause mortality within 30 days of follow-up

Overall, in all trials a high fraction of inspired oxygen of 60% to 90% compared with 30% to 40% oxygen used during anaesthesia and

surgery was not associated with all-cause mortality within 30 days of follow-up in a model using the Peto odds ratio (POR 0.83, 95% CI 0.54 to 1.29; P value = 0.41; $I^2 = 60\%$; 4229 participants; six trials; [Analysis 1.4](#)).

All-cause mortality within 30 days of follow-up according to overall risk of bias in the included trials

Within 30 days of follow-up in trials with overall low risk of bias ([Greif 2000](#); [Meyhoff 2009](#); [Myles 2007](#); [Williams 2013](#)), an FIO₂ of 60% to 90% compared with 30% to 40% oxygen used during anaesthesia and surgery was not associated with mortality within 30 days of follow-up (POR 0.99, 95% CI 0.61 to 1.60; participants = 4058; trials = 4; $I^2 = 77\%$; [Analysis 1.4](#)). In trials with overall high or unclear risk of bias ([Belda 2005](#); [Pryor 2004](#); [Schietroma 2013](#); [Stall 2013](#)), a high fraction of oxygen during anaesthesia and surgery was not associated with all-cause mortality within 30 days of follow-up in a random-effects model (POR 0.37, 95% CI 0.13 to 1.05; participants = 860; trials = 4; $I^2 = 0\%$; [Analysis 1.4](#)). The test of interaction for a subgroup difference was not statistically significant (P value = 0.09; $I^2 = 64.7\%$).

2. Respiratory insufficiency

Respiratory insufficiency, defined as the need for respiratory assistance through ventilator therapy or non-invasive ventilation within the longest follow-up period, was explicitly reported in only three trials ([Kotani 2000](#); [Meyhoff 2009](#); [Zorembo 2010](#)) and could not be meta-analysed, as two trials ([Kotani 2000](#); [Zorembo 2010](#)) reported no events during 24 hours of observation; however, in the other trial ([Meyhoff 2009](#)), a high fraction of inspired FIO₂ was not statistically significantly associated with respiratory insufficiency (RR 1.25, 95% CI 0.79 to 1.99; [Analysis 1.22](#)).

3. Serious adverse events (SAEs)

An SAE, defined ([Directive 2001](#)) as "any event that led to death, was life-threatening, required in-patient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability, and any important medical event which might jeopardise the patient or required intervention to prevent it", was reported in only three trials ([Meyhoff 2009](#); [Myles 2007](#); [Pryor 2004](#)). A high FIO₂ compared with 30% to 40% oxygen used during anaesthesia and surgery was not associated with the proportion of SAEs in a random-effects model (RR 0.96, 95% CI 0.65 to 1.43; [Analysis 1.23](#)). In trials with overall low risk of bias, a high FIO₂ compared with 30% to 40% oxygen used during anaesthesia and surgery was not associated with risk of an SAE in a random-effects model (RR 0.91, 95% CI 0.63 to 1.31; [Analysis 1.23](#)) nor in trials with high risk of bias in a random-effects model (RR 5.00, 95% CI 0.60 to 41.85; [Analysis 1.23](#)), and the test for subgroup differences was not statistically significant (P value = 0.12).

4. Duration of postoperative hospitalizations

Overall, in all trials, supplemental oxygen with an FIO₂ 60% to 90% compared with 30% to 40% oxygen used during anaesthesia and surgery was not associated with LOS in days in a random-effects model (MD -0.06, 95% CI -0.44 to 0.32; P value = 0.77; $I^2 = 62\%$; 4702 participants; nine trials; [Analysis 1.24](#)).

Duration of postoperative hospitalization according to overall risk of bias

In trials with an overall low risk of bias, an FIO₂ of 60% to 90% compared with 30% to 40% oxygen used during anaesthesia and surgery was not associated with LOS in a random-effects model (MD -0.13 days, 95% CI -0.49 to 0.24; participants = 4041; studies = 4; I² = 41%; [Analysis 1.24](#)) nor in trials with overall high or unclear risk of bias (MD 0.69 days, 95% CI -0.82 to 2.20; participants = 661; studies = 5; I² = 80%; [Analysis 1.24](#)). The test for subgroup differences was not significant (P value = 0.30; I² = 6.6%).

5. Quality of life

Quality of life was not reported in any of the articles reporting trial results. However, we obtained data on Short Form (SF)-36 from the Grief et al trial ([Greif 1999](#)) through Daniel Sessler, who was a co-author of this trial report. Accordingly, no meta-analysis could be performed for this outcome, but the trial reporting this outcome did not show an association between a high fraction of inspired oxygen and 30% to 40% oxygen and quality of life, as SF-36 scores on the various domains were as follows.

SF-36 domain	80% oxygen	30% oxygen
Physical functioning	61 ± 31	67 ± 29
Role physical	78 ± 34	79 ± 37
Role emotional	84 ± 32	84 ± 33
Vitality	60 ± 16	61 ± 20
Bodily pain	72 ± 27	74 ± 29
General health	72 ± 20	79 ± 31
Social functioning	84 ± 21	80 ± 25
Mental health	72 ± 18	70 ± 20

Meta-regression

Univariate meta-regression did not show an association between the intervention effect, Log(RR), of a high inspired fraction of oxygen and the mean age of included trial populations (MD -0.007 years, 95% CI -0.016 to 0.0023 years; P value = 0.14). However, meta-regression of characteristics on the trial level may reveal both false-positive and false-negative results, and may not be applicable for the inference of the impact of age on the effect of a high inspired fraction of oxygen on outcomes at the patient level.

As information was lacking for most trials, we were not able to perform meta-regression analyses of the intervention effect of a high inspired fraction of oxygen on mean BMI of the trial population at baseline; the fraction of diabetic patients in the trial population at baseline; the fraction of smokers in the trial population at baseline; and the fraction of patients with a contaminated or dirty infected surgical field during surgery.

DISCUSSION

Summary of main results

Our systematic review reveals several important findings. Analysis of the eight trials reporting on mortality suggests that no statistically significant association can be found between postoperative mortality and a high fraction of inspired oxygen (FIO₂) during anaesthesia, surgery and recovery when we disregard risks of bias. Meta-analysis of the four trials with low risk of

bias in all bias domains ([Analysis 1.1](#)) did not show a statistically significant association between a high inspired fraction of oxygen and mortality (risk ratio (RR) 1.12, 95% confidence interval (CI) 0.93 to 1.36). Follow-up was within 30 days in the trial of Greif et al ([Greif 2000](#)), and median time of follow-up was longer than three years in two trials ([Meyhoff 2012](#); [Myles 2007](#)). [Meyhoff 2009](#) reported a statistically significant increase in all-cause mortality in the high inspiratory oxygen group within one year and within long-term follow-up with a median of 3.9 years ([Meyhoff 2014](#)). During long-term follow-up of the [Myles 2007](#) trial, Leslie et al ([Leslie 2011](#)) reported no statistically significant differences in all-cause mortality within a median follow-up of 3.5 years. However, [Meyhoff 2009](#) and [Greif 2000](#) did not use nitrous oxide in the control group, and these trials were specifically designed to investigate the effects of 80% oxygen versus 30% oxygen during surgery and recovery; [Myles 2007](#) used nitrous oxide in the control group and the trial was actually designed to investigate the effects of nitrous oxide versus oxygen on mortality, surgical site infection and adverse events. In the group of trials with unclear or high risk of bias, which reported only mortality within 30 days of follow-up (RR 0.43, 95% CI 0.15 to 1.20), no association was found between a high inspired fraction of oxygen and mortality in a random-effects model, and the test for subgroup differences between trials with low and high or unclear risk of bias was not statistically significant (P value = 0.07; I² = 69.5%). A fixed-effect meta-analysis does not noticeably change the results. The required information size to detect or reject a relative risk increase (RRI) of 35% is surpassed, and we can refute such an intervention effect. However, trial sequential analysis (TSA) ([Figure](#)

2; Figure 3) showed that only 36% of the diversity-adjusted required information size has been accrued to detect or reject an RRI of 20% in a random-effects model. The effect of a high fraction of inspiratory oxygen during surgical and recovery periods of 20% RRI or relative risk reduction (RRR) on mortality may be noted when further data arrive. The TSA of the four trials with low risk of bias (Figure 1) indicates that an RRI or RRR of 20% cannot be refuted in the light of sparse data and repetitive updating of the cumulative meta-analysis. However, the estimate of the intervention effect is likely to change when future trial data become available and are added to the cumulative meta-analysis. A post hoc analysis (POR 0.83, 95% CI 0.54 to 1.29; Analysis 1.4) showed that the effect of a high fraction of inspired oxygen versus routine use of oxygen was not statistically significantly associated with all-cause mortality within 30 days of follow-up; however, the required information size was far from reached, and effect as well as lack of effect cannot be excluded.

Overall, in 15 trials, an FIO₂ of 60% to 90% compared with 30% to 40% oxygen used during anaesthesia and surgery was not associated with risk of surgical site infection in a random-effects model (RR 0.87, 95% CI 0.71 to 1.07; Analysis 1.5), but in a fixed-effect model (RR 0.87, 95% CI 0.77 to 0.99; Analysis 1.6), a high FIO₂ compared with routine use of oxygen seemed to be associated with reduced risk of surgical site infection. Given the substantial clinical and statistical heterogeneity among all trials with I² of 60%, and among trials with low risk of bias with I² of 47%, a fixed-effect model seems to lack robustness. Even though the point estimate (RR 0.87) of the intervention effect is the same in both models, a considerably wider confidence interval is seen in the random-effects model compared with the fixed-effect model. In the subgroup analysis of trials with overall low risk of bias compared with trials with unclear or high risk of bias, the intervention with high inspiratory oxygen was not associated with surgical site infection in any of the groups, and the test for subgroup differences was not statistically significant (P value = 0.96); however, heterogeneity was substantial in both groups. TSA (Figure 3), using a random-effects model, showed that only 55% of the required information size of 13,189 randomly assigned participants has been reached so far, and neither the conventional boundary (P value = 0.05) nor the trial sequential monitoring boundaries for benefit, harm and futility have been crossed.

In the subgroup analysis of trials using adequate blinding of outcome assessment, use of a high FIO₂ compared with routine use of oxygen during anaesthesia and surgery was associated with risk of surgical site infection in both fixed-effect and random-effects models, and the test for subgroup differences between trials with adequate blinding of outcome assessment and trials with unclear or inadequate blinding of outcome assessment was statistically significant (P value = 0.003). However, many of the trials using adequate blinding in outcome assessment had other types of unclear or high risk of bias, and the estimate of the intervention effect is likely to change if further trials with adequate blinding are included. The information size required to detect or reject an intervention effect of 20% on surgical site infection has not been reached.

In the subgroup of eight trials with colorectal or abdominal surgery, use of a high FIO₂ compared with routine use of oxygen during anaesthesia and surgery was not associated with risk of surgical site infection in a random-effects model, and the test for subgroup

differences was not statistically significant (P value = 0.10). In a fixed-effect model, the high inspiratory oxygen fraction was associated with a decrease in surgical site infection (P value = 0.04), but the fixed-effect model seems inappropriate in the light of substantial clinical and statistical heterogeneity between trials included in this analysis (I² = 64%; P value = 0.010). Further, several trials had unclear or high risk of bias, and the information size required to detect or reject an RRR of 20% is far from being reached.

In the subgroup of trials including various types of surgery (Myles 2007; Thibon 2012), use of a high FIO₂ compared with routine use of oxygen was associated with risk of surgical site infection in both fixed-effect and random-effects models, but the test for subgroup differences was not statistically significant (P value = 0.10).

In the post hoc subgroup analysis of trials using antibiotics administered before surgery commenced, use of a high FIO₂ compared with routine use of oxygen was associated with risk of surgical site infection in both fixed-effect and random-effects models, and the test for subgroup differences between trials with preoperative use of antibiotics and trials not using preoperative antibiotics (or lack of reporting) was statistically significant (P value = 0.03). However, only two of the trials using preoperative antibiotics had overall low risk of bias in all bias domains, and in these trials a high FIO₂ compared with routine use of oxygen was not associated with a change in the risk of surgical site infection.

We were not able to exclude a 20% excess in all-cause mortality of a high FIO₂ compared with routine use of oxygen in trials with overall low risk of bias (RR 1.12, TSA adjusted CI 0.80 to 1.59) nor in all trials (RR 1.07, TSA adjusted CI 0.73 to 1.60) because the cumulative Z-curve in the TSA did not reach the futility area. Further, best/worst and worst/best case analyses show that the results are highly sensitive to the loss to follow-up noted during long-term follow-up, especially in the ENIGMA trial (Leslie 2011; Myles 2007), as the effect in these analyses is estimated to be RR 0.56, with 95% CI 0.25 to 1.25, and RR 1.50, with 95% CI 1.04 to 2.15, respectively. We did not find consistent evidence that a high FIO₂ compared with routine use of oxygen is associated with risk of surgical site infection, respiratory insufficiency, serious adverse events (SAEs) or length of stay during the index admission. The effect on quality of life was reported in only one trial (Greif 1999) and accordingly could not be meta-analysed, but the trial did not report an association between a high fraction of inspired oxygen and quality of life as measured by Short Form (SF)-36 score. Some of the subgroup analyses performed in both fixed-effect and random-effects models indicate that a high FIO₂ compared with routine use of oxygen was associated with a reduction in surgical site infection in trials of various types of surgical procedures; using preoperative antibiotics; and using adequate blinding of the outcome assessment. However, the evidence is sparse in all of these analyses, not reaching the required information size, and all subgroup analyses have considerable drawbacks according to other types of confounders and bias risks; analysis of trials using antibiotics was a post hoc defined analysis, performed after the protocol had been published.

