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Review Article

REVIEW ARTICLES

Safety of 80% *vs* 30–35% fraction of inspired oxygen in patients undergoing surgery: a systematic review and meta-analysis

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Abstract

Background: Evidence-based guidelines from the World Health Organization (WHO) have recommended a high (80%) fraction of inspired oxygen (FiO_2) to reduce surgical site infection in adult surgical patients undergoing general anaesthesia with tracheal intubation. However, there is ongoing debate over the safety of high FiO_2. We performed a systematic review to define the relative risk of clinically relevant adverse events (AE) associated with high FiO_2.
Methods: We reviewed potentially relevant articles from the WHO review supporting the recommendation, including an updated (July 2018) search of EMBASE and PubMed for randomised and non-randomised controlled studies reporting AE in surgical patients receiving 80% FiO_2 compared with 30–35% FiO_2. We assessed study quality and performed meta-analyses of risk ratios (RR) comparing 80% FiO_2 against 30–35% for major complications, mortality, and intensive care admission.
Results: We included 17 moderate–good quality trials and two non-randomised studies with serious-critical risk of bias. No evidence of harm with high FiO_2 was found for major AE in the meta-analysis of randomised trials: atelectasis RR 0.91 [95% confidence interval (CI) 0.59–1.42); cardiovascular events RR 0.90 (95% CI 0.32–2.54); intensive care admission RR 0.93 (95% CI 0.7–1.12); and death during the trial RR 0.49 (95% CI 0.17–1.37). One non-randomised study reported that high FiO_2 was associated with major respiratory AE [RR 1.99 (95% CI 1.72–2.31)].
Conclusions: No definite signal of harm with 80% FiO_2 in adult surgical patients undergoing general anaesthesia was demonstrated and there is little evidence on safety-related issues to discourage its use in this population.

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Keywords: adverse events; general anaesthesia; high FiO_2; hyperoxia; peri-operative outcome; surgical site infection; surgical wound infection

Editor's key points

- While guidelines from the WHO recommend a high FiO_2 to reduce surgical site infection in adult surgical patients undergoing general anaesthesia, there is ongoing debate over its safety.
- This systematic review and meta-analysis of 17 RCTs did not find robust evidence that perioperative 80% FiO_2 is associated with a significant risk of harm compared with 30–35% oxygenation.
- The available evidence indicated that high FiO_2 has no significant deleterious effect on hard outcomes, such as ICU admissions and mortality.
- Future studies should focus on adverse events as the main predefined outcome with rigorous monitoring and transparent reporting.

In 2016, the WHO issued a set of recommendations on practical measures to prevent surgical site infection (SSI).[1,2] As part of the WHO guideline development process, a systematic review and meta-analyses were conducted on the effect of a high fraction of inspired oxygen (FiO_2) on SSI. The reviewers reported that 80% FiO_2 showed a significant benefit in reducing SSI when compared with a standard FiO_2 of 30% or 35% in intubated patients without any evidence of harm.[3] Nevertheless, concerns regarding the potential harmful effects of high FiO_2 have generated intense discussion on the benefit *vs* harm balance of high FiO2 in preventing SSI, and a recent meta-analysis found that liberal oxygen use in acutely ill patients was associated with increased mortality.[4–7]

The trade-off between the benefits and risks of high FiO_2 continue to be debated in the scientific literature, with concerns raised regarding increased risk of respiratory and cardiovascular adverse events (AE) and mortality.[8–10] One specific criticism was that the WHO systematic review and guidelines had failed to adequately analyse the potential negative effects of high FiO_2.[8–10] These concerns about the harms of high FiO_2 have been countered by the observation that the studies cited were based on evidence from animal studies and clinical settings differing from perioperative care.[11] Nevertheless, this ongoing debate highlighted the urgent need for a thorough evaluation of studies examining AE associated with high FiO_2 in patients undergoing surgery. We conducted a systematic review aimed specifically at extracting AE data from randomised trials (including those reported in the accompanying efficacy review) and non-randomised studies related to the perioperative administration of 80% FiO_2 (I) compared with 30–35% (C) in patients undergoing surgery (P) for the purpose of reducing the risk of SSI (O).[12]

Methods

Study selection criteria

Our inclusion criteria for studies followed those of the original WHO guidelines[1] by using the same intervention and comparators as the efficacy review, but with the additional parameter of the inclusion of non-randomised studies. We selected relevant studies that had: (i) between-group comparisons, either of a randomised or a non-randomised design; (ii) patients of any age undergoing any type of surgical procedure; and (iii) perioperative administration of high FiO_2 (80%) *vs* a control or comparator group, where the comparator was the perioperative administration of standard FiO_2 (30–35%).

Search strategy

We identified potentially relevant studies from several sources, starting with a new database search with no restriction on study design or outcome. This specific search focusing on articles with AE terms is fully reported in Supplementary Table S1 and was first conducted on June 5, 2017 based on free-text and the indexing terms used in PubMed and EMBASE. To capture all relevant new articles, we set up automated notifications from PubMed (most recent update, July 2018). We then went on to evaluate all the trials included in the accompanying efficacy review.[12] As there may have been studies of a non-randomised design or trials that had not reported on SSIs relevant to the efficacy endpoint, but could contribute AE data, we also checked all full-text articles classified as 'wrong design' or 'wrong outcome' in the efficacy review. Finally, we checked reference lists of included articles and systematic reviews and consulted with experts from WHO in the event that they might be aware of other potentially relevant articles that specifically reported AE associated with high FiO_2.

Study selection

Two reviewers (Y.K.L. and K.M.) independently screened titles and abstracts of retrieved references for relevant studies based on population, intervention, and comparator. At this time, we did not exclude articles based on the absence of AE reporting in the abstract, as these data may not have been mentioned, even if present in the full article. We then retrieved full-text versions of these articles and both reviewers further checked these against the inclusion criteria.

Outcomes of interest

We examined the effect of high FiO_2 on the following prespecified adverse outcomes of interest: (i) mortality; (ii) ischaemic vascular events affecting coronary and cerebral circulation; (iii) respiratory AE (e.g. respiratory failure, acute respiratory distress syndrome, number of ventilator days, and lung complications, for example, pneumonia or atelectasis, reintubation or prolonged intubation); and (iv) length of hospital

stay. In addition, we used a hypothesis generating/scoping approach to capture any new or unexpected serious AE that may have been reported.

Data extraction

Two reviewers (A.S. and A.P., or Y.K.L. and K.M.) independently extracted data from all included studies onto a preformatted form. To avoid a bias towards the null that could arise from attempting to evaluate AE in patients who had never received the intervention, participant numbers were extracted based on the study population that had received the assigned intervention and where outcomes had been measured.

