BMJ Open Determining a safe upper limit of oxygen supplementation for adult patients: a systematic review

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ABSTRACT
Objective: This systematic review aimed to describe the connection between the inspired oxygen fraction and pulmonary complications in adult patients, with the objective of determining a safe upper limit of oxygen supplementation.

Methods: MEDLINE and Embase were systematically searched in August 2019 (updated July 2020) for studies fulfilling the following criteria: intubated adult patients (Population); high fractions of oxygen (Intervention) versus low fractions of oxygen (Comparison); atelectasis, acute respiratory distress syndrome (ARDS), pneumonia and/or duration of mechanical ventilation (Outcome); original studies both observational and interventional (Studies). Screening, data extraction and risk of bias assessment was done by two independent reviewers.

Results: Out of 6120 records assessed for eligibility, 12 were included. Seven studies were conducted in the emergency setting, and five studies included patients undergoing elective surgery. Eight studies reported data on atelectasis, two on ARDS, four on pneumonia and two on duration of mechanical ventilation. There was a non-significant increased risk of atelectasis if an oxygen fraction of 0.8 or above was used, relative risk (RR): 1.37 (95% CI 0.95 to 1.96). One study showed an almost threefold higher risk of pneumonia in the high oxygen fraction group (RR: 2.83 (95% CI 2.25 to 3.56)). The two studies reporting ARDS and the two studies with data on mechanical ventilation showed no association with oxygen fraction. Four studies had a high risk of bias in one domain.

Conclusions: In this systematic review, we found inadequate evidence to identify a safe upper dosage of oxygen, but the identified studies suggest a benefit of keeping inspiratory oxygen fraction below 0.8 with regard to formation of atelectases.

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INTRODUCTION
Oxygen is a molecule vital for life, as it is the cornerstone in cellular respiration in all aerobic organisms. In trauma care, during anaesthesia and in the management of respiratory failure, an oxygen fraction (FiO₂) of 0.21 may not be sufficient to maintain an acceptable oxygen concentration in arterial blood and oxygen supplementation is therefore often part of standard care.1 2

Supplementary oxygen may result in hyperoxaemia, with the risk of tissue hyperoxia. An increasing amount of evidence has connected hyperoxia and hyperoxaemia with increased mortality3-6 possibly as a consequence of a variety of factors associated with hyperoxia: atelectasis in the lungs,7 8 formation of reactive oxygen species,9 impairment of the innate immune system,10 as well as vasoconstriction with paradox tissue hypoxia to follow.11

All in all, hypoxia should be avoided, but at the same time it seems that exposure to high concentrations of oxygen may have serious consequences. Therefore, it is relevant to investigate if a safe upper dosage of oxygen can be identified.

This systematic review aimed to describe the connection between the FiO₂ and pulmonary complications in intubated adult patients, with the objective of determining a safe upper limit of oxygen supplementation. We defined pulmonary complications as atelectasis, pneumonia and acute respiratory distress syndrome (ARDS).

METHODS
Protocol and registration
Methods of the analysis and inclusion criteria were prespecified and documented in a protocol. The protocol was completed...
following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines for protocols.12 a13

**Eligibility criteria**

Studies were selected according to following predefined Population, Intervention, Comparison, Outcome and Study design (PICOS).

**Inclusion criteria**

- Population: intubated patients ≥18 years.
- Intervention and Comparison: low inspiratory FiO₂ (as defined by author) versus high FiO₂ (as defined by authors).
- Outcome: atelectasis, pneumonia, ARDS and duration of mechanical ventilation (as defined by authors).
- Study design: original studies both interventional and observational.

**Exclusion criteria**

- Hyperbaric oxygen treatment.
- Case reports, review articles and editorials.

We had no restrictions on year of publication. The search was restricted to studies published in French, English or Danish.

**Information sources and search**

We searched MEDLINE and Embase using the following predefined search string (presented search strategy is from MEDLINE).