Overall completeness and applicability of evidence

The plan to analyse the effects of a high FIO₂ compared with routine use of oxygen during anaesthesia and surgery followed our published protocol to a great extent. We included all

eligible randomized clinical trials (RCTs) up to February 2014. All trials were conducted in high-income countries. Both sexes were included (63% women, 37% men). Most participants were patients undergoing colorectal or abdominal surgery under general anaesthesia; the second largest group of participants consisted of women undergoing caesarean section, mainly under regional anaesthesia. All participants came from primary prevention trials. Moderate to substantial heterogeneity was found in all of our analyses, which unfortunately was not explained by our subgroup analyses. Although more than half of the participants were randomly assigned in trials considered to have overall low risk of bias, our analyses revealed that lack of outcome reporting could influence the effect of the estimate of the intervention on surgical site infection. Accordingly, our 'best/worst case' and 'worst/best case' analyses revealed that results were compatible with no association and a harmful association with mortality and a beneficial effect, as well as with no association with surgical site infection of a high FIO₂ compared with routine use of oxygen.

Although these extreme sensitivity analyses represent unlikely results, they reveal how few participants lost to follow-up should have died to change our lack of findings into a potentially harmful effect. On the contrary, these sensitivity analyses also reveal how few participants lost to follow-up should have developed surgical site infection to change our lack of finding an effect on surgical site infections into a potentially beneficial effect.

Two trials were stopped early for benefit (meta-analytical estimate of effect: 65% RRR for surgical site infection) (Bickel 2011; Greif 1999), one trial was stopped early for harm (estimate of effect: 100% RRI for surgical site infection) (Pryor 2004) and three trials were stopped early for futility (meta-analytical estimate of effect: 16% RRI) (Gardella 2008; Thibon 2012, Williams 2013). Three trials did not report a sample size estimation (meta-analytical estimate of effect: 46% RRR) (Kotani 2000; Mayzler 2005; Schietroma 2013). All of these trials were stopped early on invalid stopping criteria (one-sided P values, $P < 0.05$) and on criteria not accepted by the Food and Drug Administration (FDA) or the European Medicines Agency (EMA), increasing the risk of random errors, that is, the risk of finding a difference that is not true and the risk of overlooking a difference that actually is true (Tikkinen 2011).

All of our meta-analyses fall short of the required information size of 13,264 participants (Thorlund 2011a) to detect or reject a 20% RRI or RRR for mortality and surgical site infection. In this respect, they are merely interim analyses performed to reach or not reach conclusive evidence of a 20% effect. When evaluating benefits and harms, we used trial sequential analysis to control for random errors, and we applied congruence (i.e. we requested the same thresholds for beneficial and harmful effects). This may not be ethically defensible in the case of harms, as we usually require more solid evidence for benefits than for harms. Moreover, many interventions that may offer benefits have been withdrawn from the market because some patients have died in association with the intervention. Accordingly, societies and regulatory agencies do not have congruent requirements for evidence on benefits and harms. Therefore, we may have been too stringent when dealing with risks of harm.

Quality of the evidence

A total of eight trials including 4918 participants reported on mortality. Fifteen trials with 7219 participants reported on surgical site infection.

A major drawback of some of the included trials is the proportion of participants lost to follow-up. This opens up the potential for attrition bias, and our 'best/worst' and 'worst/best' intention-to-treat analyses demonstrate that the intervention effect of a high FIO₂ compared with routine use of oxygen during anaesthesia and surgery may be either beneficial or harmful. This observation calls for more comprehensive meta-analyses of individual participant data plus further large RCTs. We have abstained from conducting 'uncertainty' analyses (Gamble 2005), which accept the point estimate from the complete participant analysis, while assuming that the distribution of surgical site infections among participants lost to follow-up is equal to the distribution of deaths among all participants. Actually, the distribution of surgical site infections among participants lost to follow-up may indeed be different from the distribution of participants actually followed through the whole observation period, making the 'uncertainty' analyses themselves uncertain.

We conducted various subgroup analyses. We observed no statistically significant differences in the intervention effect of a high FIO₂ compared with routine use of oxygen on mortality and surgical site infections in subgroup analyses of trials with overall low risk of bias compared with trials with overall unclear or high risk of bias; nor of trials using nitrogen compared with no nitrous oxide in the control group; trials using a high inspiratory oxygen fraction in the recovery period compared with trials using the intervention only during surgery; trials using a supplemental inspiratory oxygen fraction equal to or greater than 80% during the intervention compared with trials using 60% to 80% oxygen during the intervention; trials using a follow-up period shorter than 14 days compared with trials using follow-up of 30 days or longer; and trials in colorectal and abdominal surgical patients compared with trials in other types of surgery. However, in a post hoc analysis of trials using preoperative antibiotics compared with trials not using or not reporting use of preoperative antibiotics, we observed subgroup differences in effects of the intervention. Furthermore, it may be worthwhile to analyse whether the effects of a high FIO₂ compared with routine use of oxygen depend on the type of anaesthesia (general or regional anaesthesia) used during surgery. We did not plan such an analysis, and analysis may be complicated by the fact that some trials used both types of anaesthesia.

In addition to the six trials reporting mortality, nine trials reported on surgical site infection but not on mortality. Most of these trials were RCTs conducted to assess the effects of high FIO₂ compared with routine use of oxygen on surgical site infection; two trials reported exclusively on surrogate outcomes. A high FIO₂ compared with routine use of oxygen decreased surgical site infection on the fixed-effect model meta-analysis, but heterogeneity was substantial. The random-effects model did not reveal a statistically significant effect of a high FIO₂ compared with routine use of oxygen on surgical site infection. Accordingly, the decrease in the proportion of surgical site infections in a fixed-effect model may be due to an assumption that the intervention effect is equal across included trials - an assumption that probably is not valid because the incidence of surgical site infection and the bacteria involved differ substantially (e.g. in abdominal surgery vs other types of surgery).

We present our main results on all investigated outcomes in a summary of findings table (Summary of findings for the

main comparison) and have graded the quality of the evidence, including imprecision, according to Grades of Recommendation, Assessment, Development and Evaluation (GRADE) (Guyatt 2011; Guyatt 2013), stressing that results of meta-analyses reflect data derived from trials of low or very low quality.

The finding of a lack of significant association between a high FIO_2 of 60% to 90% and 30% to 40% oxygen and mortality and surgical site infection may be due to a type 2 error - a false-negative finding. This is exemplified by the fact that the cumulative Z-curve did not cross the trial sequential monitoring boundaries for futility nor for benefit or harm nor for the boundaries of futility for an anticipated effect of 20% RRR. However, such an analysis cannot remove risks of bias - detected or undetected. One should discuss, however, how much evidence one would require when dealing with potential benefit or harm. On the one hand, estimated beneficial or harmful effects can occur as the result of random errors. Therefore, sufficient information needs to be assessed to demonstrate benefit or harm beyond reasonable doubt. In this review, the TSA performed was based on anticipation of rather big intervention effects, undoubtedly clinically relevant but possibly not realistic. To detect or reject even smaller intervention effects, much larger information sizes are required.

Potential biases in the review process

We repeatedly searched several databases and contacted authors of trials investigating a high fraction of inspired oxygen of 60% to 90% compared with 30% to 40% oxygen used during anaesthesia and surgery. Therefore, we assume that we have not overlooked important RCTs. On the other hand, in general only about every second trial is reported (Gluud 2008), so we cannot exclude reporting biases, and inspecting our funnel plot for the effect of high supplemental oxygen on surgical site infection may suggest small trial bias. On the positive side, we managed to obtain more information on several trials than was revealed by any previously conducted reviews and meta-analyses. However, this does not detract from the fact that we did not have access to individual participant data. Accordingly, we have no chance of analysing the effect of an FIO_2 of 60% to 90% compared with 30% to 40% oxygen used during anaesthesia and surgery in patients receiving epidural analgesia, in patients kept normothermic during anaesthesia and surgery and in those with adequate fluid balance postoperatively. We selected all trials and extracted all data in duplicate, and we reached a high level of agreement. We did not conduct quality assessments nor data extractions while blinded to study authors and bias risks, and four of the authors of this review have been involved in one of the included trials (Meyhoff 2009). In this review, we present a conservative and, we believe, a more correct interpretation of findings compared with interpretations given in some other reviews and meta-analyses previously published outside The Cochrane Collaboration.

Agreements and disagreements with other studies or reviews

Previous meta-analyses of preventive trials of a high fraction of inspired oxygen with FIO_2 60% to 90% compared with 30% to 40% oxygen have provided substantially less information and have not examined the separate influence of different ways of using the intervention (Brar 2009; Brar 2011; Chura 2007; Fakhry 2012; Hovaguimian 2013; Kao 2012; Klingel 2013; Patel 2012; Qadan 2009;

Togioka 2012). None of these meta-analyses or systematic reviews conducted a proper bias assessment according to the Cochrane method, investigated the effect of bias in the seven domains as recommended by The Cochrane Collaboration or conducted analyses of possible subgroup differences in the effects of a high fraction of inspired oxygen between trials with overall low risk of bias and trials with one or more domains having high or unclear risk of bias. We conducted a thorough review in accordance with The Cochrane Collaboration methodology (Higgins 2011), implementing findings of methodological studies (Kjaergard 2001; Lundh 2012; Moher 1998; Savović 2012; Schulz 1995; Wood 2008). Between-trial heterogeneity was moderate to substantial in all of our meta-analyses. This may emphasize the inconsistency of our findings but also the diversity of the populations and settings included in the different trials, making results more generalizable (Ioannidis 2006). Furthermore, all-cause mortality generally should be connected with unbiased estimates (Savović 2012; Wood 2008). We also performed trial sequential analyses to control the risk of random errors in a cumulative meta-analysis and to prevent premature statements of superiority of a high fraction of inspired oxygen compared with routine use of oxygen (Brok 2008; Brok 2009; Thorlund 2009; Thorlund 2011; Thorlund 2011a; Wetterslev 2008; Wetterslev 2009).

Several trials (Goll 2001; Greif 1999; Joris 2003; McKeen 2009; Purhonen 2003; Purhonen 2006; Simurina 2010; Turan 2006) using a high fraction of inspired oxygen during surgery did not report on mortality or surgical site infection but reported exclusively on nausea and vomiting or surrogate outcomes for respiratory complications.

The number of meta-analyses conducted so far and the fact that meta-analyses have been updated several times from 2007 until now underline the necessity to take into account multiple testing on accumulating data when evaluating cumulative meta-analyses (Thorlund 2009; Wetterslev 2008). Further, when data are sparse and have not reached the required information size, the effect on, for example, mortality (Brar 2011) and surgical site infection (Qadan 2009) seems to be subject to change when data from further trials are included. However, none of the previously conducted meta-analyses or systematic reviews estimated a required information size for a realistic intervention effect on all-cause mortality or surgical site infection. Accordingly, they were not able to adjust the CI for increased risk of random errors when data were sparse and repetitive testing due to numerous updates was performed.

Despite discrepancies between our review and other meta-analyses and systematic reviews, we agree strongly with recently published reviews reporting no firm evidence that a high fraction of inspired oxygen of 60% to 90% compared with 30% to 40% oxygen during surgery (and for some trials also during the recovery room period) reduces all-cause mortality and surgical site infection. Further, meta-analyses and reviews concluding that a high inspiratory fraction of oxygen during surgery has an effect on surgical site infection have not demonstrated this convincingly by using both fixed-effect and random-effects models. Moreover, our analyses did not refute a clinically relevant effect, and lack of information is not the same as information of lack of effect. Therefore, further trials with low risk of bias and many more randomly assigned participants may very well change the estimates of effects on mortality and surgical site infection of a high fraction of inspired oxygen during surgery and recovery.

AUTHORS' CONCLUSIONS

Implications for practice

We could not exclude benefits or harms from use of a high inspired oxygen fraction (0.6 to 0.9) compared with a standard approach (0.3 to 0.4). Available randomized data do not suggest that either strategy is to be preferred. Further targeted research may provide definitive guidance in this area. As the risk of adverse events, including mortality, may be higher, and robust evidence for a beneficial effect on surgical site infection is lacking, overall our results suggest that evidence is insufficient to support the routine use of a high fraction of inspired oxygen beyond what is needed to maintain normal arterial oxygen saturation.

Implications for research

Additional RCTs are needed on the effects of a high fraction of inspired oxygen of 60% to 90% compared with 30% to 40% oxygen on mortality and on surgical site infection in all kinds of surgical patients. Before definitive conclusions can be drawn, we need more large trials with low risk of bias in all bias domains, testing effects of a fraction of 60% to 90% inspired oxygen versus 30% to 40% on patient important outcomes of all-cause mortality, surgical site infection and health-related quality of life. Future RCTs ought to be conducted with long-term follow-up and ought to stratify participants by type of surgery and documented risk

factors for mortality and surgical site infection. Future trials ought to be designed according to the SPIRIT guidelines ([Chan 2013](#)) and reported according to the CONSORT guidelines (www.consort-statement.org). Future trials also ought to report individual participant data, so that proper individual participant data meta-analyses of the effects of a high fraction of inspired oxygen of 60% to 90% compared with 30% to 40% oxygen adjusted for relevant confounders can be conducted. Further, in future updates of this review, we will seek to conduct subgroup analyses of the effects of a high inspiratory fraction of oxygen in trials using regional anaesthesia compared with trials using only general anaesthesia.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Belda 2005

Methods	Multi-centre trial at 14 sites in Spain. Exclusion: surgery less than 1 hour, DM, HA < 30 g/L, weight loss > 20 kg in 3 months, HIV, leucocytes < 2500 cells/mL. Surgical site infection follow-up within 14 days. Antibiotics used to a similar extent in both groups: metronidazole, cefoxitin, cefalosporine or aminoglycoside	
Participants	Patients with major open colorectal resection. Mean age 63 years. F = 52% vs 36%. 65% of participants with cancer. 21% smokers. BMI 27 kg/m ²	
Interventions	80% oxygen vs 30% oxygen. N ₂ O not used. Mechanical bowel preparation the night before surgery. Intervention 6 hours postoperatively	
Outcomes	Mortality, surgical site infection within 15 days and LOS reported. Surgical site infection defined by CDC criteria. Mortality and surgical site infection reported according to modified ITT (excluding participants post randomization with exclusion criteria)	
Notes	Imbalance between groups not reported on epidural or vasopressor treatment	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers

Belda 2005 (Continued)

Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Surgical teams and postoperative care personnel were blinded. Anaesthetists were not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Evaluators of whether or not wound infection occurred were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	9 participants did not participate in the final analyses because of incomplete data (loss to follow-up?), laparoscopic surgery or low preoperative HA
Selective reporting (reporting bias)	Low risk	Mortality and surgical site infection were reported. However, SAEs including respiratory insufficiency were not reported
Other bias	Unclear risk	Complementary funding by Air-Liquide Medicinal and Air-Liquide Santé, which participated in design and logistics but not in analyses, interpretation and writing

Bhatnagar 2005

Methods	Randomized parallel 3-group trial
Participants	Women undergoing radical mastectomy
Interventions	30%, 50% and 80% inspired fractions of oxygen with no use of nitrous oxide
Outcomes	PONV within 24 hours
Notes	20 participants in each group; sample size of 60 participants

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization according to random numbers on a computer spread sheet
Allocation concealment (selection bias)	Unclear risk	No comments on this in the manuscript
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Reported a blinded trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Reported a blinded trial
Incomplete outcome data (attrition bias)	Unclear risk	Not reported and no specific statement on none lost to follow-up

Bhatnagar 2005 (Continued)

All outcomes

Selective reporting (reporting bias)	Low risk	Reported on PONV as intended; no other outcomes protocolized
Other bias	Unclear risk	We do not know, as study authors were impossible to reach

Bickel 2011

Methods	Single-centre study, Israel. Follow-up within 14 days. Antibiotics against gram-negative and anaerobic bacteria to all participants lasting for 5 days when appendix was perforated or gangrenous	
Participants	Patients with appendicitis scheduled for open appendectomy. ASA 1 to 2, age > 15 years. 1.3% of patients with diabetes. Exclusion of patients with malnutrition, immunodeficiency and COPD	
Interventions	80% oxygen vs 30% oxygen during and 2 hours after surgery. N ₂ O was used during surgery	
Outcomes	Surgical site infection within 2 weeks and LOS	
Notes	Stopped early for benefit without an adequate a priori stopping rule. Stopped because of "the impression that a statistically significant result had already been obtained" Included in this review, although some participants were younger than 18 years of age	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	High flow mask vs nasal cannula oxygen. Surgical team blinded. Anaesthetists not blinded and recovery team not blinded. FIO ₂ in sealed envelopes until unblinding of trial
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Evaluators of whether or not wound infection occurred were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	None lost to follow-up; no participants withdrew
Selective reporting (reporting bias)	Low risk	Surgical site infection reported; mortality, SAE and respiratory insufficiency not reported
Other bias	Unclear risk	Unclear whether participants 14 years of age or younger participated. No commercial funding

Duggal 2013

Methods	Multi-centre in USA. Follow-up at 3 days, 14 days and 6 weeks. Antibiotics administered as cefazolin IV after cord clamping
Participants	Women for caesarean section
Interventions	80% vs 30% oxygen during delivery and for 1 hour postoperatively
Outcomes	Surgical site infection within 30 days and endometritis defined by CDC criteria. Mortality not reported
Notes	Published

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random table computer generated
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Obstetrician and participants blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Surgeons and participants blinded to the intervention, exact FIO ₂ and randomization number kept in safe not accessible to investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	16.4% lost to follow-up despite attempts to reach participants at 6 weeks. Attempts were made to contact by phone or in home participants not showing up at 14 days or at 6 weeks. Reasons for dropout described as not able to contact participants
Selective reporting (reporting bias)	Low risk	Surgical site infection and endometritis
Other bias	Low risk	Groups well matched for age, DM, previous section, emergency section. Figures reported

García-Botello 2006

Methods	Single centre in Spain. N ₂ O unclear, not stated. Antibiotics used 2 hours before surgery: amoxicillin-clavunate 2 gr and 1 gr × 3 the following day
Participants	Colorectal surgery. Exclusion: mental disability, psychotropic drugs, other trials, emergency surgery, ASA ≥ 4, diabetes, HIV, weight loss > 20% 3 months before surgery, HA < 30 g/L, leucocytes < 2500 cells/microL, current/recent infection
Interventions	80% oxygen vs 30% oxygen during and 6 hours after surgery. N ₂ O unclear, not stated
Outcomes	Primary outcome pH _i and CO ₂ gaps

García-Botello 2006 (Continued)

Notes Primary outcome ph_i and CO_2 gaps. Reported anastomotic dehiscence but not wound infections within 7 days

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers sequence
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Surgical team blinded. Anaesthetist not blinded. Recovery team not blinded. Participants not described
Blinding of outcome assessment (detection bias) All outcomes	High risk	Postoperative assessors of ph_i and CO_2 gaps were not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	Only anastomosis leakage reported. Surgical site infection, mortality, LOS and respiratory insufficiency not reported
Other bias	Low risk	No withdrawals, but 6 participants needed increased FIO_2

Gardella 2008

Methods	Single centre in USA. Follow-up within 14 days. All participants but 1 received prophylactic antibiotics
Participants	Regional anaesthesia and clinical indication for section after onset of labour. Exclusion: emergency section, general anaesthesia planned, HIV or clinical chorion amnionitis
Interventions	80% oxygen vs 30% oxygen on non-rebreathing mask without N_2O during surgery and regional anaesthesia and 2 hours postoperatively. FIO_2 not described if anaesthesia was converted to GA
Outcomes	Only surgical site infection within 14 days and LOS reported
Notes	Stopped early for futility after 25% of sample size estimated with P value = 0.13. P value ≥ 11 was the estimated critical value for futility. Recruiting problems?

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers table used

Gardella 2008 (Continued)

Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Obstetrical teams, participants, postoperative care personnel blinded. Anaesthetists not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Evaluators of whether or not wound infection occurred were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomly assigned participants followed up and analysed
Selective reporting (reporting bias)	Unclear risk	Only surgical site infection reported. Mortality and SAEs not reported
Other bias	Low risk	No commercial funding. No obvious baseline imbalance

Golfam 2011

Methods	Single centre in Iran. Follow-up of 14 days. Use of antibiotics not reported
Participants	Patients for breast surgery. Exclusion criteria not reported. Participant characteristics not reported
Interventions	100% oxygen vs 30% oxygen in air and halothane anaesthesia exclusively during the intraoperative period
Outcomes	Surgical site infection reported within 14 days
Notes	Only reported as an abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Reported as a double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Unclear risk	Not reported

Golfam 2011 (Continued)

All outcomes

Selective reporting (reporting bias)	Low risk	So far only surgical site infection reported
Other bias	Unclear risk	Not reported

Goll 2001

Methods	Single-centre trial in Austria. 3-group parallel randomized trial
Participants	Women 17 to 70 years of age undergoing gynaecological laparoscopy
Interventions	80% oxygen in nitrogen vs 30% oxygen in nitrogen vs 30% oxygen in nitrogen and ondansetron. No nitrous oxide used
Outcomes	PONV, QoL: SF-36, choice of future anaesthesia, time to discharge home
Notes	Sample size estimation reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Sealed envelopes until used. According to study authors: "Allocation was concealed until just before induction of anaesthesia"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Anaesthesiologist not blinded. Separate teams managed intraoperative and postoperative aspects of the trial. Participants, nurses and surgeons blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Separate teams managed intraoperative and postoperative aspects of the trial and observers were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants were lost to follow-up
Selective reporting (reporting bias)	Low risk	Participant satisfaction, time to discharge home, QoL: SF-36, choice of future anaesthesia. According to study authors: "Mortality, surgical site infection, LOS, and respiratory insufficiency not registered. SF-36: provided by the authors"
Other bias	Low risk	According to study authors: "There was no corporate support or involvement whatsoever". Transport sickness skewed distribution

Greif 1999

Methods	Single-centre trial in Austria. 2-parallel group randomized trial
Participants	Patients undergoing colon resection 18 to 80 years of age
Interventions	80% oxygen vs 30% oxygen in nitrogen during and for 2 hours after surgery
Outcomes	PONV within 24 hours postoperatively
Notes	No sample size estimation reported. Possible overlap with Greif 2000

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was based on computer-generated codes
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes maintained until just before induction of anaesthesia
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Anaesthesiologist not blinded. Participants, surgeons and personnel blinded. Cardboard shields over flowmeters used intraoperatively and in the recovery room
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Nurses blinded to group allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants lost to follow-up
Selective reporting (reporting bias)	Low risk	Mortality, surgical site infection, LOS and respiratory insufficiency not reported
Other bias	Low risk	No conflicts of interest

Greif 2000

Methods	Multi-centre trial in Austria and Germany. Exclusion: recent history of fever/infection, HA < 3.3 g/dL, weight loss > 20%, bowel obstruction, leucocytes < 2.5. Surgical site infection follow-up within 15 days. Most participants received antibiotics: metronidazole and (ceftazidime, cefazolin, amoxicillin or clavulanate or mezlocillin) 100% before skin incision. Answer from study authors: "All operations were elective colectomy, which surgeons usually consider "clean-contaminated"
Participants	Elective, open colorectal surgical patients. Mean age 57 years. M/F = 280/220. 7.4% DM 2 patients. 26.5 smokers at baseline. 60% cancer patients
Interventions	80% oxygen vs 30% oxygen. N ₂ O not used. Mechanical bowel preparation the night before surgery
Outcomes	Mortality, surgical site infection and LOS reported. Surgical site infection was diagnosed when bacteria were cultured from the pus from the wound

Greif 2000 (Continued)

Notes Stopped early with a 1-sided stopping rule. P value < 0.012 as Fisher 1-sided P value = 0.0108 (2-sided Fisher P value = 0.02)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Surgeons and care personnel blinded. Anaesthetists not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Evaluators of whether or not wound infection occurred were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 participants withdrew consent (for the intervention) and are analysed as having no surgical site infection. Answer from study authors: "I (Daniel Sessler) don't know what happened to the patients who withdrew consent, but we surely stopped following them and I would assume that they were dropped from the analysis"
Selective reporting (reporting bias)	Low risk	Mortality and surgical site infection reported. However, SAEs including respiratory insufficiency not reported. Answer from study authors: "We recorded ICU admission and probably obvious respiratory complications, but I (Daniel Sessler) no longer have access to these data. Curiously, they aren't included in my export summary. We did not measure QoL. This important issue wasn't really on anyone's radar screen at the time"
Other bias	Low risk	Imbalance between groups not reported on diabetic patients types 1 and 2, epidural and vasopressor treatment

Joris 2003

Methods	Single-centre trial in Belgium. 3-parallel group randomized trial
Participants	Patients undergoing thyroidectomy
Interventions	80% oxygen vs 30% oxygen vs 30% oxygen with droperidol. Interventions continued into the recovery period on non-rebreathing face masks (Trident Medical International, Copenhagen, Denmark) for 2 hours at 9 L/min
Outcomes	PONV
Notes	Sample size estimation reported by study authors as 50 in each group

Risk of bias

Bias	Authors' judgement	Support for judgement
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Joris 2003 (Continued)

Random sequence generation (selection bias)	Low risk	Randomly assigned
Allocation concealment (selection bias)	Low risk	Randomly assigned after induction of anaesthesia
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Anaesthetist not blinded. Surgeons, personnel blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded observers
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	According to study author correspondence: "some patients, but I cannot tell you how many, were lost to follow-up but replaced by others to achieve 50 randomized patients"
Selective reporting (reporting bias)	Low risk	According to study author correspondence: "mortality, surgical site infection, LOS and respiratory insufficiency not registered"
Other bias	Low risk	According to study author correspondence: no conflicts of interest

Kotani 2000

Methods	Single centre in Japan. Parallel-group trial
Participants	Orthopaedic surgical patients with surgery lasting longer than 6 hours
Interventions	100% oxygen during surgery and not during recovery room period, when all participants breathed 40% oxygen on a rebreathing mask. No use of nitrous oxide
Outcomes	Gene expression of pro-inflammatory cytokines, PF ratio, atelectasis and pulmonary complications
Notes	Follow-up time not described. Sample size estimation not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Computer generated. The words "randomized", "random allocation" and "randomly assigned" not used anywhere in the article
Allocation concealment (selection bias)	Low risk	Sealed, sequentially numbered envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Surgeons, nurses and participants blinded. However, investigator and anaesthesiologist aware of group allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigator and anaesthesiologist aware of group allocation. However, evaluator of pulmonary complications unaware of group allocation

Kotani 2000 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	Surgical site infection and mortality not reported. Pulmonary complications reported: "failed to identify any"
Other bias	Low risk	No financial support from companies; study authors did not receive honoraria or own stocks in companies related to this research. No baseline imbalance detectable

Mackintosh 2012

Methods	Single-centre trial in USA. 2 × 2 factorial design with 90% oxygen or more vs 30% oxygen and 2 levels of PEEP. Use of antibiotics revealed in answer from study authors: according to recommended drugs for common procedures: primarily cefazolin (75%), cefoxitin and alternately if primary drug contraindicated: cefuroxime, clindamycin and gentamicin or ciprofloxacin	
Participants	Adults 18 to 70 years of age scheduled for endotracheal anaesthesia. Exclusion: major open abdominal surgery, spine or craniotomy surgery, prone position, SpO ₂ < 90% in room air, obstructive sleep apnoea, planned postoperative intubation or ICU stay	
Interventions	100% (94% in actuality due to low gas flow and off-gassing of nitrogen (inspired oxygen)) oxygen vs 30% (35% in actuality due to need to maintain SpO ₂) and 2 levels of PEEP	
Outcomes	Requirement for postoperative supplemental oxygen if SpO ₂ < 90% and SpO ₂ on room air	
Notes	Co-study authors published on benefits of high fraction of inspiratory oxygen	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated sequence of numbers
Allocation concealment (selection bias)	Low risk	Security, opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants blinded. Anaesthetists not blinded. Statisticians blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators blinded to group assignment until data collection had been completed
Incomplete outcome data (attrition bias) All outcomes	Low risk	None lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Study authors' answer: no registration of surgical site infection or mortality. SAEs comprising only ICU admission, ventilator requirement and respiratory insufficiency within 24 hours