Assessment of study validity

The risk of bias of the RCTs included in the effectiveness review was assessed by two authors (J.S. and S.W.),[12] whereas another two pairs of reviewers (A.S. and A.P., and Y.K.L. and K.M.) were involved in the independent assessment of the validity of included AE studies using the Cochrane Collaboration tools for assessing the risk of bias in non-randomised studies of interventions (ROBINS-I),[13,14] and components from the specific McMaster Harms tool for AE trials.[15] We focused on whether AE were pre-specified, the degree of rigour of postoperative monitoring, and the amount of reported detail on AE. We aimed to assess publication bias using a funnel plot if there were more than 10 studies in a meta-analysis and the absence of significant statistical heterogeneity.[16]

For the overall body of evidence, we used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (GRADE Pro software; http://gradepro.org/).

Statistical analysis

We focused our analysis on the measure of relative effect measure between intervention and control to minimise the impact of the fact that the monitoring, measurement, and case definition of participants and their AE were often *ad hoc* or *post hoc* in studies, thus leading to inconsistencies in absolute rates. Assuming that randomisation was adequate and both

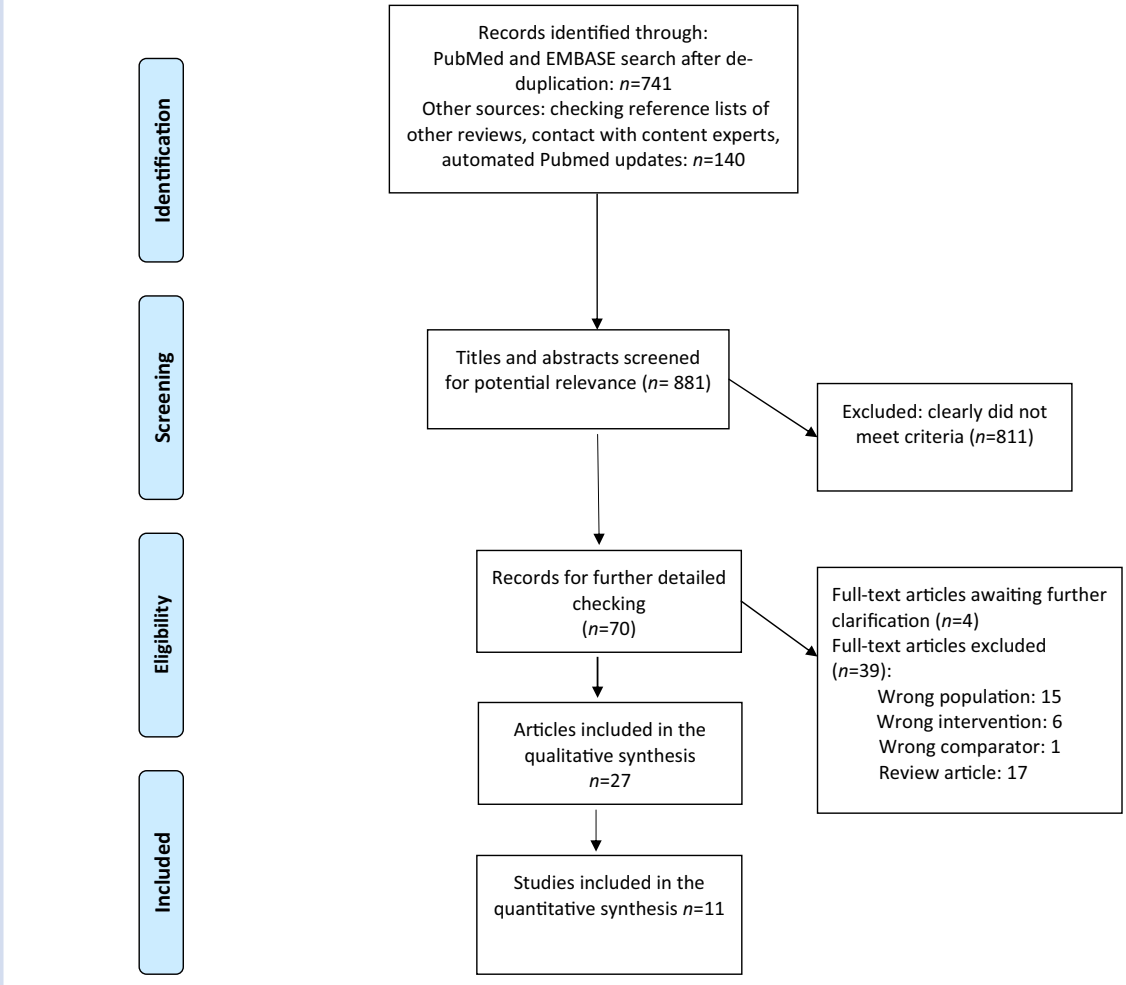


Fig 1. Flowchart of study selection.

study arms were measured in the same (good or bad) way, the relative effect should be a more consistent measure that allows pooling and a comparison between trials. This is because any misclassification is non-differential within that study and any relative difference between study arms is maintained. Meta-analyses of the risk of AE were conducted using Review Manager v 5.3 (Nordic Cochrane Centre, Copenhagen, Denmark) if there were quantitative data of sufficient quantity and similarity. Depending on the reported effect measures and extent of statistical heterogeneity (assessed using the I^2 statistic), we planned to pool risk ratios (RR) or mean differences with a fixed effects model if there was an absence of heterogeneity and random effects models when substantial heterogeneity (50% or above) was detected.[17,18] If the data were sparse or clinically heterogeneous, we aimed to report a narrative synthesis.

Results

We identified 32 full-text articles, and subsequently excluded five reports (Fig. 1).[19–49] One article was a symposium report that contained atelectasis data from another trial,[22] and four trials (one has already been retracted) had discrepant findings in the statistical analysis. We have not included these latter studies pending a request for further clarification.[37,38,48,49] A total of 27 studies were included in the final analysis. These consisted of two non-randomised studies[43,46] and 17 separate RCTs with eight *post hoc* or subgroup analyses.[19–36,39–42,44,45,47] Several trials had overlapping or multiple reports. Outcome data of participants in the RCT by Greif and Sessler[32] were also mentioned in other publications (i.e. data on imaging for pulmonary complications from Akça and colleagues,[19] on atelectasis from Horn,[22] and on long-term mortality from Podolyak and colleagues[26]). Long-term mortality from the trial of Kurz and colleagues[23] was reported in the article by Podolyak and colleagues.[26] The Meyhoff and colleagues[34] PROXI trial was further described in several subsequent reports: Fonnes and colleagues[21] reported on cerebrovascular outcomes; Meyhoff and colleagues[24] on long-term mortality; Meyhoff and colleagues[25] on cancer; Staehr and colleagues[28] on a subgroup of patients with obesity; and Staehr[27] on a subgroup with ovarian cancer at a single centre.[28] The key features of the RCTs are fully reported in the accompanying article related to the systematic review on effectiveness.[12] To avoid duplication, Table 1 shows the baseline characteristics of the non-randomised studies and Supplementary Table S2 reports full details on outcomes and monitoring of AE across all studies.

