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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 (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 significantly increased risk of atelectasis if an oxygen fraction of 0.8 or above was used, Relative Risk (RR): 1.44 [1.05-1.97] (figure 2). One study showed an almost three-fold higher risk of pneumonia in the high oxygen fraction group (RR 2.83 [2.25-3.56]). 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 adequate 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 regards to formation of atelectases.

PROSPERO registration number CRD42020154242

Strengths and limitations of this study

- The use of predefined Population, Intervention, Comparison, Outcome and Study design to asses studies for eligibility.
- The use of a wide search string in two databases.
- Two independent reviewers screening and including studies, assessing risk of bias and extracting data.
- There is a risk of publication bias that arises due to the possibility of missing unpublished studies.
- It is possible that our search did not identify all relevant studies.

Funding

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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 anesthesia and in the management of respiratory failure, an oxygen fraction 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 mortality (3–6) 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 inspired oxygen fraction FiO_2 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) and was registered in PROSPERO, the international prospective register of systematic reviews (13) (CRD42020154242).

Eligibility criteria

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

Inclusion criteria:

- **P**opulation: intubated patients ≥ 18 years

- **I**ntervention and **C**omparison: low inspiratory oxygen fraction (FiO_2) (as defined by author) vs high FiO_2 (as defined by authors)
- **O**utcome: atelectasis, pneumonia, ARDS and duration of mechanical ventilation
- **S**tudy 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 6th of August 2019. The search was updated the 6th of July 2020. Modifications were made to fit Embase.

We identified one additional record (14) by obtaining the full-text article of an abstract identified through the search string. Another record (15) was identified by screening the reference list of an article.

Selection process

Two independent reviewers (MLL, BR) screened all titles and abstracts yielded by the search against the inclusion criteria using Covidence (an online program 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, 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-randomized 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, categorized into three domains: selection of the study group, comparability of cohorts, and evaluation of the outcome of interest.

For randomized 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 was calculated where possible and a forest plot was used to illustrate the results.

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 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 (CI: 0.26 to 0.6) 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 summarized in table 1. Eight of the 12 included studies were randomized controlled trials. Among the four remaining there were two retrospective observational studies (18,19) 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 study (22) included patients with septic shock, four studies (14,18,21,23) recruited surgical, medical and trauma patients that were mechanically ventilated in the intensive care unit, one study (20) included patients with acute lung injury and the last study (24) recruited patients with traumatic brain injury. The remaining five studies included patients undergoing different types of elective surgery.
The administered FiO_2 varied substantially among the studies, with oxygen fraction ranging from 0.26 to 0.6 in the low FiO_2 group and from 0.36 to 1.0 in the high FiO_2 group.

Table 2 presents the outcomes of interest reported in the included studies. Eight studies reported on the 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 FiO_2 group, as two studies (22,25) showed almost two-fold higher risk of atelectasis in the high FiO_2, with RR: 1.875 [0.42-8.37] and RR: 2.0 [1.06-3.79], respectively. One study (15) suggested a minor benefit of treatment with low FiO_2, but this was not statistically significant, RR: 1.46 [0.97-2.2]. Another study (24) found RR: 0.914 [0.56-1.5] suggesting a benefit of treatment with high FiO_2, but this was not statistically significant. These studies are illustrated in the forest plot (figure 2), which shows that in general treatment with high FiO_2 was associated with higher risk of atelectasis formation, RR: 1.44 [1.05-1.97].

Rothen et al (8) found a 16.8 times greater area of atelectasis in the high FiO_2 group and similarly, the study by *Benoit et al* (26) found a three-fold bigger atelectatic surface in the high FiO_2 group. *Suzuki et al* (21) estimated atelectasis as time weighted averages, and also found a beneficial effect of a low FiO_2. In the study by *Ishii et al* (18) additional information on intubated patients were found in an abstract (27) from the same study. They found a higher incidence of atelectasis in the high FiO_2 group, but the total number of patients was not reported.

ARDS

Panwar et al (14) showed an increase of new-onset ARDS in the low FiO_2 group, RR: 0.87 (0.43-1.75), but this was not statistically significant. The study by *Lång et al* (24) found three patients with ARDS in the low FiO_2 group, while no patients with ARDS were identified in the group receiving high FiO_2.

Pneumonia

The study by *Staehr-Rye et al* (19) showed a significant increase in the incidence of pneumonia, RR: 2.83 [2.25-3.56] in the high FiO_2 group. Similarly, *Barrot et al* (23) showed a small, but nonsignificant, tendency to ventilator-associated pneumonias in the high FiO_2 group, RR: 1.26 [0.71-2.22]. The two other studies, *Asfar et al* (22) and *Lång et al* (24), found a nonsignificant tendency for pneumonia in the low FiO_2 group with RR: 0.94 [0.59-1.49] and RR: 0.71 [0.26-1.97], respectively.