1. (((((oxygen [Title/Abstract]) OR oxygen[MeSH Terms]) OR hyperoxia[Title/Abstract]) OR “supplemental oxygen”[Title/Abstract]) OR “oxygen supplementation”[Title/Abstract]) OR fio2[Title/Abstract])

2. ( ((((((((atelectasis[Title/Abstract]) OR pulmonary atelectasis[MeSH Terms]) OR pneumonia[Title/Abstract]) OR pneumonia[MeSH Terms]) OR “lung collapse”[Title/Abstract]) OR “collapsed lung”[Title/Abstract]) OR “acute lung injury”[Title/Abstract]) OR acute lung injury[MeSH Terms]) OR ARDS[Title/Abstract]) OR “acute respiratory distress syndrome”[Title/Abstract]) OR respiratory distress syndrome, adult[MeSH Terms])

3. (intub*) OR “mechanical ventilation”

4. #1 AND #2 AND #3.

The search was done the 6 August 2019. The search was updated the 6 July 2020. Modifications were made to fit Embase.

We identified one additional record14 by obtaining the full-text article of an abstract identified through the search string. Another record15 was identified by screening the reference list of an article.

**Selection process**

Two independent reviewers (MLL and BR) screened all titles and abstracts yielded by the search against the inclusion criteria using Covidence (an online programme facilitating the production of systematic reviews developed by the Cochrane group).16 A Cohen’s Kappa for inter-rater reliability was calculated. The same reviewers obtained full text articles for all titles that appeared to meet the inclusion criteria or where there was any uncertainty. Disagreements were resolved through discussion until consensus. All full-text articles were assessed by the same two independent reviewers and those not meeting the inclusion criteria were excluded.

**Data collection and data items**

Data extraction was done by two authors (MLL and BR), and was facilitated by the data-extraction tool Covidence and by using predefined forms. We collected study characteristics including trial design, trial size, country, period and year of publication. From the included studies we extracted the dosage of oxygen, type of control used, duration of treatment, patient characteristics (gender, age, patient type) as well as data on the predefined outcomes (atelectasis, pneumonia, ARDS) as defined by the authors.

**Risk of bias**

Risk of bias for non-randomised studies were assessed by using the Newcastle-Ottawa Scale.17 Here each study can be awarded from zero to nine stars, with zero stars representing a high risk of bias, and nine stars a low risk. Each study can be judged and awarded stars on eight items, categorised into three domains: selection of the study group, comparability of cohorts, and evaluation of the outcome of interest.

For randomised studies we used the Cochrane Collaboration tool for assessing risk of bias (Table 8.5.a in the Cochrane Handbook for Systematic Reviews of Intervention) in Covidence, which covers: sequence generation, allocation concealment, blinding, incomplete data and selective outcome reporting. A judgement as to the possible risk of bias on each domain were made from the extracted information, rated as ‘high risk’, ‘low risk’ or ‘unclear’ risk of bias. These judgements were made based on the criteria for judging the risk of bias (Table 8.5.d in the Cochrane Handbook Higgins 2011).

**Summary measures and synthesis of results**

This systematic review was expected to be a descriptive summary of the current evidence on oxygen supplementation and pulmonary complications. Relative risk (RR) was calculated where possible and a forest plot was used to illustrate the results. RRs with 95% CIs, was calculated in studies where this information was missing and the calculation was possible. The forest plot was made with a random-effects model.

**Patient and public involvement**

No patient involved.

**RESULTS**

**Study selection**

Our initial search strategy identified 7734 records. After duplicates were removed and two additional records from
incidence of atelectasis, two studies reported on ARDS, four studies reported on pneumonia and two studies reported on the duration of mechanical ventilation.