RCTs

Sample sizes ranged from 30 to 2050 patients with a wide range of international locations. Age groups were wide-ranging between trials, but comparable between intervention and comparator groups. Of the 17 original RCTs, a broad range of surgical procedures was studied. These included colorectal surgery (n=5), appendectomy (n=2), Caesarean section (n=5), laparotomy (n=1), orthopaedic surgery for fractures (n=1), and mixed surgery (n=3). Most trials were conducted in intubated patients; five trials were performed in participants who were non-intubated or given regional anaesthesia.[30,31,39,42,45]

Non-randomised studies

Two non-randomised studies were identified.[43,46] The first was a retrospective cohort study that analysed 73 922 intubated patients undergoing non-cardiothoracic surgery in a large university teaching hospital and two community hospitals in the USA.[43,46] Patients were divided into five groups based on a quintile of the median FiO_2 between the time of intubation and extubation. As this was a retrospective non-

Table 1 Study characteristics of non-randomised studies. IQR, inter-quartile range; SD, standard deviation

Study (and year)	Study design, setting, type of surgery	Patient characteristics	Intervention	Control
Kurz and colleagues[46] (2018)	Two-weekly alternating intervention study in operating rooms in the Cleveland Clinic, USA Major intestinal surgery January 2013 to March 2016	Total number of patients: 5749 30% O_2: 2853 80% O_2: 2896 Mean age (SD): 30% O_2: 52 yr (17) 80% O_2: 52 yr (17) % Male: 48 in both groups	Notices and signs on each anaesthesia machine with an alert system if FiO_2 <70% or >90% Median FiO_2 delivered was 80% (IQR 77–82%)	Enough oxygen to achieve oxygen saturations of >95% in addition to an alert system if FiO_2 >35% Median FiO_2 delivered was 39% (IQR 35–52%)
Staehr-Rye and colleagues[43] (2017)	Retrospective cohort Massachusetts General Hospital and two community hospitals, USA Non-cardiothoracic surgery January 2007– August 2014	Total number: 73922 Mean age 30% O_2: 55 yr 80% O_2: 57 yr % Male 30% O_2: 47 80% O_2: 44 Excluded: age <18 yr, previous surgery within the last 4 weeks, missing information in any of the variables used in the primary regression model	Five patient groups, of which Group 1 had received median 30% O_2 and Group 5 median 80% O_2 Quintiles of groups defined by median intraoperative FiO_2 between intubation and extubation	Non-randomised study with no protocolised intervention before start of study Duration of anaesthetic Group 1: median 155 min Group 5: median 89 min

randomised study, there was no description of whether preoperative, perioperative, and postoperative interventions were protocolised or standardised among the patient groups. The second study was a quality improvement project that evaluated outcomes in 5749 patients undergoing major intestinal surgery in a US single centre where operating rooms alternated between 30% and 80% FiO_2.[23] The inspired fraction was changed every 2 weeks on a non-randomised basis; clinicians were not blinded to the FiO_2 received by the patient. As this was not a prospective RCT with a pre-specified follow-up, clinical outcomes were obtained from the clinical registry and hospital billing system.

Study quality (risk of bias)

The internal validity of the RCTs was considered to be moderate–good overall; details are fully reported in the accompanying effectiveness review.[12] In general, there were no major areas with consistently high risk of bias,[23] although one trial was at risk of selective outcome reporting, while another was affected by lack of blinding.[39] However, our review included several subgroup or *post hoc* analyses of completed trials, which may be of lower quality and at greater risk of bias than the original publications. The definitions, measurement, and reporting of pulmonary and cardiovascular AE were clearly specified in only two trials; these two studies were judged as adequate overall.[34,35] All the other trials were judged to have inadequate areas in their measurement and reporting of AE data (Table 2).

In particular, the study by Staehr-Rye and colleagues[43] was considered to be at critical risk of bias based on several of the ROBINS-I criteria (Table 3). Although a large set of variables was used in the regression model, these were applied in a blanket manner to all outcomes, rather than tailored to the specific outcome as stipulated in the ROBINS-I criteria.[14] We considered it highly unlikely that the relevant adjustment of confounding variables for pneumonia would be the same as those for pulmonary oedema, and even less likely for wound dehiscence or stroke (all of which would be affected by completely different factors). At baseline, there was an imbalance between Group 1 and Group 5 in the proportion of patients with an ASA physical status 3 and above (i.e. 25% in Group 1 compared with 39% in Group 5). The type of surgery also differed with 16% *vs* 40% having general surgery in Group 1 and Group 5, respectively. This raises the possibility of other residual confounding causing bias (e.g. co-morbid conditions such as cancer or congestive heart failure). Other major areas of concern were the absence of blinding for outcome assessors, lack of specification of how and when AE were coded, and the exclusion of more than 35 000 potentially eligible study participants, because of missing information on single covariates such as height, BMI, age and multi-morbidity score. Co-interventions (such as wound care and antibiotics) were not equally delivered between groups (e.g. median duration of anaesthesia was 155 min in the quintile that received low FiO_2 compared with 89 min in the quintile that received high FiO_2). Finally, the protocol-specified outcome of SSI was not reported in the study and the analysis appears to have been changed to the outcome of 'wound dehiscence' instead.

We judged the alternating intervention study by Kurz and colleagues[46] to be at serious risk of bias (Table 3) according to the ROBINS-I scale. Major weaknesses included lack of blinding and the use of registry and billing data, rather than investigator-led outcome ascertainment. We identified deviation from the intervention in the 30% FiO_2 group where the median inspired fraction was 39%, with an inter-quartile range of 35–52%, thus indicating that 25% of patients were receiving >52% FiO_2. This would have reduced the ability of the trial to differentiate between high and low FiO_2. Finally, we noted that

Table 2 Adequacy of collection, measurement, and reporting of adverse events data (adapted from components of the McHarm quality scale)