Mackintosh 2012 (Continued)

Other bias	Low risk	Imbalance not detected on age, sex, smoking status, SpO ₂ at baseline, BMI, duration of anaesthesia, types of surgery, blood loss, fluid administration or administration of opioids
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Mayzler 2005

Methods	Single-centre trial in Israel. Surgical site infection follow-up within 14 days. Timing of antibiotic treatment not reported	
Participants	Patients with major open colorectal resection. Mean age 68 years. M/F = 22/16. 100% of patients had cancer. BMI 26 kg/m ² . Exclusion: ASA ≥ 3, DM, HA < 3.3 g/dL, weight loss > 20%, preoperative immunosuppressive therapy, leucocytes < 2500 cells/mL	
Interventions	80% oxygen vs 30% oxygen with N ₂ O. Supplemental oxygen administered for 2 hours postoperatively. Mechanical bowel preparation before surgery	
Outcomes	Mortality and surgical site infection within 15 days reported. Surgical site infection defined by CDC criteria. Mortality and surgical site infection reported according to modified ITT (excluding participants post randomization with exclusion criteria)	
Notes	No sample size estimation reported	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Lottery of closed envelopes
Allocation concealment (selection bias)	Low risk	Closed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding of participants, care personnel, surgical teams and recovery personnel not reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Evaluators of whether or not wound infection occurred were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	None withdrawn
Selective reporting (reporting bias)	Unclear risk	Surgical site infection reported. Mortality, SAEs and respiratory insufficiency not reported
Other bias	Low risk	Imbalance between groups not reported on smoking, wound contamination, fraction of participants with epidural, temperature and fluid treatment

McKeen 2009

Methods	Single-centre trial in Canada
Participants	ASA 1 and 2; women undergoing laparoscopic tubal ligation
Interventions	Inspiratory fraction of oxygen of 80% vs 30% in nitrogen
Outcomes	Postoperative nausea and vomiting. VAS score and post discharge. Time to discharge home
Notes	Sample size estimation reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random assignment
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes broken after induction of anaesthesia
Blinding of participants and personnel (performance bias) All outcomes	Low risk	For PONV during 24 hours postoperatively
Blinding of outcome assessment (detection bias) All outcomes	Low risk	For PONV during 24 hours postoperatively
Incomplete outcome data (attrition bias) All outcomes	Low risk	12 participants excluded from analyses with reasons
Selective reporting (reporting bias)	Low risk	No reported side effects related to FIO ₂ within 24 hours. Mortality, surgical site infection, LOS and respiratory insufficiency not registered
Other bias	Low risk	Study authors report no conflicts of interest

Meyhoff 2009

Methods	Multi-centre trial at 14 sites in Denmark. Follow-up of surgical site infection within 30 days. Long-term follow-up of mortality. Antibiotics administered 1 hour before skin incision: cefuroxime, metronidazole or ampicillin, metronidazole, gentamicin
Participants	Patients for abdominal surgery including gynaecological patients and appendectomy. Median age 64 years. 42% males. Mean BMI = 25 kg/m ² . 30% smokers. 2.7% contaminated or dirty infected. 27.6% emergency surgery. 7.4% diabetic patients
Interventions	80% oxygen vs 30% oxygen during surgery and for 2 hours postoperatively. No use of nitrous oxide
Outcomes	Surgical site infection within 30 days, mortality, LOS, respiratory insufficiency and SAEs
Notes	Long-term follow-up for mortality was not a preplanned outcome but was due to a perceived possible difference within 30 days; post hoc analysis of mortality was performed

Meyhoff 2009 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers sequence
Allocation concealment (selection bias)	Low risk	Interactive voice response service, telephone-based central allocation from independent centre
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Surgical team blinded. Participants blinded. Outcome assessor blinded. Anaesthetists not blinded. Anaesthesia record in participant file, but FIO ₂ in sealed envelope not accessed in any cases. Statistician and authors of the first draft of abstracts blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Evaluators of whether or not wound infection occurred were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	14 participants excluded post randomization because surgery and withdrawals described
Selective reporting (reporting bias)	Low risk	Mortality, surgical site infection, SAEs, LOS and respiratory insufficiency reported
Other bias	Low risk	No commercial funding. No detectable imbalance

Myles 2007

Methods	Multi-centre, multi-national trial with 19 sites in Australia and Hong Kong. Follow-up 30 days or longer. Antibiotics used in accordance with institutional practice: prophylaxis in 90% of participants
Participants	Major, mixed types of surgery lasting longer than 2 hours. Mean age 55 years. 53% males. Mean body weight 71 kg. 40% emergency surgery. 14% diabetic patients. All types of surgery
Interventions	Aimed for 80% oxygen vs 30% oxygen with N ₂ O; for the intervention group, mean oxygen fraction in inspiratory gas was 73% ± SD of 17%
Outcomes	Mortality, surgical site infection within 30 days, SAEs but may not have been reported systematically. Long-term mortality reported with median follow-up of 3.9 years in 1660 participants (340 lost to follow-up)
Notes	This trial primarily studied anaesthesia with supplemental N ₂ O vs N ₂ O-free anaesthesia with supplemental oxygen, thereby allowing for comparison of the effects of supplemental oxygen around 73% vs N ₂ O in 30% oxygen

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated sequence of random numbers

Myles 2007 (Continued)

Allocation concealment (selection bias)	Low risk	Interactive voice response service, central telephone-based allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Surgical team blinded. Participants blinded. Anaesthetists not blinded. Anaesthesia record in participant file, but research staff precluded from accessing the record
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Evaluators of whether or not wound infection occurred were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes for 23 + 15 who developed exclusion criteria postoperatively are not described
Selective reporting (reporting bias)	Low risk	Mortality, surgical site infection and nearly every possible SAE are counted
Other bias	Low risk	No commercial funding. No detectable baseline imbalance

Pryor 2004

Methods	Single centre in USA. Follow-up approximately 14 days. Antibiotics administered at arrival to the operating room or before: cefoxitine, cefazolin
Participants	Patients for major laparotomy, including those with laparoscopic assisted procedure. Exclusion: ASA 5, bleomycin, SBP < 90 mmHg, need for more than 35% oxygen, risk of respiratory depression with more than 80% oxygen
Interventions	80% oxygen vs 35% oxygen with N ₂ O during anaesthesia. Supplemental oxygen administered with face mask and reservoir for 2 hours postoperatively
Outcomes	Surgical site infection within 14 days, length of stay during index admittance
Notes	Stopped early for "harm" after 165 participants out of 300, with P value = 0.02, claimed to be less than a LanDeMets critical P value of 0.03

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers table
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Surgical team blinded. Participants blinded. Anaesthetists not blinded. Anaesthesia record in participant file. Study author responded to question on blinding: "Hospital regulations mandate that the anaesthesia record must be part of the patient's chart. So the anaesthesia records were part of the chart, but were kept in a separated section at the back. The charts used at the time did not indicate FiO ₂ , but did show gas flows. I am aware that criticism was levelled at

Pryor 2004 (Continued)

		the possibility that surgeons could have been unblinded. However, in practice, I think this was extraordinarily unlikely"
Blinking of outcome as- essment (detection bias) All outcomes	High risk	Evaluators of whether or not wound infection occurred had access to partici- pant file with gas flows in anaesthesia records
Incomplete outcome data (attrition bias) All outcomes	Low risk	5 participants in the 80% oxygen group were excluded because of change in surgery and change in anaesthesiologist and never received 80% oxygen
Selective reporting (re- porting bias)	Low risk	Surgical site infection, mortality and SAEs reported. Study author responded to questions on QoL: "Sorry, we had no QoL measurement"
Other bias	Low risk	Imbalance between groups for BMI and for smoking at baseline postsurgical site infection not reported on epidural. No commercial funding

Purhonen 2003

Methods	2-centre trial in Finland. 2-parallel group, randomized trial
Participants	Women, ASA 1 to 2, undergoing ambulatory gynaecological laparoscopy
Interventions	80% oxygen vs 30% oxygen; both groups with oxygen in nitrogen during surgery and for 2 hours post- operatively. Postoperative mask used: adhesive continuous positive air pressure mask (Vital Signs, To- towa, NJ)
Outcomes	PONV 24 hours postoperatively obtained by nurse via telephone. Satisfaction with anaesthesia
Notes	Sample size estimation reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence genera- tion (selection bias)	Low risk	Computer-generated numbers in permuted blocks
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinking of participants and personnel (perfor- mance bias) All outcomes	Low risk	For PONV during 24 hours of follow-up
Blinking of outcome as- essment (detection bias) All outcomes	Low risk	For PONV during 24 hours of follow-up
Incomplete outcome data (attrition bias) All outcomes	Low risk	Five participants lost to follow-up described
Selective reporting (re- porting bias)	Low risk	Mortality, surgical site infection, LOS and respiratory insufficiency not reported

Purhonen 2003 (Continued)

Other bias	Unclear risk	Conflicts of interest not reported
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Purhonen 2006

Methods	Single-centre trial in Finland; 3-parallel group randomized trial
Participants	ASA 1 to 3; women for breast surgery between 18 and 75 years of age
Interventions	80% oxygen vs 30% oxygen vs 30% oxygen and ondansetron; all 3 groups with oxygen in nitrogen during surgery and for 2 hours postoperatively. Postoperative mask used: adhesive continuous positive air pressure mask (Vital Signs, Totowa, NJ)
Outcomes	PONV within 24 hours postoperatively. VAS score and quantity of escape medication for PONV. Satisfaction with anaesthesia
Notes	Sample size estimation reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated numbers in permuted blocks
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	For PONV during 24 hours of follow-up
Blinding of outcome assessment (detection bias) All outcomes	Low risk	For PONV during 24 hours of follow-up
Incomplete outcome data (attrition bias) All outcomes	Low risk	5 participants lost to follow-up described
Selective reporting (reporting bias)	Unclear risk	Mortality, surgical site infection, LOS and respiratory insufficiency not reported
Other bias	Unclear risk	Conflicts of interest not reported

Schietroma 2013

Methods	Parallel, single-centre trial in Italy. Antibiotics used 1 hour before surgery: cefotaxime 2 gr × 3
Participants	Patients with cancer or lymphoma for total gastrectomy. Patients with diabetes excluded. None of the patients with contaminated or dirty infected surgical site. None of the patients with emergency surgery. ASA 1 to 3

Schietroma 2013 (Continued)

Interventions	80% oxygen vs 30% oxygen during surgery and for 6 hours postoperatively. No use of nitrous oxide. Cefotaxime 2 gr × 3 in both intervention groups
Outcomes	Mortality, surgical site infection within 14 days: Study author wrote in specific communication: "Only those infections diagnosed during the first 14 postoperative days were included. During the postoperative period we have not registered serious adverse events"; LOS
Notes	Rebreathing mask 16 L/min. Sample size estimation not reported: Study author wrote in specific communication: "Concerning the sample size, a projected sample size was not mentioned in the article itself (it was about 210 patients). The decision to conclude the study of this stage (171 patients) was made owing [to] the impression that statistical results had already been obtained"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study author wrote in specific communication: "Patients were randomly assigned to an oxygen/air mixture with a fraction of inspired oxygen (FiO ₂) of 30% or 80%, according to a computer-generated table of random numbers. Randomization was performed by an independent computer consultant"
Allocation concealment (selection bias)	Low risk	Study author wrote in specific communication: "Yes, the allocation sequence was concealed for the investigators when patients were asked to participate in the trial"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study author wrote in specific communication: "Yes, the participants and personnel were blinded during the trial interventions"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Surgeons assessed wounds for surgical site infection. Study author wrote in specific communication: "Yes, the persons assessing the outcomes were blinded for the interventions"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Study author wrote in specific communication: "No patient was lost to follow-up"
Selective reporting (reporting bias)	Low risk	Surgical site infection and LOS described. Mortality and SAEs not described
Other bias	Unclear risk	Similar articles by the same study authors were retracted in 2013 because of fraud

Scifres 2011

Methods	Single centre in USA. Follow-up approximately 14 days. Antibiotics administered before skin incision: cefazolin or clindamycin
Participants	Women for caesarean section during regional anaesthesia. 0% contaminated. 75% of participants with BMI > 30 kg/m ² . 13% to 17% smokers. 5% to 6% pregestational DM, 6% to 7% gestational DM. Exclusion: emergency surgery, HIV, immune suppressive treatment, extrauterine infection
Interventions	80% vs 25% to 30% oxygen on nasal cannula during surgery and 2 hours perioperatively

Scifres 2011 (Continued)

Outcomes	Surgical site infection as wound infection within 4 weeks and endometritis. Mortality for neonates. Neonatal sepsis	
Notes	Baseline imbalance: fewer smokers in 80% FIO ₂ group, more participants overweight	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported how participants were "randomly assigned"
Allocation concealment (selection bias)	Low risk	Use of opaque envelopes stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	None were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT analysis unclear, as ITT analysis was not performed on randomly assigned participants minus participants lost to follow-up. 6 patients in each group lost to follow-up
Selective reporting (reporting bias)	Low risk	Mortality for neonates reported. Maternal mortality not reported. Respiratory insufficiency not reported. SAEs reported only as neonatal sepsis. LOS and QoL not reported
Other bias	Low risk	Fewer smokers in 80% FIO ₂ group, more participants overweight

Simurina 2010

Methods	Single-centre trial in Croatia. Randomized 3-parallel group trial	
Participants	Women, ASA 1 and 2, between 21 and 76 years of age for elective gynaecological laparoscopic surgery	
Interventions	Inspiratory fractions of 80%, 50% and 30% oxygen in air and sevoflurane. All participants breathed room air postoperatively during 24 hours of follow-up	
Outcomes	Postoperative nausea and vomiting. VAS score	
Notes	120 participants randomly assigned. 36 × 3 analysed	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers

Simurina 2010 (Continued)