Atelectasis

The eight studies reporting on atelectasis, generally showed better outcomes for patients in the low FiO₂ group, as two studies²²,²⁵ showed almost two-fold higher risk of atelectasis in the high FiO₂, with RR: 1.875 (95% CI 0.42 to 8.37) and RR: 2.0 (95% CI 1.06 to 3.79), respectively. One study¹⁵ suggested a minor benefit of treatment with low FiO₂, but this was not statistically significant, RR: 1.46 (95% CI 0.97 to 2.20). Another study²⁴ found RR: 0.91 (95% CI 0.56 to 1.50) suggesting a benefit of treatment with high FiO₂, but this was not statistically significant. These studies are illustrated in the forest plot (figure 2), which shows that in general treatment with high FiO₂ was associated with higher risk of atelectasis formation, RR:1.37 (95% CI 0.95 to 1.96). The heterogeneity (I²) of the meta-analysis presented in figure 2 is 31%, which corresponds to a moderate heterogeneity (Cochrane Handbook for Systematic Reviews of Intervention, section 9.5.2 Identifying and measuring heterogeneity).

Rothen et al²⁶ found a 16.8 times greater area of atelectasis in the high FiO₂ group and similarly, the study by Benoit et al²⁶ found a threefold larger atelectatic surface in the high FiO₂ group. Suzuki et al²³ estimated atelectasis as time-weighted averages, and also found a beneficial effect of a low FiO₂. In the study by Ishii et al²⁸ additional information on intubated patients were found in an abstract²⁷ from the same study. They found a higher incidence of atelectasis in the high FiO₂ group, but the total number of patients was not reported.

Acute respiratory distress syndrome

Panwar et al²⁹ showed an increase of new-onset ARDS in the low FiO₂ group, RR: 0.87 (95% CI 0.43 to 1.75), but this was not statistically significant. The study by Lång et al³⁰ found three patients with ARDS in the low FiO₂ group, while no patients with ARDS were identified in the group receiving high FiO₂.

Pneumonia

The study by Staehr-Rye et al³¹ showed a significant increase in the incidence of pneumonia, RR: 2.83 (95% CI 2.25 to 3.56) in the high FiO₂ group. Similarly, Barrot et al³² showed a small, but non-significant, tendency to ventilator-associated pneumonias in the high FiO₂ group, RR: 1.26 (95% CI 0.71 to 2.22). The two other studies, Asfar et al³³ and Lång et al³⁴ found a non-significant tendency for pneumonia in the low FiO₂ group with RR: 0.94 (95% CI 0.59 to 1.49) and RR: 0.71 (95% CI 0.26 to 1.97), respectively. These studies are illustrated in the forest plot (figure 3), which shows a non-significant tendency that treatment with high FiO₂ was associated with higher risk of pneumonia, RR: 1.32 (95% CI 0.65 to 2.70).

other sources were added, 6120 records were screened. Of these, 6100 were excluded as they did not fulfil eligibility criteria leaving 20 records for full-text screening. Cohen’s kappa for inter-rater reliability of 0.43 (95% CI 0.26 to 0.60) was calculated, which is judged to be moderate agreement. After full-text review, 12 records fulfilled the inclusion criteria (figure 1).

Study characteristics

Study characteristics are summarised in table 1. Eight of the 12 included studies were randomised controlled trials. Among the four remaining there were two retrospective observational studies¹⁸,¹⁹ and two prospective observational studies.²⁰,²¹ About half of the studies were conducted in Europe. Seven studies were conducted in the acute care setting. Of these seven, one study²² included patients with septic shock, four studies¹⁴,¹⁸,¹⁹,²¹,²⁵ recruited surgical, medical and trauma patients that were mechanically ventilated in the intensive care unit, one study²⁰ included patients with acute lung injury and the last study²⁴ recruited patients with traumatic brain injury. The remaining five studies included patients undergoing different types of elective surgery.

The administered FiO₂ varied substantially among the studies, with FiO₂ ranging from 0.26 to 0.60 in the low FiO₂ group and from 0.36 to 1.0 in the high FiO₂ group.