Study (and year)	Adequate specification or definition of pulmonary or cerebrovascular adverse events	Adequate method and frequency of pulmonary or cerebrovascular monitoring	Independent data safety monitoring	Completeness of follow-up	Comprehensive reporting of adverse events
Belda and colleagues[20] (2005)	Inadequate	Inadequate	Adequate	Adequate	Inadequate
Bickel and colleagues[29] (2011)	Inadequate	Inadequate	Inadequate	Adequate	Inadequate
Chen and colleagues[44] (2013)	Inadequate	Inadequate	Inadequate	Adequate	Inadequate
Duggal and colleagues[30] (2013)	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate
Fariba and colleagues[45] (2016)	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate
Gardella and colleagues[31] (2008)	Inadequate	Inadequate	Inadequate	Adequate	Inadequate
Greif and Sessler[32] (2000)	Adequate for pulmonary	Inadequate	Inadequate	Adequate	Adequate for pulmonary
Kurz and colleagues[23] (2015)	Inadequate	Inadequate	Inadequate	Adequate	Inadequate
Kurz and colleagues[46] (2018)	Inadequate	Inadequate	Inadequate	Inadequate	Adequate
Mayzler and colleagues[33] (2005)	Inadequate	Inadequate	Adequate	Adequate	Inadequate
Meyhoff and colleagues[34] (2009)	Adequate	Adequate	Adequate	Adequate	Adequate
Myles and colleagues[35] (2007)	Adequate	Adequate	Adequate	Adequate	Adequate
Pryor and colleagues[36] (2004)	Inadequate	Inadequate	Inadequate	Adequate	Inadequate
Scifres and colleagues[39] (2011)	Inadequate	Inadequate	Inadequate	Adequate	Inadequate
Staehr-Rye and colleagues[43] (2017)	Inadequate	Inadequate	Inadequate	Inadequate	Adequate
Stall and colleagues[40] (2013)	Inadequate	Inadequate	Adequate	Adequate	Inadequate
Thibon and colleagues[41] (2012)	Inadequate	Inadequate	Inadequate	Adequate	Inadequate
Wasnik and colleagues[47] (2015)	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate
Williams and colleagues[42] (2013)	Inadequate	Inadequate	Inadequate	Adequate	Inadequate

Table 3 Assessment of study validity of non-randomised studies. ROBINS-I, risk of bias in non-randomised studies of interventions

Study (and year)	Bias as a result of confounding	Bias in selection	Bias in classification of intervention	Bias as a result of deviation from intervention	Bias as a result of missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall ROBINS-I judgment
Kurz and colleagues[46] (2018)	Moderate	Low	Low	Serious	Moderate	Serious	Serious	Serious
Staehr-Rye[43] (2017)	Critical	Low	Serious	Serious	Critical	Critical	Serious	Critical

the protocol had a pre-specified SSI composite outcome, but this had been changed in the study to a composite of mortality and surgical infection.

Results of individual studies

We listed the number of study participants that received the assigned intervention (per protocol) and had analysable outcome data (Table 4). Included studies reported on the following AE: atelectasis; pneumonia; respiratory complications and serious AE that included respiratory failure, pneumothorax, cough, and respiratory difficulty; ICU admission; cardiovascular events; thromboembolic events; death (short- and long-term); and length of hospital stay. Overall, no evidence of statistically significant harm was observed in any of the adverse outcomes. However, AE data were sparsely and inconsistently reported (Table 4).

Outcomes: atelectasis

Three studies reported on atelectasis with 219/1932 events in the high FiO_2 arm and 255/1966 events in the low FiO_2 arm (Fig. 2).[32,34,35] Overall, high FiO_2 was not associated with an increased risk of atelectasis {pooled RR 0.91 [95% confidence interval (CI) 0.59–1.42]}. There was considerable heterogeneity in the analysis (I^2=85%).

Outcomes: pneumonia

Three trials reported on pneumonia with 57/1712 events in the high FiO_2 arm and 75/1746 events in the low FiO_2 arm (Fig. 2). The pooled estimates did not demonstrate a significant association between high FiO_2 and pneumonia [overall pooled RR 0.78 (95% CI 0.55–1.09)].[21,35,44] There was mild heterogeneity (I^2=29%). In contrast, the observational study reported an adjusted odds ratio (OR) of 1.72 (95% CI 1.30–2.28) for pneumonia in the high FiO_2 group.

Outcomes: composite measure of respiratory AE

Two studies reported on composite measures of respiratory AE. Myles and colleagues[35] described respiratory complications (pneumonia, atelectasis, pneumothorax, and pulmonary embolism), and Meyhoff and colleagues[34] mentioned serious respiratory AE, but with no further definition. However, the composite data were not pooled because of variations in case definitions when constructing the composite. We did not identify any significant harm related to high FiO_2 in either study. In contrast, the observational study reported an adjusted OR of 1.99 (95% CI 1.72–2.31) for major respiratory complications in the high FiO_2 group.

Outcomes: ICU admission

Five studies reported on ICU admission with 190/2165 events in the high FiO_2 arm and 208/2189 events in the low FiO_2 arm (Fig. 2).[20,32,34–36] High FiO_2 was not associated with an increased likelihood of ICU admission [RR 0.93 (95% CI 0.77–1.12)]. Low heterogeneity was observed in the analysis (I^2=3%). In contrast, the observational study by Staehr-Rye and colleagues[43] reported an adjusted OR of 1.64 (95% CI 1.38–1.95) for ICU admission in the high FiO_2 group. However, we noted that the raw or crude OR for ICU admission was actually 0.94 (95% CI 0.82–1.08). Notably, the statistical adjustment appears to have converted a non-significant decrease in risk to a statistically significantly association in increased risk with high FiO_2.

Outcomes: cardiovascular AE

Three studies reported on cardiovascular AE, consisting of acute coronary syndrome and myocardial infarction with 25/1705 events in the high FiO_2 arm and 25/1744 events in the low FiO_2 arm (Fig. 2).[21,35,44] Overall, high FiO_2 was not associated with cardiovascular AE [pooled RR 0.90 (95% CI 0.32–2.54)]. One of the trials had sparse raw data and there was significant heterogeneity (I^2=58%). We conducted a sensitivity analysis including myocardial infarction rather than acute coronary syndrome as the outcome measure from the Fonnes and colleagues[21] study, and this yielded an overall pooled RR of 0.94 (95% CI 0.28–3.21). Similarly, there were no significant associations reported for myocardial infarction and stroke in the observational study. However, our analysis of the raw or crude OR found that high FiO_2 was associated with a reduced risk of stroke [OR 0.52 (95% CI 0.38–0.71)], but the regression model subsequently generated an adjusted OR of 0.90 (95% CI 0.59–1.37) for stroke in the high FiO_2 group.

Outcomes: thromboembolic events

Two studies reported adjusted estimates on thromboembolic events, one on pulmonary embolism and one on any thromboembolic event (Fig. 2).[21,35] There was no significant association between high FiO_2 and thromboembolic events [pooled RR 0.89 (95% CI 0.28–2.91)], but there was heterogeneity (I^2=74%).

Table 4 Matrix of adverse events. Outcomes reported by the included trials showing numbers of patients affected by adverse events/total number, according to intervention of high (80%) FiO_2 compared with low (30–35%) FiO_2. ACS, acute coronary syndrome; NR, not reported; OR, odds ratio; PE, pulmonary embolism; SAE, serious adverse event; SD, standard deviation.