Allocation concealment (selection bias)	Unclear risk	According to study author response, misunderstanding surrounds adequate allocation concealment, as blinding of participants, personnel and outcome assessors is taken for adequate allocation concealment: "One of the main investigators did not perform anaesthesia procedures and did not know which anaesthetics were given to the intervention group and that investigator collected postoperative data only"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	During 24 hours and for PONV
Blinding of outcome assessment (detection bias) All outcomes	Low risk	During 24 hours and for PONV
Incomplete outcome data (attrition bias) All outcomes	Low risk	Explained in CONSORT diagram
Selective reporting (reporting bias)	Low risk	According to study author response: "there were no side effects registered within 24 hrs. Mortality, surgical site infection, LOS and respiratory insufficiency not registered"
Other bias	Low risk	Study authors report no financial conflicts of interest

Stall 2013

Methods	Parallel single-centre trial in USA. Antibiotics used preoperatively: 1 to 2 gr cefazolin every 8 hours (max × 3) if open fracture up to 48 hours after surgery
Participants	High energy fractures of the tibia or calcaneus with delayed osteosynthesis to avoid contamination of wounds
Interventions	80% oxygen vs 30% oxygen during surgery and for 2 hours postoperatively. No use of nitrous oxide. Nasal cannula in control patients. Cefazolin 1 to 2 gr every 8 hours up until 48 hours in both intervention groups
Outcomes	Surgical site infection within 12 weeks, SAEs, LOS assessed daily during admission and at 2, 6 and 12 weeks
Notes	Rebreathing mask 15 L/min

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Third party random-number generator
Allocation concealment (selection bias)	Low risk	Opaque sealed sequentially numbered envelopes
Blinding of participants and personnel (performance bias)	Unclear risk	Participants, surgeons and principal investigator blinded; however control participants treated with oxygen delivered through nasal cannulas. Randomization list locked up

Stall 2013 (Continued)

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Surgeons blinded to the intervention evaluated wounds for surgical site infection
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawals and participants lost to follow-up described, but 10 fractures in 11 participants lost to follow-up is inconsistent
Selective reporting (reporting bias)	Low risk	Surgical site infection and LOS described. Study authors' answer: zero mortality in both groups within 30 days. SAEs not registered; QoL not registered
Other bias	Unclear risk	Reporting and analysing of numbers of wounds/injuries instead of numbers of participants

Thibon 2012

Methods	4 centres in France, parallel design. Prophylactic antibiotic in 115 vs 109 participants, respectively, in the 2 intervention groups	
Participants	Participants undergoing routine elective abdominal, gynaecological and breast surgery	
Interventions	80% oxygen vs 30% oxygen during surgery. No supplemental oxygen postoperatively. No use of nitrous oxide	
Outcomes	Surgical site infection and adverse events: dry cough, hypotension, sternal pain, visual and auditory disturbances	
Notes	No postoperative oxygen protocolized. Sample size reported to 540; trial stopped after 438 because of elapsed time. Study authors report 94% of estimated sample size enrolled	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated allocation list without blocking or stratification. Balance within centres maintained
Allocation concealment (selection bias)	High risk	Random allocation via computer, but anaesthesiologist, who enrolled participants into the trial, had access to the allocation list on the computer
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Surgeons, team, participants blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Surgeons evaluating wound blinded for intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals and participants lost to follow-up described

Thibon 2012 (Continued)

Selective reporting (reporting bias)	Low risk	Surgical site infection and adverse events described. SAEs and mortality not described
Other bias	Unclear risk	Air Liquide co-sponsoring the trial, but influence unclear

Turan 2006

Methods	Multi-centre trial at 3 centres in Turkey, USA and Germany. Part of a factorial design, parallel-group randomized trial	
Participants	Participants with at least a 40% risk for PONV undergoing various elective surgical procedures	
Interventions	80% oxygen vs 30% oxygen in nitrogen. Postoperatively, all participants received 30% to 40% oxygen at a flow of 6 litres	
Outcomes	PONV within 24 hours	
Notes	Sample size estimation reported	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly allocated
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Regarding PONV within 24 hours. Anaesthetist not blinded. Other personnel blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Regarding PONV within 24 hours. Assessors blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant excluded from analyses because of incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	Mortality, surgical site infection, LOS and respiratory insufficiency not reported
Other bias	Low risk	No conflicts of interest

Williams 2013

Methods	Single centre in USA. Aerosol mask with a high flow oxygen blender. Antibiotics administered at umbilical cord clamping: Cefazolin or clindamycin × 1	
Participants	Women for caesarean section	

Williams 2013 (Continued)

Interventions	80% vs 30% oxygen during both surgery and the postoperative period. No use of N ₂ O
Outcomes	Surgical site infection within 30 days
Notes	Trial stopped early after 179 participants enrolled, although a sample size of 932 to detect or reject a 50% decrease in surgical site infection was calculated. Stopped for "futility" on inadequate stopping rule, assuming the trend would continue. Group imbalance reported as without significant differences in age, BMI, gestational age or chorioamnionitis. Participants with diabetes 13.2% vs 6.3% but not significantly different

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list
Allocation concealment (selection bias)	Low risk	Sealed closed envelopes sequentially numbered. Envelopes broken only after participants entered the trial before surgery. Study author answered the question: "Randomization was completed prior to enrolment by a third party study coordinator using computerized randomization software. Randomization information was placed in sequentially numbered and sealed opaque envelopes (manila envelopes). Randomization envelopes were provided to the anaesthesia provider in numerical order corresponding to order of patient enrolment"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and surgeons were blinded to the FIO ₂ used. Anaesthetists were not blinded. Study author answered the question: "Operating physicians and their management teams, patients, and all other providers were blinded to randomization"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Wound evaluation teams were blinded to the interventions
Incomplete outcome data (attrition bias) All outcomes	Low risk	179 participants were randomly assigned but only 160 were analysed because of loss to follow-up
Selective reporting (reporting bias)	Low risk	Surgical site infection reported. Mortality, SAEs not registered. Study authors answered question on QoL: "We did not administer a quality of life questionnaire. We did not record information on length of stay, though this information could be gleaned from the electronic record if indicated. There were no deaths in either treatment group for the study duration"
Other bias	Low risk	Reported no conflicts of interest

Zorembo 2010

Methods	Single centre in Germany. Follow-up 24 hours
Participants	Moderately obese adult patients: BMI 25 to 35 kg/m ² . ASA I to III patients, scheduled for minor surgery. Exclusion of laparoscopic surgery, gastrointestinal reflux or hiatus hernia, pregnancy, asthma requiring therapy, cardiac disease > NYHA II, severe psychiatric disorder
Interventions	80% oxygen vs 30% oxygen without N ₂ O

Zorembo 2010 (Continued)

Outcomes Pulse oximetry saturation SpO₂ measured during air breathing, lung function tests FRC and FVC
MEF-25, etc. No imbalance detected in age, BMI, surgical duration and type of surgery

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	173 randomly assigned and data were analysed for only 142 participants
Selective reporting (reporting bias)	Unclear risk	Surgical site infection, mortality, SAEs not reported
Other bias	Low risk	No conflicts of interest reported

ASA = American Society of Anesthesiology.

BMI = body mass index.

CDC = Centers for Disease Control and Prevention.

CONSORT = Consolidated Standards of Reporting Trials.

COPD = chronic obstructive pulmonary disease.

DM = diabetes mellitus.

FRC = functional residual capacity.

FVC = forced ventilatory capacity.

GA = general anaesthesia.

HA = human albumin.

ICU = intensive care unit.

ITT = intention-to-treat.

IV = intravenous.

LOS = length of stay.

PEEP = post end-expiratory pressure.

PF = peak flow.

PONV = postoperative nausea and vomiting.

QoL = quality of life.

SAE = serious adverse event.

SD = standard deviation.

VAS = visual analogue score.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Agarwal 2002	Trial period within 30 minutes of intubation; no intervention hereafter and no postoperative observation
Akca 1999	Subgroup of Greif 2000
Anthony 2010	Bundle of core interventions. 80% oxygen and 30% oxygen groups differed with respect to 4 more interventions: omnisurgical site infection on bowel preparation, normothermia, restrictive fluid administration and wound edge protection
Brar 2011	Not an RCT. Meta-analysis of 5 RCTs
Butler 1987	Wrong intervention: 28% oxygen exclusively postoperatively
Chura 2007	Not an RCT. Systematic review including 4 RCTs
Fakhry 2012	Not an RCT. Narrative review of 7 RCTs. Without meta-analysis
Kabon 2010	Wrong intervention: supplemental oxygen only postoperatively for 12 to 18 hours
Karu 2007	Wrong intervention. Supplemental oxygen could be administered only before cardioplegia in coronary artery bypass surgery. Outcomes included myocardial enzymes and postoperative haemodynamic indices
Kirkpatrick 2011	Not an RCT. Commentary on Meyhoff 2009
Lee 2004	Letter to the editor. Not an RCT
Niinikoski 1977	Review article. Not an RCT
Ochmann 2010a	Retracted for fraud in 2012
Piper 2006	Retracted for fraud in 2012
Qadan 2009	Not an RCT. Meta-analysis of 5 RCTs
Qadan 2010	Not an RCT. In vitro study of the effects of 80% oxygen vs 21% oxygen on TNF-alfa and reactive oxygen species in venous blood from young healthy volunteers
Roseau 2000	Letter to the editor. Not an RCT
Schietroma 2012	Retracted by editors because of plagiarism, as undue similarities with another study of Buchs NC et al were noted
Schweon 2006	Review article. Not an RCT
Treschan 2005	Includes participants younger than 18 years of age. Follow-up 24 hours. Outcomes not relevant for this review
Turtiainen 2011	Wrong intervention. Only postoperative administration of 30% oxygen in the supplemental oxygen group
Wadhwa 2010a	Wrong intervention. Only a comparison of 80% oxygen vs 30% oxygen in the postoperative period, with both groups receiving 80% oxygen intraoperatively
Wadhwa 2010b	Wrong intervention. Only a comparison of 80% oxygen vs 30% oxygen in the postoperative period, with both groups receiving 80% oxygen intraoperatively

Study	Reason for exclusion
Yu H 2010	Letter to the editor. Not an RCT

RCT = randomized clinical trial.

TNF-alfa = tumour necrosis factor alfa.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Gin 2013

Methods	Randomized clinical trial, 3 groups, parallel assignment
Participants	Patients for major surgery
Interventions	30% and 80% oxygen and 70% nitrous oxide
Outcomes	DNA damage and surgical site infection
Notes	Published only as an abstract

Schietroma 2014

Methods	Randomized clinical trial, parallel assignment
Participants	81 patients having colorectal surgery
Interventions	80% and 30% oxygen during and 6 hours after surgery
Outcomes	Surgical site infection
Notes	

Characteristics of ongoing studies *[ordered by study ID]*

Osvaldo 2011

Trial name or title	Supplemental perioperative oxygen to reduce the incidence of post-caesarean wound infection
Methods	Randomized clinical trial, parallel assignment
Participants	Women for emergency caesarean section with gestational age > 37 weeks
Interventions	FIO ₂ of 80% vs 35% in air/no nitrous oxide
Outcomes	Surgical site infection
Starting date	2011
Contact information	Osvaldo A. Reyes T., Saint Thomas Hospital, Panama
Notes	Stipulated to include 362 participants. NCT01340534

Santa Clara Valley Health

Trial name or title	Supplemental oxygen and risk of surgical site infection (PORSSI)
Methods	Randomized clinical trial, parallel assignment. Double-blind study
Participants	Women older than 18 years of age for caesarean section
Interventions	FIO ₂ of 80% vs 30% by mask
Outcomes	Surgical site infection
Starting date	2010
Contact information	NNeena Duggal, MD; 408-885-5550; neena.duggal@hhs.sccgov.org
Notes	NCT00876005