Table 2 presents the outcomes of interest reported in the included studies. Eight studies reported on the
| Reference and year of publication | Country | Setting | Study design | Sample size | Low-dose oxygen | High-dose oxygen | Primary outcome |
|----------------------------------|---------|---------|--------------|-------------|----------------|-----------------|----------------|
| Akca et al. (1999)¹⁵             | Austria | Elective surgery | Randomised controlled trial | 30          | 0.3            | 0.8             | Atelectasis    |
| Asfar et al. (2017)²²           | France  | Septic shock | Randomised controlled trial | 434         | SpO₂ between 88% and 95% | 1.0            | Mortality day-28 |
| Barrot et al. (2020)²³          | France  | Critical care | Randomised controlled trial | 205         | SpO₂ ≥96% | SpO₂ ≥96% | Mortality day-28 |
| Benoît et al. (2002)²⁶          | Switzerland | Elective surgery | Randomised controlled trial | 20          | 0.4            | 1.0             | Atelectasis    |
| Ishii et al. (2015)¹⁸           | Japan   | Trauma | Retrospective cohort study | 911         | <0.6           | >0.6            | Atelectasis    |
| Lång et al. (2018)²⁴            | Finland | Critical care | Randomised controlled trial | 65          | 0.4            | 0.7             | Levels of ROS, IL-6 and NSE |
| Panwar et al. (2015)¹⁴          | Australia, New Zealand and France | Critical care | Randomised controlled trial | 104         | Mean=0.26 | Mean=0.36 | Mean AUC for SpO₂, SaO₂, PaO₂, and FiO₂ on days 0–7 |
| Rachmale et al. (2012)²⁰        | USA     | Critical care | Prospective, observational study | 210         | Mean=0.4 | Mean=0.6 | Duration of exposure to excessive FiO₂ during the first 48 hours of mechanical ventilation |
| Rothen et al. (1995)⁸           | Sweden  | Elective surgery | Randomised controlled trial | 24          | 0.3            | 1.0             | Atelectasis    |
| Staehr et al. (2012)²⁵          | Denmark | Laparotomy for ovarian cancer | Randomised controlled trial | 35          | 0.3            | 0.8             | Change in PaO₂/FiO₂ |
| Staehr-Rye et al. (2017)¹⁹      | USA     | Non-cardiothoracic surgery | Register study | 26841       | 0.31           | 0.79            | Major respiratory complications |
| Suzuki et al. (2015)²¹          | Australia | Critical care | Prospective before-and-after study | 105         | 0.27           | 0.40            | Changes in atelectasis score |

Lung complications were atelectasis, ARDS, pneumonia and duration of mechanical ventilation.

ARDS, acute respiratory distress syndrome; AUC, area under the curve; FiO₂, oxygen fraction; IL-6, interleukin-6; NSE, neuron-specific enolase; PaO₂, arterial oxygen tension; ROS, reactive oxygen species; SaO₂, oxygen saturation as measured by blood analysis.
Duration of mechanical ventilation

The two studies reporting the duration of mechanical ventilation pointed in opposite direction. Lång et al\textsuperscript{24} reported slightly more time spent on mechanical ventilation in the low FiO\textsubscript{2} group, while Rachmale et al\textsuperscript{20} reported a twofold increase in time in the high FiO\textsubscript{2} group.

Risk of bias assessment

Risk of bias for randomised studies are illustrated in table 3. Three studies had no blinding of participants, personal or outcome assessment, leaving them with a high risk of bias on these domains.\textsuperscript{8 14 22} In the study by Rothen et al\textsuperscript{8} it was unclear if a randomisation was performed between the low FiO\textsubscript{2} group and the high FiO\textsubscript{2} group, indicating a high risk of bias.

Lång et al\textsuperscript{24} was an open-label trial, and was therefore awarded a high risk of bias on the domain of blinding of participants and personnel, however, the outcome assessor was blinded.