Duration of mechanical ventilation

The two studies reporting the duration of mechanical ventilation pointed in opposite direction. *Lång et al* (24) reported slightly more time spent on mechanical ventilation in the low FiO_2 group, while *Rachmale et al* (20) reported a two-fold increase in time in the high FiO_2 group.

Risk of bias assessment

Risk of bias for randomized 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 (8,14,22). In the study by *Rothen et al* (8) it was unclear if a randomization was performed between the low FiO_2 group and the high FiO_2 group, indicating a high risk of bias.

Lång et al (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-randomized studies were assessed using the New-Castle Ottawa Scale (17). One study

(20) scored six stars, two studies (18,19) scored seven stars and one study (21) scored 8 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_2. In some studies the oxygen fraction in the low FiO_2 group was higher than in the high FiO_2 group in other studies.

Regarding atelectasis, seven of the eight studies favored a conservative oxygen strategy with low FiO_2 and an FiO_2 above 0.8 seemed to be associated with higher risk of atelectasis formation.

Strengths and limitations

This study was conducted according to the PRISMA 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 nonpublished studies, and the possibility that our search did not identify all relevant studies. The patient population was determined in very broad terms (intubated adult patients), resulting in more heterogeneity among the included studies.

Half of the randomized 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 (8,15,25) used CT-scans and they all considered densities between -100 to +100 Hounsfield as atelectasis. Of these three, one (8) measured areas of atelectasis in cm^2 whereas the two others (15,25) measured if atelectases were present or not. *Ishii et al* (18) 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* (25) did not define specific criteria on when densities were judged as atelectasis or not.
Asfar et al (22) and *Suzuki et al* (21) used chest x-rays, without defining atelectasis specifically, as this was decided by the individual physician. *Lång et al* (24) used chest x-rays in the same manner, however they allowed the appliance of positive end-expiratory pressure to minimize atelectasis, which makes it hard to directly compare results with other studies. Only *Suzuki et al* (21) used more than one radiologist to perform the outcome assessment.

In *Panwar et al* (14), 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 (29). *Lång et al* (24) did not report their definition of ARDS.

Regarding pneumonia, the database study of 26841 patients performed by *Staehr-Rye et al* (19) found a significant, almost three-fold 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* (30) 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* (31). 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 *Wetterslev et al* (32), comparing low (FiO_2 0.30-0.40) vs high (FiO_2 0.60-0.90) perioperative inspiratory oxygen fractions, they found no association between perioperative FiO_2 and postoperative surgical site infection and mortality. In another Cochrane review from 2016 performed by *Cabello et al* (33), 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* (4) 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 indicate 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 anesthesia, 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 (1, 31-33). Our study contributes to the current evidence in a different way, by looking at the association between FiO_2 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 maximize benefits and minimize 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 $FiO_2 \leq 0.8$ with regards to formation of atelectasis.

Figure caption

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flow diagram of identification, screening, eligibility and inclusion process (28) on a search for studies comparing low dose oxygen supplementation with high dose oxygen supplementation with pulmonary complications as an outcome.

Figure 2: Forest plot of formation of atelectasis in studies comparing low FiO_2 with high FiO_2

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Table 1: Characteristics of studies comparing low FiO_2 with high FiO_2, with lung complications as an outcome. Lung complications were atelectasis, ARDS, pneumonia and duration of mechanical ventilation.

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	Randomized controlled trial	30	0.3	0.8	Atelectasis
Asfar et al (2017) (22)	France	Septic shock	Randomized controlled trial	434	SpO2 between 88 and 95%	1.0	Mortality day-28
Barrot et al (2020) (23)	France	Critical care	Randomized controlled trial	205	SpO_2 between 88 and 92%	$SpO_2 \geq$ 96%	Mortality day-28
Benoît et al (2002) (26)	Switzerland	Elective surgery	Randomized 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	Randomized controlled trial	65	0.4	0.7	Levels of ROS, IL-6 and NSE
Panwar et al (2015) (14)	Australia, NZ & France	Critical care	Randomized 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, obser-vational study	210	Mean = 0.4	Mean = 0.6	Duration of exposure to excessive FiO_2 during the first 48 h of mechanical ventilation
Rothen et al (1995) (8)	Sweden	Elective surgery	Randomized controlled trial	24	0.3	1.0	Atelectasis
Staehr et al (2012) (25)	Denmark	Laparo-tomy for ovarian cancer	Randomized controlled trial	35	0.3	0.8	Change in PaO2/FiO2
Staehr-Rye et al (2017) (19)	USA	Non-cardiothora cic 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