Study (and year)	Number of patients	Atelectasis	Pneumonia	Other respiratory adverse events	Cardiovascular adverse events	ICU admission	Length of stay [days (SD)]	Mortality (*n*)	Other (e.g. cancer, stroke, embolism, SAE)
Belda and colleagues[20] (2005)	Low FiO_2=143* High FiO_2=148*	NR	NR	NR	NR	Low FiO_2: 5/143 High FiO_2: 4/148	Low FiO_2: 10.5 (4.4) High FiO_2: 11.7 (7.0)	Low FiO_2: 2/143 High FiO_2: 0/148	NR
Bickel and colleagues[29] (2011)	Low FiO_2=103 High FiO_2=107	NR	NR	NR	NR	NR	Low FiO_2: 2.9 High FiO_2: 2.5	NR	NR
Chen and colleagues[44] (2013)	Low FiO_2=30 High FiO_2=30	NR	Low FiO_2: 1/30 High FiO_2: 1/30	NR	Low FiO_2: 3/30 High FiO_2: 1/30	NR	NR	Low FiO_2: 0/30 High FiO_2: 030	NR
Duggal and colleagues[30] (2013)	Low FiO_2=415 High FiO_2=416	NR	NR	NR	NR	NR	NR	NR	NR
Fariba and colleagues[45] (2016)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Gardella and colleagues[31] (2008)	Low FiO_2=74* High FiO_2=69*	NR	NR	NR	NR	NR	Low FiO_2: 3 (range 2–6) High FiO_2: 3 (range 2–5)	NR	NR
Greif and Sessler[32] (2000)	Low FiO_2=250 High FiO_2=250	Low FiO_2: 78/250 High FiO_2: 90/250	NR	NR	NR	Low FiO_2: 12/250 High FiO_2: 5/250	Low FiO_2: 11.9 High FiO_2: 12.2	Low FiO_2: 6/250 High FiO_2: 1/250	NR
Mayzler and colleagues[33] (2005)	Low FiO_2=19 High FiO_2=19	NR	NR	NR	NR	NR	NR	NR	NR
Meyhoff and colleagues[34] (2009)	Low FiO_2=685* High FiO_2=701*	Low FiO_2: 50/685 High FiO_2: 54/701	Low FiO_2: 44/685 High FiO_2: 41/701	Respiratory SAE Low FiO_2: 25/685 High FiO_2: 27/701 Respiratory failure (Low FiO_2: 31/685 High FiO_2: 38/701)	NR	Low FiO_2: 44/685 High FiO_2: 30/701	NR	Low FiO_2: 20/685 High FiO_2: 30/701	Any SAE Low FiO_2: 154/685 High FiO_2: 165/701 Circulatory SAE Low FiO_2: 20/685; High FiO_2: 24/701
Myles and colleagues[35] (2007)	Low FiO_2=1015* High FiO_2=997*	Low FiO_2: 127 High FiO_2: 75	Low FiO_2: 30 High FiO_2: 15	Any pulmonary complication Low FiO_2: 132 High FiO_2: 78 Pneumothorax (Low FiO_2: 3 High FiO_2: 1)	Low FiO_2: 13 High FiO_2: 7 Adjusted OR myocardial infarction 0.58 (95% CI 0.22–1.50)	Low FiO_2: 140 High FiO_2: 122	Low FiO_2: 7.0 High FiO_2: 7.1	Low FiO_2: 9 High FiO_2: 3 Adjusted OR 0.33 (95% CI 0.09–1.22)	Thromboembolism Low FiO_2: 10; High FiO_2: 16 Adjusted OR 1.60 (95% CI 0.72–3.55) Stroke Low FiO_2: 1; High FiO_2: 1
Pryor and colleagues[36] (2004)	35%= 80* High FiO_2=85	NR	NR	NR	NR	35: 7/80 High FiO_2: 9/85	35%: 6.4 High FiO_2: 8.3	35%: 1/80 High FiO_2: 0/85	NR
Scifres and colleagues[39] (2011)	Low FiO_2=297* High FiO_2=288*	NR	NR	NR	NR	NR	NR	NR	NR
Stall and colleagues[40] (2013)	Low FiO_2=116* High FiO_2=119*	NR	NR	NR	NR	NR	Low FiO_2: 2.8 High FiO_2: 3.5	NR	NR
Thibon and colleagues[41] (2012)	Low FiO_2=208 High FiO_2=226	NR	NR	NR	NR	NR	NR	NR	Hypotension Low FiO_2: 0/208 High FiO_2: 3/226
Williams[42] (2013)	Low FiO_2=83* High FiO_2=77*	NR	NR	NR	NR	NR	NR	NR	NR

Continued

Table 4 Continued

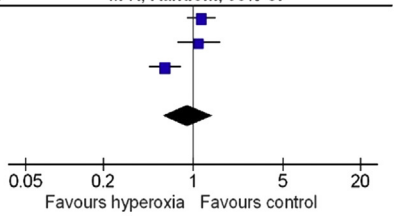
Study (and year)	Number of patients	Atelectasis	Pneumonia	Other respiratory adverse events	Cardiovascular adverse events	ICU admission	Length of stay [days (SD)]	Mortality (n)	Other (e.g. cancer, stroke, embolism, SAE)
Akça and colleagues[19] (1999) [subgroup Greif and Sessler[32] (2004)]	Low FiO_2=14 High FiO_2=16	CT-determined atelectasis Low FiO_2: 9/14 High FiO_2: 15/16	NR	Cough/respiratory difficulty Low FiO_2: 3/14 High FiO_2: 5/16	NR	NR	NR	NR	NR
Fonnes and colleagues[21] (2016)	Low FiO_2=699 High FiO_2=678	NR	NR	NR	Adjusted hazard ratio: Acute coronary syndrome 1.96 (95% CI 0.86–4.48) Myocardial Infarction 2.58 (95% CI 0.97–6.88)	NR	NR	ACS/death Low FiO_2: 190/699 High FiO_2: 219/678	Pulmonary embolism adjusted hazard ratio: 0.48 (95% CI 0.19–1.19)
Horn[22] (2002) [data from Akça and colleagues[19] (1999) & Greif and Sessler[32] (2004)]	Low FiO_2=14 High FiO_2=16	Low FiO_2: 5 High FiO_2: 7	NR	NR	NR	NR	NR	NR	NR
Kurz and colleagues[23] (2015)	Low FiO_2=270* High FiO_2=285*	NR	NR	NR	NR	NR	Low FiO_2: 7.7 (4.6) High FiO_2: 8.8 (5.4)	Low FiO_2: 1/270 High FiO_2: 0/285	Major complications Low FiO_2: 34/270 High FiO_2: 42/285
Meyhoff and colleagues[24] (2012)	Low FiO_2=701* High FiO_2=685*	NR	NR	NR	NR	NR	NR	Adjusted hazard ratio 1.31 (95% CI 1.03–1.55)	NR
Meyhoff and colleagues[25] (2014)	Low FiO_2=699* High FiO_2=678*	NR	NR	NR	NR	NR	NR	Adjusted hazard ratio 1.29 (95% CI 1.05–1.58)	New cancer diagnosis Low FiO_2: 30/699 High FiO_2: 25/678
Podolyak[26] (2016) [Kurz and colleagues[23] and Greif and Sessler[32] (2004) together]	Low FiO_2=459* High FiO_2=468*	NR	NR	NR	NR	NR	NR	Hazard ratio 0.93 (95% CI 0.72–1.20)	NR
Staehr and colleagues[28] (2011)	Low FiO_2=111* High FiO_2=102*	Low FiO_2: 7 High FiO_2: 9	Low FiO_2: 5 High FiO_2: 6	Respiratory failure Low FiO_2: 5/111 High FiO_2: 8/102		Low FiO_2: 9/111 High FiO_2: 11/102	Low FiO_2: 5 days High FiO_2: 6 days	Low FiO_2: 3/111 High FiO_2: 1/102	SAE Low FiO_2: 22/111 High FiO_2: 22/102
Staehr and colleagues[27] (2012)	Low FiO_2=15 High FiO_2=20	Low FiO_2: 2/15 High FiO_2: 5/20	NR	NR	NR	NR	NR	NR	NR
Wasnik and colleagues[47] (2015)	Low FiO_2=32 High FiO_2=32	NR	NR	NR	NR	NR	Low FiO_2: 9.84 (3.68) High FiO_2: 7.37 (3.57)	NR	NR