DATA AND ANALYSES

Comparison 1. 60% to 90% oxygen vs 30% to 40% oxygen perioperatively

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality within longest follow-up stratified according to overall risk of bias	8	4918	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.87, 1.33]
1.1 Trials with overall low risk of bias	4	4058	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.93, 1.36]
1.2 Trials with overall unclear or high risk of bias	4	860	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.15, 1.20]
2 Mortality within longest follow-up best/worst case scenario of participants lost to follow-up	8	4918	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.25, 1.25]
3 Mortality within longest follow-up worst/best case scenario of participants lost to follow-up	8	4918	Risk Ratio (M-H, Random, 95% CI)	1.50 [1.04, 2.15]
4 Mortality within 30 days of follow-up stratified according to overall risk of bias	8	4918	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.83 [0.54, 1.29]
4.1 Trials with overall low risk of bias	4	4058	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.99 [0.61, 1.60]
4.2 Trials with overall high or unclear risk of bias	4	860	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.37 [0.13, 1.05]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Surgical site infection stratified according to overall risk of bias in a random-effects model	15	7219	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.71, 1.07]
5.1 Trials with low risk of bias	5	4201	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.63, 1.17]
5.2 Trials with high or unclear risk of bias	10	3018	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.64, 1.18]
6 Surgical site infection stratified according to overall risk of bias in a fixed-effect model	15	7219	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.77, 0.99]
6.1 Trials with low risk of bias	5	4201	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.73, 1.00]
6.2 Trials with high or unclear risk of bias	10	3018	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.74, 1.11]
7 Surgical site infection stratified according to use of nitrous oxide	14	7159	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.71, 1.08]
7.1 No use of nitrous oxide	10	4739	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.71, 1.11]
7.2 Use of nitrous oxide	4	2420	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.45, 1.61]
8 Surgical site infection stratified according to FIO ₂ in the intervention group higher or lower than 80%	15	7219	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.71, 1.07]
8.1 FIO ₂ in the intervention group 80% or higher	12	4216	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.66, 1.15]
8.2 FIO ₂ in intervention group lower than 80% and higher than 60%	3	3003	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.65, 1.02]
9 Surgical site infection stratified according to use of high FIO ₂ during operation and the postoperative period	15	7219	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.71, 1.07]
9.1 Use of high FIO ₂ during both surgery and the postoperative period	13	6725	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.70, 1.09]
9.2 Use of high FIO ₂ only during surgery	2	494	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.45, 1.73]
10 Surgical site infection stratified according to type of surgery	15	7219	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.71, 1.07]
10.1 Colorectal and abdominal surgery	7	2761	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.50, 1.09]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.2 Caesarean section	4	1719	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.91, 1.60]
10.3 Orthopaedic surgery	1	233	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.37, 1.34]
10.4 Breast surgery	1	60	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.87]
10.5 Mixed types of surgery	2	2446	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.59, 0.99]
11 Surgical site infection according to follow-up longer or shorter than 14 days	15	7219	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.71, 1.07]
11.1 Follow-up longer than 14 days	8	6141	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.05]
11.2 Follow-up of 14 or fewer days	7	1078	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.48, 1.47]
12 Surgical site infection stratified according to use of preoperative antibiotics	15	7219	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.71, 1.07]
12.1 Use of preoperative antibiotics	10	5440	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.60, 0.97]
12.2 Lack of use or lack of reporting use of preoperative antibiotics	5	1779	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.91, 1.58]
13 Surgical site infection stratified according to sequence generation	15	7219	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.71, 1.07]
13.1 Adequate sequence generation	10	6155	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.71, 1.11]
13.2 Unclear/inadequate sequence generation	5	1064	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.36, 1.31]
14 Surgical site infection stratified according to allocation concealment	16	7264	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.71, 1.07]
14.1 Adequate allocation concealment	12	5894	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.67, 1.09]
14.2 Unclear/inadequate allocation concealment	4	1370	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.66, 1.40]
15 Surgical site infection according to blinding of participants and personnel	15	7219	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.71, 1.07]
15.1 Adequate blinding of participants and personnel	7	4668	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.61, 1.03]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.2 Unclear/inadequate blinding of participants or personnel	8	2551	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.70, 1.37]
16 Surgical site infection stratified according to outcome assessment	15	7219	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.71, 1.07]
16.1 Adequate blinding of outcome assessment	12	6414	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.66, 0.96]
16.2 Unclear/inadequate blinding of outcome assessment	3	805	Risk Ratio (M-H, Random, 95% CI)	1.57 [1.04, 2.37]
17 Surgical site infection stratified according to completeness of outcome data	15	7219	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.71, 1.07]
17.1 Complete outcome data	11	5841	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.71, 1.11]
17.2 Incomplete outcome data	4	1378	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.41, 1.43]
18 Surgical site infection stratified according to outcome reporting	15	7219	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.71, 1.07]
18.1 Adequate outcome reporting	15	7219	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.71, 1.07]
18.2 Unclear/inadequate outcome reporting	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
19 Surgical site infection stratified according to presence of other bias	15	7219	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.71, 1.07]
19.1 No presence of other bias	13	6489	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.71, 1.13]
19.2 Unclear or definite presence of other bias	2	730	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.48, 1.07]
20 Surgical site infection best/worst case scenario of participants lost to follow-up	15	7219	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.54, 0.93]
21 Surgical site infection worst/best case scenario of participants lost to follow-up	15	7219	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.78, 1.42]
22 Respiratory insufficiency stratified according to overall risk of bias	3	1588	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.79, 1.99]
22.1 Trials with low risk of bias	1	1386	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.79, 1.99]
22.2 Trials with unclear or high risk of bias	2	202	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
23 Serious adverse events	3	3558	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.65, 1.43]
23.1 Trials with low risk of bias	2	3398	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.63, 1.31]
23.2 Trials with high risk of bias	1	160	Risk Ratio (M-H, Random, 95% CI)	5.0 [0.60, 41.85]
24 Length of stay after surgery	7	4702	Mean Difference (IV, Random, 95% CI)	-0.06 [-0.44, 0.32]
24.1 Trials with low risk of bias	4	4041	Mean Difference (IV, Random, 95% CI)	-0.13 [-0.49, 0.24]
24.2 Trials with high or unclear risk of bias	3	661	Mean Difference (IV, Random, 95% CI)	0.69 [-0.82, 2.20]

Analysis 1.1. Comparison 1 60% to 90% oxygen vs 30% to 40% oxygen perioperatively, Outcome 1 Mortality within longest follow-up stratified according to overall risk of bias.

Analysis 1.2. Comparison 1 60% to 90% oxygen vs 30% to 40% oxygen perioperatively, Outcome 2 Mortality within longest follow-up best/worst case scenario of participants lost to follow-up.

Analysis 1.3. Comparison 1 60% to 90% oxygen vs 30% to 40% oxygen perioperatively, Outcome 3 Mortality within longest follow-up worst/best case scenario of participants lost to follow-up.

Analysis 1.4. Comparison 1 60% to 90% oxygen vs 30% to 40% oxygen perioperatively, Outcome 4 Mortality within 30 days of follow-up stratified according to overall risk of bias.

Analysis 1.5. Comparison 1 60% to 90% oxygen vs 30% to 40% oxygen perioperatively, Outcome 5 Surgical site infection stratified according to overall risk of bias in a random-effects model.

Analysis 1.6. Comparison 1 60% to 90% oxygen vs 30% to 40% oxygen perioperatively, Outcome 6 Surgical site infection stratified according to overall risk of bias in a fixed-effect model.

Analysis 1.7. Comparison 1 60% to 90% oxygen vs 30% to 40% oxygen perioperatively, Outcome 7 Surgical site infection stratified according to use of nitrous oxide.

Analysis 1.8. Comparison 1 60% to 90% oxygen vs 30% to 40% oxygen perioperatively, Outcome 8 Surgical site infection stratified according to FIO₂ in the intervention group higher or lower than 80%. **Analysis 1.9. Comparison 1 60% to 90% oxygen vs 30% to 40% oxygen perioperatively, Outcome 9 Surgical site infection stratified according to use of high FIO₂ during operation and the postoperative period.**

Analysis 1.10. Comparison 1 60% to 90% oxygen vs 30% to 40% oxygen perioperatively, Outcome 10 Surgical site infection stratified according to type of surgery.

Analysis 1.11. Comparison 1 60% to 90% oxygen vs 30% to 40% oxygen perioperatively, Outcome 11 Surgical site infection according to follow-up longer or shorter than 14 days.

Analysis 1.12. Comparison 1 60% to 90% oxygen vs 30% to 40% oxygen perioperatively, Outcome 12 Surgical site infection stratified according to use of preoperative antibiotics.

Analysis 1.13. Comparison 1 60% to 90% oxygen vs 30% to 40% oxygen perioperatively, Outcome 13 Surgical site infection stratified according to sequence generation.

Analysis 1.14. Comparison 1 60% to 90% oxygen vs 30% to 40% oxygen perioperatively, Outcome 14 Surgical site infection stratified according to allocation concealment.

Analysis 1.15. Comparison 1 60% to 90% oxygen vs 30% to 40% oxygen perioperatively, Outcome 15 Surgical site infection according to blinding of participants and personnel.

Analysis 1.16. Comparison 1 60% to 90% oxygen vs 30% to 40% oxygen perioperatively, Outcome 16 Surgical site infection stratified according to outcome assessment.

Analysis 1.17. Comparison 1 60% to 90% oxygen vs 30% to 40% oxygen perioperatively, Outcome 17 Surgical site infection stratified according to completeness of outcome data.

Analysis 1.18. Comparison 1 60% to 90% oxygen vs 30% to 40% oxygen perioperatively, Outcome 18 Surgical site infection stratified according to outcome reporting.

Analysis 1.19. Comparison 1 60% to 90% oxygen vs 30% to 40% oxygen perioperatively, Outcome 19 Surgical site infection stratified according to presence of other bias.

Analysis 1.20. Comparison 1 60% to 90% oxygen vs 30% to 40% oxygen perioperatively, Outcome 20 Surgical site infection best/worst case scenario of participants lost to follow-up.

Analysis 1.21. Comparison 1 60% to 90% oxygen vs 30% to 40% oxygen perioperatively, Outcome 21 Surgical site infection worst/best case scenario of participants lost to follow-up.

Analysis 1.22. Comparison 1 60% to 90% oxygen vs 30% to 40% oxygen perioperatively, Outcome 22 Respiratory insufficiency stratified according to overall risk of bias.

Analysis 1.23. Comparison 1 60% to 90% oxygen vs 30% to 40% oxygen perioperatively, Outcome 23 Serious adverse events.

Study or subgroup	60-90% oxygen n/N	30-40% oxygen n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: $Z=0.21(P=0.84)$					
Test for subgroup differences: $\text{Chi}^2=2.41$, $\text{df}=1$ ($P=0.12$), $I^2=58.44\%$					
			0.01 0.1 1 10 100		
			60-90% oxygen		30-40% oxygen

Analysis 1.24. Comparison 1 60% to 90% oxygen vs 30% to 40% oxygen perioperatively, Outcome 24 Length of stay after surgery.

APPENDICES

Appendix 1. Centers for Disease Control and Prevention criteria for surgical site infection

Surgical site infection

Superficial incisional surgical site infection

Infection occurring within 30 days after the operation and infection involving only skin or subcutaneous tissue of the incision and at least one of the following.

1. Purulent drainage, with or without laboratory confirmation, from the superficial incision.
2. Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision.
3. At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness or heat; superficial incision is deliberately opened by surgeon, unless incision is culture-negative.
4. Diagnosis of superficial incisional surgical site infection by a surgeon or attending physician.

Do not report the following conditions as surgical site infection.

1. Stitch abscess (minimal inflammation and discharge confined to the points of suture penetration).
2. Infection of an episiotomy or newborn circumcision site.
3. Infected burn wound.
4. Incisional surgical site infection that extends into the fascial and muscle layers (see deep incisional surgical site infection).

Deep incisional surgical site infection.

Infection occurring within 30 days after the operation if no implant† is left in place, or within one year if implant is in place and the infection appears to be related to the operation and infection involves deep soft tissues (e.g. fascial and muscle layers) of the incision and at least one of the following.

1. Purulent drainage from the deep incision but not from the organ/space component of the surgical site.
2. A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever ($> 38^{\circ}\text{C}$), localized pain or tenderness, unless site is culture-negative.
3. An abscess or other evidence of infection involving the deep incision found on direct examination, during reoperation or by histopathological or radiological examination.
4. Diagnosis of a deep incisional surgical site infection by a surgeon or attending physician.

Notes

1. Report infection that involves both superficial and deep incision sites as deep incisional surgical site infection.
2. Report an organ/space surgical site infection that drains through the incision as a deep incisional surgical site infection.

Organ or space surgical site infection.

Infection occurring within 30 days after the operation if no implant† is left in place, or within one year if implant is in place and the infection appears to be related to the operation and infection involves any part of the anatomy (e.g. organs, spaces), other than the incision, which was opened or manipulated during an operation, and at least one of the following.

1. Purulent drainage from a drain that is placed through a stab wound‡ into the organ or space.
2. Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ or space.
3. An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation or by histopathological or radiological examination.
4. Diagnosis of an organ or space surgical site infection by a surgeon or attending physician.

† National Nosocomial Infection Surveillance definition: a non-human-derived implantable foreign body (e.g. synthetic hernia mesh, prosthetic heart valve, non-human vascular graft, mechanical heart, hip prosthesis) that is permanently placed within a patient during surgery.

‡ If the area around a stab wound becomes infected, this is not a surgical site infection. It is considered a skin or soft tissue infection, depending on its depth.

Appendix 2. Search strategy: MEDLINE

- 1 exp Surgical-Wound-Infection/ or Wound-Infection/
- 2 (((surgic* adj5 wound*) or (surgic* adj5 site*)) and infect*).mp. or ((site* or wound*) adj5 infect*).ti,ab. or (operat* adj3 wound*).mp. (47494)
- 3 1 or 2
- 4 Oxygen/ or exp Oxygen-Inhalation-Therapy/ or exp Hyperoxia/
- 5 (((inspirator* or fraction* or supplement* or concentrat*) adj5 oxygen*) or hyperoxia or oxygenat*).mp.
- 6 4 or 5
- 7 3 and 6
- 8 ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (animals not (humans and animals)).sh.
- 9 7 and 8

Appendix 3. Search strategy: EMBASE

- 1 exp surgical infection/ or exp wound infection/
- 2 (((surgic* adj5 wound*) or (surgic* adj5 site*)) and infect*).mp. or ((site* or wound*) adj5 infect*).ti,ab. or (operat* adj3 wound*).mp.
- 3 1 or 2
- 4 oxygen/ or exp oxygen therapy/ or exp hyperoxia/
- 5 (((inspirator* or fraction* or supplement* or concentrat*) adj5 oxygen*) or hyperoxia or oxygenat*).mp.
- 6 4 or 5
- 7 3 and 6
- 8 (randomized-controlled-trial/ or randomization/ or controlled-study/ or multicenter-study/ or phase-3-clinical-trial/ or phase-4-clinical-trial/ or double-blind-procedure/ or single-blind-procedure/ or (random* or cross?over* or factorial* or placebo* or volunteer*).mp. or ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask*).ti,ab.) not (animals not (humans and animals)).sh.
- 9 7 and 8

Appendix 4. Search strategy: Cochrane CENTRAL

- #1 MeSH descriptor Surgical Wound Infection explode all trees
- #2 MeSH descriptor Wound Infection explode all trees
- #3 (((surgic* near wound*) or (surgic* near site*)) and infect*) or ((site* or wound*) near infect*):ti,ab or (operat* near wound*)
- #4 (#1 OR #2 OR #3)
- #5 MeSH descriptor Oxygen, this term only
- #6 MeSH descriptor Oxygen Inhalation Therapy explode all trees
- #7 MeSH descriptor Hyperoxia explode all trees
- #8 ((inspirator* or fraction* or supplement* or concentrat*) near oxygen*) or hyperoxia or oxygenat*
- #9 (#5 OR #6 OR #7 OR #8)
- #10 (#4 AND #9)

Appendix 5. Search strategy: Web of Science

- #1 TS= ((surgic* SAME wound*) or (surgic* SAME site*)) and TS=infect*
- #2 TS=(site* or wound*) SAME TS=infect*
- #3 TS=(operat* SAME wound*)
- #4 #3 OR #2 OR #1
- #5 TS=(inspirator* or fraction* or supplement* or concentrat* or therapy) SAME TS=oxygen*
- #6 TS=(hyperoxia or oxygenat*)
- #7 #6 OR #5
- #8 #7 AND #4

Appendix 6. Search strategy: CINAHL

- S1 (MM "Surgical Wound Infection") or (MM "Surgical Wound") or (MH "Wound Infection") or (MH "Surgical Wound Care")
- S2 TX ((surgic* and wound*) or (surgic* and site*)) and TX infect*
- S3 AB (site* or wound*) and AB infect*

- S4 operat* and wound*
- S5 S1 or S2 or S3 or S4
- S6 (MH "Oxygen") or (MH "Hyperbaric Oxygenation")
- S7 (MM "Hyperoxia")
- S8 TX (inspirator* or fraction* or supplement* or concentrat*) and TX oxygen*
- S9 hyperoxia or oxygenat*
- S10 S6 or S7 or S8 or S9
- S11 S5 and S10

Appendix 7. Data extraction form

Effects of high perioperative inspiratory oxygen fraction for adult surgical patients

Study selection, quality assessment and data extraction form

First author	Journal/Conference proceedings, etc	Year

Study eligibility

RCT	Relevant participants	Relevant interventions	Relevant outcomes
Yes/No/Unclear	Yes/No/Unclear	Yes/No/Unclear	Yes/No*/Unclear

* Issue relates to selective reporting when study authors may have taken measurements for particular outcomes but did not report these within the paper(s). Review authors should contact trialists for information on possible surgical site infection, non-reported outcomes and reasons for exclusion from publication. Study should be listed in 'Studies awaiting assessment' until clarified. If no clarification is received after three attempts, study should be excluded.