Abbreviations: AUC: area under the curve

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 (15)	9 (64%)	15 (94%)	1.46 (0.97-2.2)
Asfar et al (22)	13 (6%)	26 (12%)	2.0 (1.06-3.79)
Benoit et al (26)	2.5% of total surface	7% of total surface	-
Ishii et al (18)	64% of patients	76.8% of patients	-
Lång et al (24)	14 (52%)	18 (47%)	0.914 (0.56-1.5)
Rothen et al (8)	0.25 cm^2 ± 0.4	4.2 cm^2 ± 5.6	-
Staehr et al (25)	2 (13.3%)	5 (25%)	1.88 (0.42-8.37)
Suzuki et al (21)	TWA AS = 1.5 (0.7-2)	TWA AS = 2 (1.2-2.2)	-
ARDS			
Lång et al (24)	3 (11%)	0 (0%)	-
Panwar et al (14)	11 (32%)	11 (28%)	0.87 (0.43-1.75)
Pneumonia			
Asfar et al (22)	32 (15%)	30 (14%)	0.94 (0.59-1.49)
Barrot et al (23)	17 (17.2%)	22 (21.6%)	1.26 (0.71-2.22)
Lång et al (24)	6 (22.2%)	6 (15.8%)	0.71 (0.26-1.97)
Staehr-Rye et al (19)	104 (0.7%)	227 (1.9%)	2.83 (2.25-3.56)
Duration of mechanical ventilation			
Lång et al (24)	6.3 days (4.7-10)	5 days (2.5-7.5)	-
Rachmale et al (20)	2.8 days (1-6)	6 days (3-10.5)	-

Continuous data is presented as mean (SD) or median (IQR). Relative risk (RR) is presented with high dose oxygen in the numerator.

Abbreviations: RR: relative risk, CI: confidence interval, TWA AS: time weighted average atelectasis, SD: standard deviation, IQR: interquartile range

Table 3: Risk of bias assessment for randomized controlled trials comparing low dose oxygen supplementation with high dose oxygen supplementation. 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).

	Akca et al	Asfar et al	Barrot et al	Benoit et al	Lång et al	Panwar et al	Rothen et al	Staehr et al
Random sequence generation								
Allocation concealment								
Blinding of participants and personal								
Blinding of outcome assessment								
Incomplete outcome data								
Selective reporting								
Other bias								