The four non-randomised studies were assessed using the New-Castle Ottawa Scale.\textsuperscript{17} One study\textsuperscript{20} scored six stars, two studies\textsuperscript{18 19} scored seven stars and one study\textsuperscript{21} scored eight stars, indicating an overall high quality of the studies.

**DISCUSSION**

**Summary of findings**

In this study, we were not able to determine a safe upper limit of oxygen supplementation, due to inadequate evidence and heterogeneity as the included studies had different endpoints with varying definitions, and also different ways of defining low and high FiO\textsubscript{2}. In some

| Table 2 | Patient outcomes comparing low doses of oxygen supplementation with high doses of oxygen supplementation |
|---------|--------------------------------------------------------------------------------------------------|
| Reference | Low-dose oxygen | High-dose oxygen | RR (95% CI) |
| Atelectasis | | | |
| Akca et al\textsuperscript{16} | 9 (64%) | 15 (94%) | 1.46 (0.97 to 2.2) |
| Asfar et al\textsuperscript{22} | 13 (6%) | 26 (12%) | 2.0 (1.06 to 3.79) |
| Benoit et al\textsuperscript{26} | 2.5% of total surface | 7% of total surface | – |
| Ishii et al\textsuperscript{18} | 64% of patients | 76.8% of patients | – |
| Lång et al\textsuperscript{24} | 14 (52%) | 18 (47%) | 0.914 (0.56 to 1.5) |
| Rothen et al\textsuperscript{8} | 0.25 cm\textsuperscript{2} ±0.4 | 4.2 cm\textsuperscript{2} ±5.6 | – |
| Staehr et al\textsuperscript{25} | 2 (13.3%) | 5 (25%) | 1.88 (0.42 to 8.37) |
| Suzuki et al\textsuperscript{21} | TWA AS=1.5 (0.7–2) | TWA AS=2 (1.2–2.2) | – |
| ARDS | | | |
| Lång et al\textsuperscript{24} | 3 (11%) | 0 (0%) | – |
| Panwar et al\textsuperscript{14} | 11 (32%) | 11 (28%) | 0.87 (0.43 to 1.75) |
| Pneumonia | | | |
| Asfar et al\textsuperscript{22} | 32 (15%) | 30 (14%) | 0.94 (0.59 to 1.49) |
| Barrot et al\textsuperscript{23} | 17 (17.2%) | 22 (21.6%) | 1.26 (0.71 to 2.22) |
| Lång et al\textsuperscript{24} | 6 (22.2%) | 6 (15.8%) | 0.71 (0.26 to 1.97) |
| Staehr-Rye et al\textsuperscript{19} | 104 (0.7%) | 227 (1.9%) | 2.83 (2.25 to 3.56) |
| Duration of mechanical ventilation | | | |
| Lång et al\textsuperscript{24} | 6.3 days (4.7–10) | 5 days (2.5–7.5) | – |
| Rachmale et al\textsuperscript{20} | 2.8 days\textsuperscript{1–6} | 6 days (3–10.5) | – |

Continuous data are presented as mean (SD) or median (IQR). RR is presented with high-dose oxygen in the numerator.
ARDS, acute respiratory distress syndrome; RR, relative risk; TWA AS, time-weighted average atelectasis.
studies the FiO2 in the low FiO2 group was higher than in the high FiO2 group in other studies.

Regarding atelectasis, seven of the eight studies favoured a conservative oxygen strategy with low FiO2 and an FiO2 above 0.8 seemed to be associated with higher risk of atelectasis formation. Looking at figure 2, there is an RR of 1.37, which suggests a clinically relevant difference with less atelectasis with a lower FiO2. However, the CI is wide (0.95–1.96), indicating that more information is needed before any firm conclusions can be made.