* Refers to participant numbers that actually received the intervention and were finally available for inclusion in the primary analysis and not the numbers originally randomly assigned to the intervention

Atelectasis

Study or subgroup (and year)	Hyperoxia Events	Hyperoxia Total	Control Events	Control Total	Weight	Risk ratio M-H, Random, 95% CI
Greif and Sessler[32] (2000)	90	250	78	250	35.0%	1.15 (0.90, 1.48)
Meyhoff and colleagues[34] (2009)	54	685	50	701	30.8%	1.11 (0.76, 1.60)
Myles and colleagues[35] (2007)	75	997	127	1015	34.2%	0.60 (0.46, 0.79)
Total (95% CI)		**1932**		**1966**	**100.0%**	**0.91 (0.59, 1.42)**
Total events	219		255			

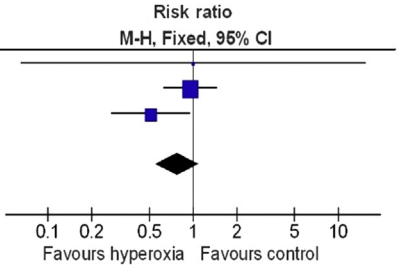
Heterogeneity: Tau²=0.13; χ^2=13.72, df =2(*P*=0.001); I²=85%
Test for overall effect: Z=0.41 (*P*=0.68)



Pneumonia

Study or subgroup (and year)	Hyperoxia Events	Hyperoxia Total	Control Events	Control Total	Weight	Risk ratio M-H, Fixed, 95% CI
Chen and colleagues[44] (2013)	1	30	1	30	1.3%	1.00 (0.07, 15.26)
Meyhoff and colleagues[34] (2009)	41	685	44	701	58.6%	0.95 (0.63, 1.44)
Myles and colleagues[35] (2007)	15	997	30	1015	40.1%	0.51 (0.28, 0.94)
Total (95% CI)		**1712**		**1746**	**100.0%**	**0.78 (0.55, 1.09)**
Total events	57		75			

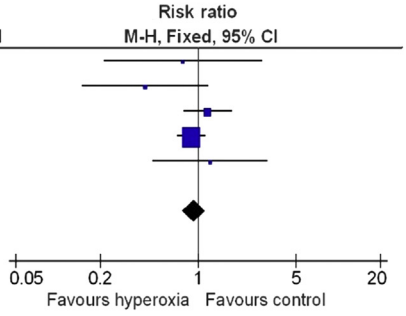
Heterogeneity: χ^2=2.81, df=2 (*P*=0.25); I²=29%
Test for overall effect: Z=1.48 (*P*=0.14)



ICU Admission

Study or subgroup (and year)	Hyperoxia Events	Hyperoxia Total	Control Events	Control Total	Weight	Risk ratio M-H, Fixed, 95% CI
Belda and colleagues[20] (2005)	4	148	5	143	2.5%	0.77 (0.21, 2.82)
Greif and Sessler[32] (2000)	5	250	12	250	5.8%	0.42 (0.15, 1.17)
Meyhoff and colleagues[34] (2009)	50	685	44	701	21.1%	1.16 (0.79, 1.72)
Myles and colleagues[35] (2007)	122	997	140	1015	67.2%	0.89 (0.71, 1.11)
Pryor and colleagues[36] (2004)	9	85	7	80	3.5%	1.21 (0.47, 3.10)
Total (95% CI)		**2165**		**2189**	**100.0%**	**0.93 (0.77, 1.12)**
Total events	190		208			

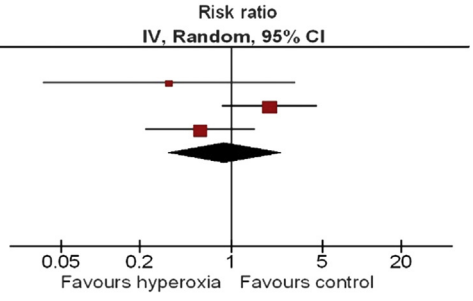
Heterogeneity: χ^2=4.14, df=4 (*P*=0.39); I²=3%
Test for overall effect: Z=0.81 (*P*=0.42)



Cardiovascular

Study or subgroup (and year)	Weight	Risk ratio IV, Random, 95% CI
2.6.1 Adjusted or randomised data		
Chen and colleagues[44] (2013)	16.1%	0.33 (0.04, 3.03)
Fonnes and colleagues[21] (2016)	43.7%	1.96 (0.86, 4.48)
Myles and colleagues[35] (2007)	40.1%	0.58 (0.22, 1.50)
Subtotal (95% CI)	**100.0%**	**0.90 (0.32, 2.54)**

Heterogeneity: Tau²=0.46; χ^2=4.73, df=2 (*P*=0.09); I²=58%
Test for overall effect: Z=0.19 (*P*=0.85)



Thromboembolism

Study or subgroup (and year)	Weight	Risk ratio IV, Random, 95% CI
2.2.1 Adjusted data		
Fonnes and colleagues[21] (2016)	48.3%	0.48 (0.19, 1.19)
Myles and colleagues[35] (2007)	51.7%	1.60 (0.72, 3.55)
Subtotal (95% CI)	**100.0%**	**0.89 (0.28, 2.91)**

Heterogeneity: Tau²=0.53; χ^2=3.82, df=1 (*P*=0.05); I²=74%
Test for overall effect: Z=0.19 (*P*=0.85)

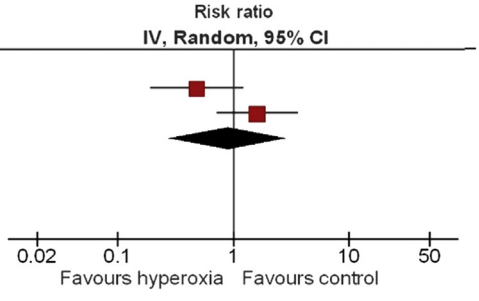


Fig 2. Pooled risk ratio for adverse events. CI, confidence interval; M-H, Mantel-Haenszel.