Do not proceed if any of the above answers is 'No'. If a study is to be included in the 'Excluded studies' section of the review, record below the information to be inserted into the 'Table of excluded studies'.

Freehand space for comments on study design and treatment:

References to trial

Check other references identified in searches. If you find further references to this trial, link the papers now and list below. All references to a trial should be linked under one Study ID in RevMan.

Code each paper	Author(s)	Journal/Conference proceedings, etc	Year
A	<i>The paper listed above</i>		
B	<i>Further papers</i>		
C			
D			
E			

Participant and trial characteristics

Participant characteristics	
Co-variate	Further details
Age (mean, median, range, etc)	
Sex of participants (numbers/%, etc)	
Disease status/type, etc (if applicable)	
BMI (mean, median, range, etc)	
Diabetes status at baseline (numbers/%, etc)	
Smoker status at baseline (numbers/%, etc)	
Contaminated or dirty-infected (numbers/%, etc)	

Methodological quality

Allocation of intervention

State here method used to generate allocation and reasons for grading

Grade (circle)

Low risk of bias (random)

High risk of bias (e.g. alternate)

Unclear

Concealment of allocation

Process used to prevent foreknowledge of group assignment in an RCT, which should be seen as distinct from blinding

State here method used to conceal allocation and reasons for grading

Grade (circle)

Low risk of bias

High risk of bias

Unclear

Blinding

Person responsible for participant care

Yes/No

Participant

Yes/No

Outcome assessor

Yes/No

Other (please specify)

Yes/No

Incomplete outcome data

Low risk of bias, if numbers and reasons for dropouts and withdrawals in the intervention groups were described, or if it was specified that no dropouts or withdrawals occurred

Yes/No

High risk of bias, if numbers or reasons for dropouts and withdrawals were not described

Yes/No

Unclear, if the report gave the impression that no dropouts or withdrawals had occurred, but this was not specifically stated

Yes/No

Selective outcome reporting

(Continued)

Low risk of bias, if predefined or clinically relevant and reasonably expected outcomes are reported on	Yes/No
---	--------

High risk of bias, if one or more clinically relevant and reasonably expected outcomes were not reported on; data on these outcomes were likely to have been recorded	Yes/No
---	--------

Unclear, not all pre-defined, or clinically relevant and reasonably expected outcomes are reported on or are not reported fully, or if it is unclear whether data on these outcomes were recorded	Yes/No
---	--------

Baseline imbalance

Low risk of bias, if no baseline imbalance in important characteristics was noted	Yes/No
---	--------

High risk of bias, if a baseline imbalance was due to chance or was due to imbalanced exclusion after randomization	Yes/No
---	--------

Unclear, if baseline characteristics were not reported	Yes/No
--	--------

Early stopping

Low risk of bias, if sample size calculation was reported and the trial was not stopped, or if the trial was stopped early by formal stopping rules at a point at which the likelihood of observing an extreme intervention effect due to chance was low	Yes/No
--	--------

High risk of bias, if the trial was stopped early because of informal stopping rules, or if the trial was stopped early by a formal stopping rule at a point at which the likelihood of observing an extreme intervention effect due to chance was high	Yes/No
---	--------

Unclear, if sample size calculation was not reported, and if it is not clear whether or not the trial was stopped early	Yes/No
---	--------

Other bias

No risk of other bias, the trial appears to be free of other components that could put it at risk of bias	Yes/No
---	--------

Risk of other bias, other factors in the trial could put it at risk of bias (e.g. 'for-profit' involvement, authors have conducted trials on the same topic)	Yes/No
--	--------

Unclear, the trial may or may not be free of other components that could put it at risk of bias	Yes/No
---	--------

Modified intention-to-treat

A modified intention-to-treat analysis is one in which all participants in a trial are operated on and analysed according to the intervention to which they were allocated, whether or not they received it

(Continued)

All participants entering the trial after surgery

15% or fewer excluded

More than 15% excluded

Not analysed as modified 'intention-to-treat'

Unclear

Were withdrawals described? Yes ? No ? Not clear ?

Discuss if appropriate.

Trial characteristics

Further details

Single centre/multi-centre

Country/Countries

How was participant eligibility defined?

How many participants were randomly assigned?

Number of participants in each intervention group

Number of participants who received intended intervention (per protocol population)

Number of participants who were analysed

Duration of surgery in minutes

Antibiotic regimen used

Time of antibiotic administration

Administration of oxygen, type of face mask?

Duration of supplemental oxygen intervention including postoperative period or not?

Mean temperature and range during anaesthesia

Mean fluid volume and range management during anaesthesia

Fraction of participants with epidural anaesthesia

Fraction of participants administered vasopressors

(Continued)

Median (range) length of follow-up reported in this paper (state weeks, months or years, or if not stated)

Time points within which surgical site infection was diagnosed during the trial?

Time points reported in the trial?

Time points you are using in RevMan

Trial design (e.g. parallel/cross-over*)

Other

* If cross-over design, please refer to the Cochrane Editorial Office for further advice on how to analyse these data.

Other design characteristics of the trial

1. The trial used inspiratory oxygen with nitrous oxide. **Yes ? No ?**
2. The trial used an FIO₂ of 80% in the intervention group. **Yes ? No ?**
3. The trial used an FIO₂ less than 80% for the intervention. **Yes ? No ?**
4. The trial included only participants for abdominal surgery. **Yes ? No ?**
5. The trial included only participants for upper laparotomy. **Yes ? No ?**
6. The trial included only participants for lower laparotomy. **Yes ? No ?**
7. The trial included only participants for laparoscopic surgery. **Yes ? No ?**
8. The trial included only participants for orthopaedic surgery. **Yes ? No ?**
9. The trial included other than abdominal/orthopaedic surgery. **Yes ? No ?**
10. Follow-up of participants for surgical site infection was within 14 days. **Yes ? No ?**
11. Follow-up of participants was within 30 days or longer. **Yes ? No ?**

Data extraction

Outcomes	Available for the trial
1.1 Overall mortality. We will use the longest follow-up data from each trial regardless of the period of follow-up.	Yes/No
1.2 Surgical site infection (surgical site infection) within the longest follow-up after surgery defined by study authors.	Yes/No
2.1 Respiratory insufficiency defined as the need for respiratory ventilator therapy or non-invasive ventilation within 30 days of randomization.	Yes/No
2.2 Serious adverse events. We have defined serious adverse events according to the International Conference on Harmonisation (ICH) Guidelines (ICH 1997) as "any event that leads to death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalisation, results in persistent or significant disability, and any important medical event which may jeopardise the patient or requires intervention to prevent it". All other adverse events are considered non-serious	Yes/No

For continuous data							
Code of paper	Outcomes (rename)	Unit of measure- ment	Intervention group		Control group		Details if outcome described only in text
			n	Mean (SD)	n	Mean (SD)	
A, etc	2.3 Duration of postoperative hospital- ization.	Days					
A, etc	2.4 Quality of life.	Score (SF-36, etc)					

For dichotomous data

Code of paper	Outcomes	Intervention group	Control group E/N
		E/N	
		E = number of events	E = number of events
		N = number of participants	n = number of participants
A	1.1 Overall mortality.		
	1.2 Surgical site infection within the longest follow-up after surgery defined by study authors.		
	2.1 Respiratory insufficiency defined as the need for respiratory assistance as ventilator therapy or non-invasive ventilation within 30 days of randomization.		
	2.2 Serious adverse events. We have defined serious adverse events according to the International Conference on Harmonisation (ICH) Guidelines (ICH 1997). All other adverse events are considered non-serious.		

Other information that you feel is relevant to the results

Indicate if any data were obtained from the primary author; if results were estimated from graphs, etc, or were calculated by you using a formula (this should be stated and the formula given). In general if results not reported in paper(s) are obtained, this should be made clear here to be cited in the review.

Freehand space for writing actions such as contact with study authors and changes:

References to other trials

Did this report include any references to published reports of potentially eligible trials not already identified for this review?

First study author

Journal/Conference

Year of publication

(Continued)

Did this report include any references to unpublished data from potentially eligible trials not already identified for this review? If yes, give list contact name and details.

Appendix 8. Criteria for risk of bias evaluation

Random sequence generation

Low risk of bias: Method used generates random sequences (e.g., random number generation, toss of coin).

Unclear: no information on random sequence generation available.

High risk of bias: alternate medical record numbers or other non-random sequence generation.

Allocation concealment

Low risk of bias: Allocation method prevents investigators or participants from knowing the next allocation (e.g. central allocation; sealed opaque envelopes; serially numbered, sequentially numbered but otherwise identical vehicles, including their contents; or other descriptions of convincing concealment of allocation).

High risk of bias: no information on allocation method available, or the description did not allow a clear distinction.

Inadequate: Allocation method allowed investigators or participants to know the next allocation (e.g. alternate medical record numbers; reference to case record numbers or date of birth; an open allocation sequence; unsealed envelopes).

Blinding

Low risk of bias: We considered blinding as adequate if participants and personnel were kept unaware of intervention allocations after inclusion of participants into the study and the method of blinding involved placebo.

Unclear: blinding not described.

High risk of bias: not double-blinded; categorized as an open-label study; or without use of placebo.

Incomplete outcome data

Low risk of bias: if numbers and reasons for dropouts and withdrawals in the intervention groups were described, or if it was specified that no dropouts or withdrawals occurred.

Unclear: if the report gave the impression that no dropouts or withdrawals had occurred, but this was not specifically stated.

High risk of bias: if numbers or reasons for dropouts and withdrawals were not described.

Selective outcome reporting

Low risk of bias: if pre-defined or clinically relevant and reasonably expected outcomes are reported on.

Unclear: if not all pre-defined or clinically relevant and reasonably expected outcomes are reported on, or if they are not reported fully, or it is unclear whether or not data on these outcomes were recorded.

High risk of bias: One or more clinically relevant and reasonably expected outcomes were not reported on; data on these outcomes were likely to have been recorded.

Baseline imbalance

Adequate: if no baseline imbalance in important characteristics was noted.

Unclear: if baseline characteristics were not reported.

Inadequate: if baseline imbalance was due to chance or was due to imbalanced exclusion after randomization.

Early stopping

Low risk of bias: if sample size calculation was reported and the trial was not stopped, or if the trial was stopped early by a formal stopping rules at a point at which the likelihood of observing an extreme intervention effect due to chance was low ([Lan 1983](#)).

Unclear: if sample size calculation was not reported, and it is not clear whether or not the trial was stopped early.

High risk of bias: if the trial was stopped early because of informal stopping rules, or if the trial was stopped early by a formal stopping rule at a point at which the likelihood of observing an extreme intervention effect due to chance was high ([Lan 1983](#)).

Other bias

To report on other bias in addition to the above mentioned (e.g. industry bias, academic bias), one should continue to use the following pattern.

Low risk of bias: Trial appears to be free of other components that could put it at risk of bias.

Unclear risk of bias: Trial may or may not be free of other components that could put it at risk of bias.

High risk of bias: Other factors in the trial could put it at risk of bias (e.g. 'for-profit' involvement, authors have conducted trials on the same topic).

We will also consider the administration of inappropriate treatment given to controls, such as a suboptimal dosage of medication or a supraoptimal dosage of medication.

FEEDBACK

Feedback from Hopf et al, 2 May 2016

Summary

[Wetterslev 2015](#) "employed Cochrane methodology" to evaluate whether perioperative high-inspired oxygen supplementation (alone) prevents surgical site infection and / or causes harm as measured by respiratory insufficiency, serious adverse events, and length of stay. They conclude that there is little, if any, benefit in reducing SSI, and that there is evidence of harm. Their statistical analysis, however, demonstrates evidence of significant benefit in preventing SSI, and no significant evidence of harm. They claim the statistical bar for evidence should be higher for benefit than for harm. While this is problematic, more problematic is the lack of attention in their review to the underlying biology and physiology in assessing the quality of the studies and arriving at conclusions. Two major omissions render their conclusions unsupported.