**Strengths and limitations**

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines,28 ensuring a systematic and broadly acknowledged approach to the present literature. The strengths of this approach include predefined PICOS criteria to assess study eligibility, use of a wide search string in two databases and two independent reviewers screened and assessed studies, including risk of bias.

Our study is limited by general weaknesses of systematic reviews. This includes risk of publication bias that arises due to the possibility of missing non-published studies. Despite the systematic search with predefined search string, and screening of reference lists of included studies, there is always a possibility that our search did not identify all relevant studies. However, the heterogeneity of the 12 studies reviewed makes us believe that potentially missed studies would not change the conclusion substantially. It is possible that more studies could have been found by searching in a wider set of databases. However, we chose the most commonly used databases MEDLINE and EMBASE, where the quality is known to be best and where most studies are found.

The patient population was determined in very broad terms (intubated adult patients), resulting in more heterogeneity among the included studies.

The trials varied in patient groups, associated clinical care and disease severity. Furthermore, in some studies it is unclear when exactly the outcome of interest was measured (early or late onset of ARDS and timing of CT/X-ray for measuring the presence of atelectasis). It is also unclear how pneumonia was defined in the four

![Figure 3](https://example.com/figure3.png)

**Figure 3** Forest plot of risk of pneumonia in studies comparing low FiO2 with high FiO2. FiO2, oxygen fraction; M.H, Random, Maentel-Haentzel.

| Study or Subgroup | High FiO2 | Low FiO2 | Risk Ratio M-H, Random, 95% CI |
|-------------------|----------|----------|-------------------------------|
|                   | Events   | Total    | Weight |                          |
| Asfar 2017        | 30       | 217      | 26.8%  | 0.94 [0.59, 1.49]          |
| Barrot 2020       | 22       | 102      | 17     | 0.99 [0.71, 1.32]          |
| Lång 2018         | 6        | 38       | 27     | 0.71 [0.26, 1.97]          |
| Staehr-Rye 2017   | 227      | 11691    | 15150  | 2.83 [2.25, 3.58]          |
| Total (95% CI)    | 12048    | 15493    | 100.0% | 1.32 [0.65, 2.70]          |
| Total events      | 285      | 159     |
| Heterogeneity: Tau² = 0.44; Chi² = 25.74, df = 3 (P < 0.0001); I² = 88% |

Table 3 Risk of bias assessment for randomised controlled trials comparing low dose oxygen supplementation with high dose oxygen supplementation

| Risk of bias assessment | Akca et al15 | Asfar et al22 | Barrot et al23 | Benoit et al26 | Lång et al24 | Panwar et al14 | Rothen et al8 | Staehr et al25 |
|-------------------------|--------------|--------------|---------------|---------------|-------------|---------------|-------------|---------------|
| Random sequence generation | Green | Green | Green | Green | Green | Green | Green | Red |
| Allocation concealment   | Green | Green | Green | Green | Green | Green | Green | Green |
| Blinding of participants and personal | Red | Red | Red | Red | Red | Red | Red | Red |
| Blinding of outcome assessment | Green | Green | Green | Green | Green | Green | Green | Green |
| Incomplete outcome data  | Green | Green | Green | Green | Green | Green | Green | Green |
| Selective reporting      | Green | Green | Green | Green | Green | Green | Green | Green |
| Other bias               | Red | Red | Red | Red | Red | Red | Red | Red |

Risk of bias was assessed using Cochrane Collaboration tool for assessing risk of bias (Table 8.5.a in the Cochrane Handbook for Systematic Reviews of Intervention).

Green, low risk of bias; Red, high risk of bias; Yellow, unclear risk of bias.
studies reporting this outcome. Therefore, conclusions should be drawn with caution.

Half of the randomised controlled trials were not blinded to personnel and participants, increasing the risk of performance bias. Three of these were not blinded to outcome assessors which increase the risk of detection bias. In general, many of the studies are relatively small, increasing the risk of other bias such as publication bias (table 3).