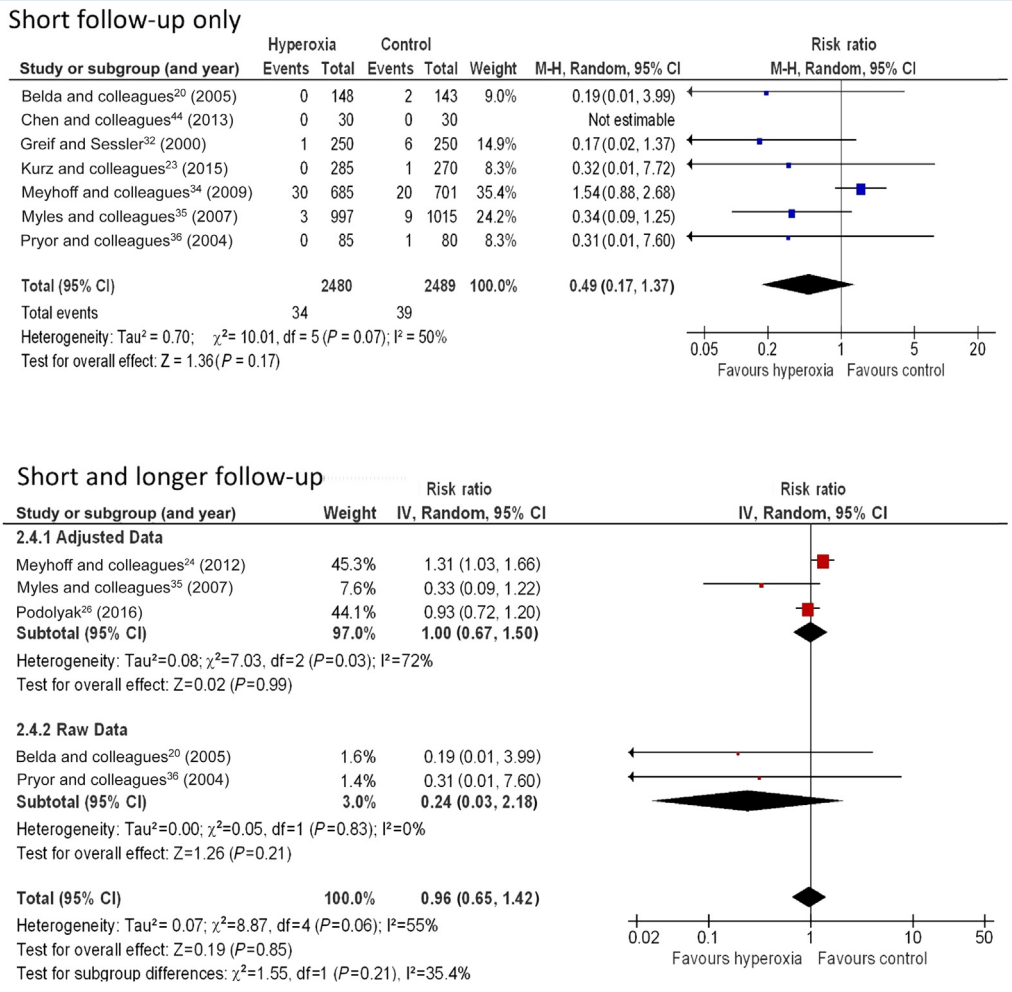


Fig 3. Pooled risk ratio for death, including short- and long-term follow-up.

Outcomes: short-term death

Seven trials reported on death in the short-term on follow-up as specified for the original trial period with 34/2480 events in the high FiO_2 arm and 39/2489 events in the low FiO_2 arm (Fig. 3).[20,23,32,34–36,44] High FiO_2 was associated with a reduced risk of death, but CIs were wide and included unity [pooled RR 0.49 (95% CI 0.17–1.37)]. There was some evidence of heterogeneity (I^2=50%). The observational study by Staehr-Rye and colleagues[43] reported an adjusted OR of 2.09 (95% CI 0.81–5.43) for mortality within 7 days in the high FiO_2 group.

Outcomes: inclusion of long-term death data in combination with short-term

As there were studies with adjusted data for *post hoc* long-term follow-up, we constructed a forest plot to show the adjusted data separately from the analysis based on raw data (Fig. 3). When the long-term data (with additional follow-up after original study period) was pooled with the two studies that reported only short-term follow-up, high FiO_2 was not significantly associated with a long-term risk of death [pooled RR 0.96 (95% CI 0.65–1.42)], with evidence of heterogeneity (I^2=55%).[20,24,26,35,36] In contrast, the observational study by Staehr-Rye and colleagues[43] reported an adjusted OR of 1.97 (95% CI 1.30–2.99) for mortality within 30 days in the high FiO_2 group. The alternating intervention study by Kurz and colleagues[46] also reported an adjusted RR of 1.97 (95% CI 0.71–5.47) for 30 day mortality associated with high FiO_2.

Outcomes: length of stay

Ten studies reported on length of stay in hospital (Table 4). However, the format of the data was inconsistent and we were unable to identify any clear trends in the results to indicate clinically important differences in length of stay between the high FiO_2 and control groups.

Other outcomes

We identified a number of *post hoc* and subgroup analyses that focused on single centres or single outcomes that were not suitable for inclusion in the meta-analysis. Meyhoff and colleagues[25] described a possible association (after a median of

3.9 yr follow-up) between high FiO_2 and poorer cancer-free survival, but the study was unable to ascertain the cause of the excess mortality. These findings led to another *post hoc* analysis conducted by Podolyak and colleagues,[26] which concluded that unlike the PROXI trial, the two trials by Greif and Sessler[32] and Kurz and colleagues[23] did not show any association between high FiO2 and mortality, either overall or in those with cancer. Another article reported on the lack of association between obesity and pulmonary complications in participants of the PROXI trial.[28]

Subgroup and sensitivity analyses

Four trials (one already retracted) are awaiting further assessment and clarification.[37,38,48,49] Of note, a sensitivity analysis based on these data did not lead to any change in direction of effect or statistical significance for AE. There were too few studies included in any particular meta-analysis to perform a meaningful analysis according to subgroups or anaesthetic techniques. For instance, all trials in the initial meta-analysis were conducted in participants who were intubated and, therefore, we could not separately evaluate AE in those with regional anaesthesia. We were also unable to construct multiple subgroups based on different types of surgery, as the included studies consisted mainly of laparotomies or a mix of major procedures.