Omission One: The biology of oxygen in immunity. Innate immunity and antibiotics are the only protections wounds have against infection. Both require oxygen to kill pathogens and do so in direct proportion to the oxygen concentration (pwO_2) in the wound. Innate immunity begins with phagocytosis of tol-marked pathogens by neutrophils and macrophages. This stimulates a burst of oxygen consumption as an NADPH-linked oxidase is activated to convert molecular oxygen to lethal reactive oxygen species (ROS) that it sequesters into the phagosomes (or other trapping mechanism). There, mixed with lysosomal proteases, ROS deliver the coup de grâce to the pathogens ([Roos 2003](#)). The importance of oxygen is illustrated by a well-known genetic defect in the NADPH-linked oxidases that renders them unable to convert O_2 to ROS, allowing bacterial ingestion but not killing by phagosomes, an effect that is duplicated by rendering neutrophils hypoxic ([Allen 1997](#)). The resulting severe immunopathy, called Chronic Granulomatous Disease, is characterized by granulomas that contain collections of ingested but still living bacteria that periodically escape and cause sepsis. Early death is prevented only by almost constant use of antibiotics. In addition, antibiotics are effective by producing microbicidal ROS ([Dwyer 2014](#)). Notably, [Wetterslev et al](#) found a statistically significant benefit to high-inspired perioperative oxygen in studies in which patients received perioperative antibiotics. In summary: increasing pwO_2 increases immunity; it is chemically axiomatic and experimentally proven.

Omission Two: The physiology of oxygen in immunity. PwO_2 is controlled by perfusion and arterial pO_2 . Subcutaneous tissue, where most SSIs originate, has a limited vascular supply, and perfusion is exceedingly sensitive to sympathetic agonists, pain, hypothermia, hypovolaemia, and stress. Therefore, PwO_2 is often low and unresponsive to supplemental oxygen especially at the end of operations when sympathetic stimulation is greatest. All but five of the trials analysed by [Wetterslev](#) contained no measures to control, ie. optimize blood flow. The results of trials in which subcutaneous blood flow was not addressed are difficult to interpret, since there is no evidence oxygen reached the wound and a likelihood, based on human studies, that it did not ([Ueno 2006](#)). This is not noted in the review nor taken into account in the evaluation of studies. Excluding these studies would lead to clear evidence of benefit in preventing SSI. [Greif 2000](#) demonstrated that when euthermia, analgesia, and generous fluids (10 to 15 mL/kg/h plus losses) are standardized, 80% inspired oxygen almost doubles pwO_2 intraoperatively and leads to a ~30% increase in the PACU. These values suggest about a doubling microbial killing capacity. Including all four trials that standardized care to maintain wound perfusion ([Belda 2005](#); [Bickel 2011](#); [Greif 1999](#); [Schietroma 2013](#)) the reduction in SSI ranged from 40 to 50%, a remarkably reproducible result. This suggests that oxygen, used in conjunction with attention to perfusion, is highly effective in preventing SSI. In contrast, in the large PROXI trial ([Meyhoff 2009](#)) that contributes heavily to the

statistical conclusions in the current Cochrane review (Wetterslev 2015), fluids were specifically restricted well below even the so-called “restricted” trials in the literature (Brandstrup 2003), and euthermia was not fully standardized. This trial had the highest infection rate (~20%) of all the trials analysed, despite a lower-risk case mix. It is likely, given the design of the study and previous work on PwO₂, that the PROXI trial demonstrated an expected effect: lack of benefit of high-inspired oxygen in patients with impaired subcutaneous perfusion.

Evidence for harm: So far, there has been no sign that toxicity or cancer complicate use of high-inspired oxygen at 1 ATA pressure for a few hours, and the statistical evidence in the present review provides further support for lack of harm. In addition, there is substantial data for lack of harm from brief, repeated exposure to much higher levels of 100% oxygen. Specifically, hyperbaric oxygen therapy exposes patients to 100% oxygen at 2 to 3 ATA for 90 to 120 minutes daily for up to 40 days.

The evidence to support the use of high-inspired oxygen in concert with maintenance of normal peripheral perfusion is strong. Although not as strong, because no such study measured PwO₂, the evidence suggests that providing high-inspired oxygen without maintenance of normal peripheral perfusion is not effective, as predicted by decades of basic and human research. Future studies that measure PwO₂ will help resolve the question, and should be a high priority. In the meantime, high-inspired oxygen appears to be both safe and effective in reducing SSI in well-perfused, high-risk patients.

Reply

We acknowledge that the interpretation of the cumulated evidence may be difficult. However, contrary to what the commentator implies we did not demonstrate evidence of significant benefit in preventing SSI, neither in the meta-analysis of trials with overall low risk of bias, nor in all trials. The only meta-analysis that showed a statistically significant effect was in the subgroup of trials using a regimen of perioperative antibiotics. This meta-analysis included seven trials with overall high risk of bias and three trials with low risk of bias, and it was far from being powered for a 20% relative risk reduction (RRR). There is no statistically significant effect on the rate of SSI among the three trials with low risk of bias. We therefore assessed the evidence of an effect of hyperoxia on SSI in trials using antibiotics perioperatively to be of low or of very low quality. Accordingly we need more research.

The commentator states that our suggestion to require more evidence for benefits than for harms is problematic. However, this just reflects how we evaluate interventions today. If new experimental interventions show serious adverse events, the developments of such drugs are usually stopped by regulatory authorities. While we generally like more evidence before potentially beneficial interventions are stopped for further scrutiny, we also recognize the detrimental effects and the ethical serious consequences of demanding too much evidence for harms. As clinical researchers, we think it is of paramount importance to keep equipoise before we invite participants to join trials.

We agree that there are in vitro as well as in vivo observations suggesting that the immune system reacts more effectively on pathogens when oxygen supply is adequate at its site of action. We would argue that these observations are briefly listed in the introduction to our review. However, there are also observations that a high oxygen concentration may have adverse effects (Hafner 2015; Sjöberg 2013) and even restrict perfusion due to hyperoxic vasoconstriction (Hafner 2015; Sjöberg 2013). These observations are also briefly touched upon in our introduction. The point, however, is if high inspiratory oxygen fractions (0.60 to 0.80) diminish the frequency of SSI without increasing the frequency of serious adverse events. Our review shows that the available data, coming from trials with overall low risk of bias, do not support that assumption. This does not mean that we can exclude a beneficial effect on SSI. If there is a beneficial effect, however, the intervention effect is probably smaller than hitherto anticipated in all the conducted trials so far as indicated by the 14% RRR in the meta-analysis of trials with overall low risk of bias (Wetterslev 2015). To prove or to disprove a 14% RRR requires many more patients in trials with low risk of bias, even if patients in these new trials receive antibiotics perioperatively. We think such trials ought to be conducted. We would also like to stress that there is eventually no guarantee that a clinically important effect will be proven if sufficient data from trials with overall low risk of bias becomes available.

We do not concur with several of these statements. First, it remains uncertain if perfusion to subcutaneous tissue was actually controlled in the five trials listed by the commentator. In the trial by Bickel et al (Bickel 2011), the documentation relied on arterial blood samples drawn in the postoperative care unit. Second, in the PROXI trial, a large fraction of patients received epidural anaesthesia which is known to increase tissue perfusion according to the extension of block. Third, we do not agree that fluid administration in the PROXI trial was especially restrictive. It aimed at adequate fluid balance in patients in both randomization groups. Fourth, several of the trials, listed by the commentator, had high risk of bias questioning the reproducibility claimed by the commentator. Fifth, recently a randomized trial (Kurz 2015) showed practically similar rates of SSI (15.6% versus 15.8%) comparing a fraction of inspired oxygen of 80% versus 30%. This result is almost exactly the same as in the PROXI trial and this new trial was conducted with a significant overlap of investigators from the trials by Greif and Belda questioning the reproducibility of the initial trials of this intervention. Sixth, a high infection rate in the PROXI trial are likely caused by the more sensitive diagnostic criteria from Center for Disease Control and Prevention, the inclusion of emergency laparotomy procedures, and the careful follow-up.

Lack of evidence does not imply lack of effect. To our knowledge, none of the randomized trials a priori had cancer, new cancer, or recurrence of former cancer as outcomes. So we do not concur with the statement made by the commentator. We did a post hoc long-term follow-up of the patients in the PROXI trial with the outcome of new cancer, or recurrence of former cancer. The results could not refute a high FiO₂ as a culprit of cancer (Meyhoff 2014).

We doubt that there is substantial and sufficient high quality evidence from randomized trials with overall low risk of bias and long follow-up to exclude excess risk of new cancer or recurrence of former cancer following perioperative high FiO₂ (80%). We do not regard data from minor observational or case reports as high quality evidence. As already stated, hyperoxia may induce vasoconstriction and subsequent hypoperfusion with the net result of ischaemia concurrent with the results from the AVOID trial ([Stubb 2015](#)). Our long-term follow-up of the patients in the PROXI trial assessing cardiovascular events showed that a high perioperative FiO₂ could be associated with an increase in long-term risk of myocardial infarction and other heart disease ([Fonnes 2016](#)).

Confirmation of the hypothesis put forward by the commentator requires a modified 2 x 2 factorial trial randomizing patients to 80% oxygen versus 30% and two different targets of PwO₂. To our knowledge no such trial has yet been conducted.

Our meta-analysis of trials with low risk of bias could not exclude a 36% relative risk increase in mortality with hyperoxia. Our Trial Sequential Analysis further estimate that 7000 more randomized patients may be needed before a 20% relative increase or decrease in mortality can be declared with adequate power. In combination with the many documented negative effects of hyperoxia in emergency medicine ([Kilgannon 2010](#); [Brenner 2012](#)), we do not consider the use of hyperoxia to be safe until further large trials with overall low risk of bias are performed. High quality evidence for a beneficial effect of 80% oxygen in the perioperative phase on SSI is presently absent. We will update our review in due course including the trials reported after our review was published.

Contributors

Summary

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We do not have any affiliation with or involvement in any organization with a financial interest in the subject matter of our comment

Reply

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WHAT'S NEW

Date	Event	Description
14 September 2016	Feedback has been incorporated	Comment and reply posted in Feedback section

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Conceiving of the review: Jørn Wetterslev (JW), Christian S. Meyhoff (CSM), Lars N. Jørgensen (LNJ), Lars S. Rasmussen (LSR), Christian Gluud (CG),

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Screening search results: JW, CSM.

Organizing retrieval of papers: JW.

Screening retrieved papers against inclusion criteria: JW, CSM.

Appraising quality of papers: JW, CSM, CG, JL.

Abstracting data from papers: JW, CSM, CG, JL.

Writing to authors of papers for additional information: JW.

Providing additional data about papers: JW.

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Managing data for the review: JW, CSM.

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Analysing RevMan statistical data: JW, CSM.

Performing other statistical analysis not using RevMan (TSA): JW.

Performing double entry of data (data entered by person one: JW; data entered by person two: CSM).

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Performing statistical analysis: JW, CSM.

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Securing funding for the review: JW, CG.

Performing previous work that served as the foundation of the present study: JW, CSM, LNJ, LSR, PROXI-Trial Group.

Serving as guarantor for the review (one review author): JW.

Taking responsibility for reading and checking the review before submission: JW.

DECLARATIONS OF INTEREST

Jørn Wetterslev (JW), Christian S Meyhoff (CSM), Lars N Jørgensen (LNJ), Christian Gluud (CG), Jane Lindschou (JL), Lars S Rasmussen (LSR).

JW, CSM, LNJ and LSR were all members of the Steering Committee for the [Meyhoff 2009](#) trial.

CSM was the principal investigator of the [Meyhoff 2009](#) trial. (JL and CG extracted data and evaluated bias for the [Meyhoff 2009](#) trial. Neither was involved in planning, conduct or analysis of the [Meyhoff 2009](#) trial.)

JW and CG are members of the task force on trial sequential analysis (TSA) at the Copenhagen Trial Unit developing and programming TSA (www.ctu.dk/tsa).

LSR is Editor-in-Chief of *Acta Anaesthesiologica Scandinavica*; he has received funding from the Tryg Foundation, a philanthropic foundation that supports research and has financed a professorship in emergency medicine.

JL have reported no conflicts of interest.

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Internal sources

- Copenhagen Trial Unit (CTU), Denmark.

CTU funded the work of JW during work with the review.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- To possibly reduce the source of heterogeneity due to substantially different lengths of follow-up, we added an analysis in which the outcome was all-cause mortality limited to follow-up of 30 days.
- We did not consider that stopping early for benefit, harm or futility on inadequate stopping rules (or no reporting of sample size at all) suggested high risk of bias in the accomplished review. In the protocol ([Wetterslev 2010](#)), this was considered a risk of bias component, but after the 11th Cochrane Symposium in Keystone, Colorado, early stopping was changed from constituting a bias risk to constituting an increased risk of random error.
- We did not consider baseline imbalance nor lack of reporting of baseline characteristics as showing high risk of bias. After the 11th Cochrane Symposium in Keystone, Colorado, baseline imbalance or lack of reporting of baseline characteristics changed from constituting a bias risk to constituting an increased risk of random error.
- We added a subgroup analysis with trials stratified according to preoperative use of antibiotics.
- We slightly changed the preplanned subgroup analyses for different types of surgery because trials investigating laparoscopic surgery were lacking, and only one trial investigating exclusively lower abdominal surgery was found. Accordingly, we divided the included trials into colorectal or abdominal surgery trials; caesarean section trials; breast surgery trials; orthopaedic trials; and mixed surgery trials.
- We added a TSA with an anticipated a priori RRI of 20% on mortality, as a 35% RRI (or RRR) could be refuted because the required information size for detecting or rejecting such an effect was surpassed.
- We added the use of GRADE methodology.
- Jane Lindschou joined as a review author and, together with Christian Gluud, performed data extraction and bias evaluation for the [Meyhoff 2009](#) trial. Neither individual was involved in the planning, conduct or analysis of the [Meyhoff 2009](#) trial.

NOTES

September 2016

Comment and reply posted in [Feedback](#)

INDEX TERMS

Medical Subject Headings (MeSH)

Anesthesia; Cause of Death; Length of Stay; Oxygen [*administration & dosage] [*adverse effects]; Oxygen Inhalation Therapy [*adverse effects] [methods] [mortality]; Randomized Controlled Trials as Topic; Respiratory Insufficiency [*etiology]; Selection Bias; Surgical Procedures, Operative [*mortality]; Surgical Wound Infection [*etiology]

MeSH check words

Adult; Aged; Humans; Middle Aged