Atelectasis was defined in different ways complicating the pooling of data and the possibility to undertake a meta-analysis. Three studies used CT-scans and they all considered densities between −100 and +100 Hounsfield as atelectasis. Of these three, one measured areas of atelectasis in cm² whereas the two others measured if atelectases were present or not. Ishii et al also used CT-scans, but defined atelectases as areas with formation of more than 10 mm thick atelectasis from the first to the second scan. The study by Staehr et al did not define specific criteria on when densities were judged as atelectasis or not.

Asfar et al and Suzuki et al used chest X-rays, without defining atelectasis specifically, as this was decided by the individual physician. Lång et al used chest X-rays in the same manner, however they allowed the appliance of positive end-expiratory pressure to minimise atelectasis, which makes it hard to directly compare results with other studies. Only Suzuki et al used more than one radiologist to perform the outcome assessment.

In Panwar et al’s new-onset ARDS was defined as subsequent occurrence of ARDS in those patients who did not have ARDS on day 0, and where ARDS was present according to the Berlin definition. Lång et al did not report their definition of ARDS.

Regarding pneumonia, the database study of 26841 patients performed by Staehr-Rye et al found a significant, almost threefold higher risk of pneumonia in the liberal oxygen group, indicating that excess levels of oxygen may be harmful. However, this is an analysis of administrative data, with risk of misclassification bias, and therefore, direct conclusions should be drawn with caution.

### Other reviews

The evidence for the use of supplemental oxygen has been investigated in recently published systematic reviews. A systematic review and meta-analysis by Damiani et al from 2014 suggests an association between hyperoxia and mortality in patients with stroke, traumatic brain injury and those resuscitated from cardiac arrest. However, they concluded that their results were limited by the heterogeneity of the included studies. The same conclusion was drawn in another meta-analysis from 2015 by Helmerhorst et al. No definite conclusions could be made due to heterogeneity in the included studies; however, the meta-analysis suggested a benefit of conservative oxygen therapy. In a Cochrane review from 2015 by Wetterlev et al, comparing low (FiO₂ 0.30–0.40) vs high (FiO₂ 0.60–0.90) perioperative inspiratory FiO₂, they found no association between perioperative FiO₂ and postoperative surgical site infection and mortality. In another Cochrane review from 2016 performed by Cabello et al, they focused on patients with acute myocardial infarctions. They included five studies and found no clear recommendations on the use of oxygen supplementation.

In a recent meta-analysis performed in 2018 by Chu et al, they included 25 randomised controlled trials on acutely ill patients and found a significant association between liberal oxygenation strategies and increased mortality in-hospital, at 30 days and at longest follow-up. Nevertheless, morbidity outcomes were similar between groups.

The available reviews are limited because of heterogeneity, including different outcome measures, overall indication that excess oxygen is harmful, stressing the need for further investigation on this subject.

Oxygen supplementation is obviously a vital part of trauma care, practice of anaesthesia, the management of respiratory distress and treatment of a variety of other conditions. However, supplemental oxygen should be carefully considered a drug and prescribed adequately. There is a general lack of strong evidence for supplemental oxygen, and an upper limit of oxygen supplementation is not included in many guidelines. Our study contributes to the current evidence in a different way, by looking at the association between FiO₂ and pulmonary complications, which is a highly relevant indicator in the search for a safe upper limit of oxygen supplementation.

As oxygen supplementation is so widely used, it is crucial that better evidence-based guidelines are developed. Future research is required to precisely define the oxygen therapy strategies to maximise benefits and minimise harms.

### Conclusion

In this systematic review, we found that there was inadequate evidence to identify a safer upper dosage of oxygen, but the identified studies suggest a benefit of conservative oxygen therapy, defined as FiO₂ ≤0.8 with regard to formation of atelectasis.

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**Data availability statement** Data are available on reasonable request. This was a systematic review and researchers can contact the authors to access the material.

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