Discussion

Our analysis of 17 RCTs did not find any robust or consistent evidence that perioperative administration of 80% FiO_2 is associated with a significant risk of harm compared with 30–35% oxygenation. The available evidence demonstrates that high FiO_2 had no significant deleterious effect on hard outcomes, such as ICU admissions and mortality. No definite signal of harm was identified for all other trial-related AE, particularly pulmonary and cardiovascular outcomes, although these findings were only backed by a low quality of evidence (GRADE, Supplementary Table S3). This stems from the small number of events and lack of statistical power, which means that the analysis of RCTs cannot completely exclude an increased risk of AE.

Although the non-randomised studies had much larger sample sizes, there were potential biases from the handling of confounders, missing data, and absence of blinding in outcome ascertainment. This was a particular concern in the study by Staehr-Rye and colleagues,[43] with an instability in results that arose after adjustment for confounding. For instance a significant beneficial association of high FiO_2 in reducing stroke risk was rendered non-significant after adjustment. Unexpectedly, the possibly beneficial associations of high FiO_2 in reducing ICU admission and wound dehiscence in this study had complete changes in direction of effect after adjustment (resulting in statistically significant harm for ICU admission with high FiO_2).

It is also not clear why certain patients were given higher concentrations of oxygen than others in the non-randomised studies. Those who received the highest concentrations in the study by Staehr-Rye and colleagues[43] were more likely to be in a higher ASA class, to have undergone general surgery, and had shorter anaesthetic durations. Protopathic bias is one possibility whereby higher concentrations of oxygen were initiated in managing patients with early or emerging (but not yet fully diagnosed) cardiorespiratory signs and symptoms. Similarly, confounding by indication occurs if patients with a past history of pneumonia or congestive heart failure/pulmonary oedema are treated with higher concentrations of oxygen. The adjusted models in the non-randomised studies do not address these two potential sources of bias.

We deliberately chose a focused set of inclusion and exclusion criteria for this systematic review to maintain direct relevance and applicability to published guidelines (i.e. the patient group, intervention, and comparator should be the same as evaluated for the development of the WHO recommendation). Otherwise, it would have been impossible to tell whether the recorded AE were as a result of the underlying disease, the surgical procedure itself, or the intervention and its comparator. In pharmaceutical evaluations, patients typically receive a single drug at the prescribed time and it is relatively easy to investigate a causal relationship for an AE after administration. This is far more difficult for the intervention targeted by our review in postoperative patients where the surgery and anaesthetic could all have contributed to these events. The outcomes selected had been identified as plausible concerns raised in the previously published literature on the safety of high FiO_2.[8–10] Of note, the concerns raised about harms resulting from high FiO_2 are from animal studies, case reports, or studies in other patient groups. For instance, Hedenstierna and colleagues[8] refer to animal studies where 70% oxygen resulted in the production of reactive oxygen species in isolated rat lungs and lung injury was detected within 24 h in live mice breathing 100% oxygen. High FiO_2 can increase peripheral vasoconstriction,[50] and reduce cardiac output[51] and perfusion to the coronary, cerebral, renal, and peripheral circulations.[52–54] High FiO_2 during anaesthesia is also thought to be potentially associated with pulmonary complications, such as atelectasis in humans,[55] but there is no published evidence apart from in live mice breathing 100% O_2.[56] The applicability and relevance of such data to perioperative hyperoxia in humans is unclear and our meta-analysis did not demonstrate any consistent confirmatory evidence behind purported AE on the cardiovascular or pulmonary systems.

Limitations

This review has some limitations. First, it was based predominantly on AE data from RCTs testing interventions based on the administration of increased oxygen and only two retrospective observational studies (judged to be at serious-critical risk of bias)[43,46] were available for inclusion. There are obvious limitations to such data, particularly where AE are not the primary focus of the study and may not be reliably defined, monitored, or reported. Although the studies reported on AE, this was not the primary aim of the data collection and considerable outcome data were missing; thus, pooled estimates were typically based only on a small fraction of the entire dataset. Indeed, only two studies adequately specified or defined pulmonary and cardiovascular AE.[34,35] Second, it is not possible to be sure that the absence of reported AE truly means that these events did not occur and there may be underlying reporting bias. Therefore, we cannot trust that 'null' findings amount to the same as actual absence of harm.[57] A further point to bear in mind is whether perceived 'null' events (safety) observed in participants taking part in RCTs can be extrapolated reliably to real-life clinical practice. For instance the findings from the trials cannot be applied to participants with chronic lung disease or serious comorbidities, as these

patients are typically excluded from trials. Third, we found that there was significant statistical heterogeneity within most of the analyses. Fourth, a substantial portion of the included studies were based on subgroup or *post hoc* studies that may carry a greater risk of bias. These include the possibility of selective analysis and reporting of *post hoc* findings, the use of subgroups, and difficulties in reliably measuring long-term outcomes that had not been pre-specified in the original trial. There is also the issue of bias arising from competing risks, variations in co-interventions after completion of the trial, and differential attrition.

Further research

Further research should focus on AE as the main predefined outcome, with rigorous monitoring and transparent reporting. Such studies could be registry-based (instead of randomised trials) with long-term follow-up across several international centres in order to capture a broader range of patients and clinical situations. There should also be steps to address protopathic bias and confounding by indication, and biases potentially arising from lack of blinding.

Conclusions

Our meta-analysis of several important outcomes did not demonstrate any definite signal of harm with 80% FiO_2 inspired oxygen. There is no substantive evidence of safety concerns that would go against implementation of the WHO and Centers for Disease Control and Prevention recommendations on the use of high FiO_2 to reduce SSI in intubated patients undergoing surgical procedures.

Authors' contributions

Devised the search strategies and conducted the searches: KM, YKL
Designed the analysis plan: YKL
Determined the eligibility of search results: KM, YKL, AS, AP
Extracted and assessed the validity of the adverse effects data: KM, YKL, AS, AP, MT
Performed the analyses: MT, YKL
Participated in the interpretation of the data: all authors.
Drafted the manuscript: KM, YKL, MT
Significantly contributed to final content of the manuscript: BA, SdJ
Guarantor: YKL
Planned the study, were involved in study design, and critically revised the manuscript: all authors.

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Declarations of interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2018.11.026.

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