Green = low risk of bias, yellow = unclear risk of bias, red = high risk of bias

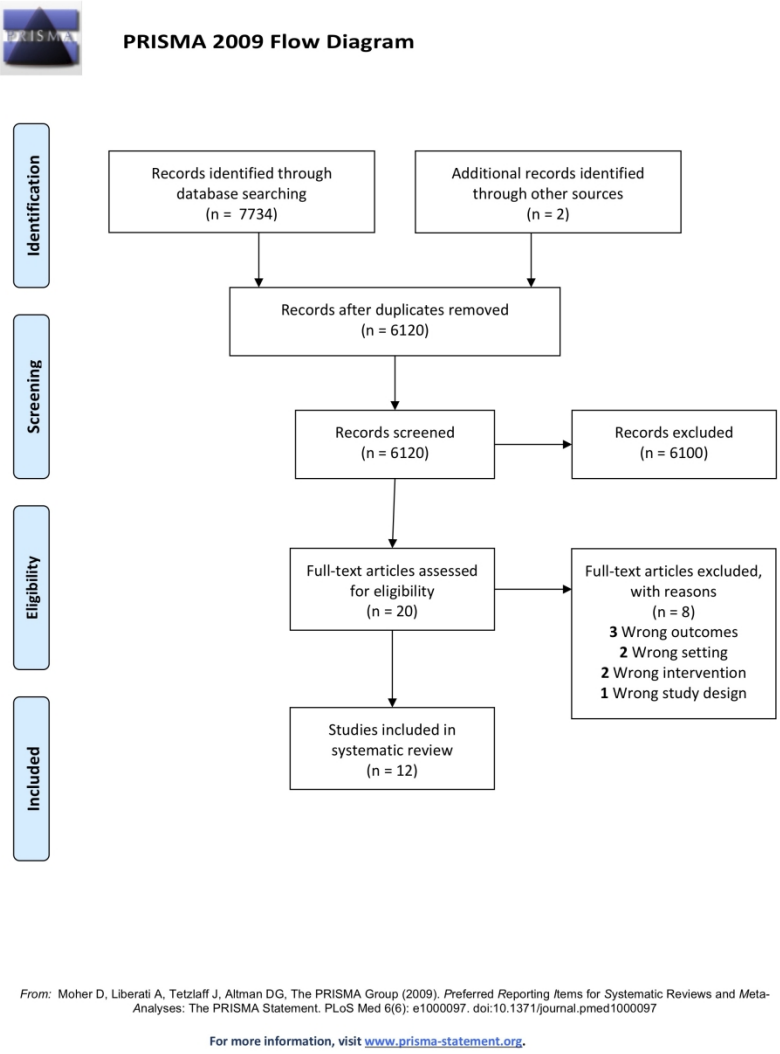

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flow diagram of identification, screening, eligibility and inclusion process (28) on a search for studies comparing low dose oxygen supplementation with high dose oxygen supplementation with pulmonary complications as an outcome.

215x279mm (300 x 300 DPI)

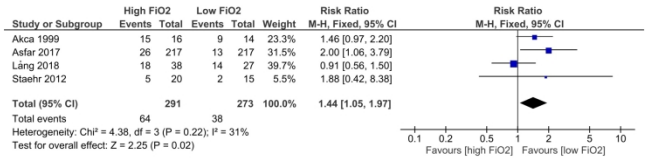

Figure 2: Forest plot of formation of atelectasis in studies comparing low FiO2 with high FiO2

209x297mm (300 x 300 DPI)

PRISMA 2009 Checklist (Adapted for KIN 4400)

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a literature review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings;	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known about your topic.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Eligibility criteria	5	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	6	Describe all information sources (e.g., databases with dates of coverage) in the search and date last searched.	4
Search	7	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	8	State the process for selecting studies (i.e., screening, eligibility).	5
Risk of bias in individual studies	9	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level).	5
Risk of bias across studies	10	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
RESULTS			
Study selection	11	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	12	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7

PRISMA 2009 Checklist (Adapted for KIN 4400)

Section/topic	#	Checklist item	Reported on page #
Synthesis of results of individual studies	13	For all outcomes considered (benefits or harms), present, for each study: (a) summary of results and (b) relationship to other studies under review (e.g. agreements or disagreements in methods, sampling, data collection or findings).	7
DISCUSSION			
Summary of evidence	14	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9
Limitations	15	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9
CONCLUSION			
Conclusions	16	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11

Adapted from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA statement. *PLoS Medicine*, 6(6), e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

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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 (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 nonsignificant increased risk of atelectasis if an oxygen fraction of 0.8 or above was used, Relative Risk (RR):1.37 [0.95, 1.96]. One study showed an almost three-fold higher risk of pneumonia in the high oxygen fraction group (RR 2.83 [2.25-3.56]). 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 regards to formation of atelectases.

PROSPERO registration number CRD42020154242

Strengths and limitations of this study

- The use of predefined Population, Intervention, Comparison, Outcome and Study design to asses studies for eligibility.
- The use of a wide search string in two databases.
- Two independent reviewers screening and including studies, assessing risk of bias and extracting data.
- There is a risk of publication bias that arises due to the possibility of missing unpublished studies.
- It is possible that our search did not identify all relevant studies.

Introduction

Oxygen is a molecule vital for life, as it is the cornerstone in cellular respiration in all aerobic organisms. In trauma care, during anesthesia and in the management of respiratory failure, an oxygen fraction 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 mortality (3–6) 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 inspired oxygen fraction FiO_2 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) and was registered in PROSPERO, the international prospective register of systematic reviews (13) (CRD42020154242).

Eligibility criteria

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

Inclusion criteria:

- **P**opulation: intubated patients ≥ 18 years

- **I**ntervention and **C**omparison: low inspiratory oxygen fraction (FiO_2) (as defined by author) vs high FiO_2 (as defined by authors)
- **O**utcome: atelectasis, pneumonia, ARDS and duration of mechanical ventilation (as defined by authors)
- **S**tudy 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 6th of August 2019. The search was updated the 6th of July 2020. Modifications were made to fit Embase.

We identified one additional record (14) by obtaining the full-text article of an abstract identified through the search string. Another record (15) was identified by screening the reference list of an article.

Selection process

Two independent reviewers (MLL, BR) screened all titles and abstracts yielded by the search against the inclusion criteria using Covidence (an online program 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, 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-randomized 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, categorized into three domains: selection of the study group, comparability of cohorts, and evaluation of the outcome of interest.

For randomized 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 was calculated where possible and a forest plot was used to illustrate the results. Relative risks with 95% confidence intervals, 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 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 (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 summarized in table 1. Eight of the 12 included studies were randomized controlled trials. Among the four remaining there were two retrospective observational studies (18,19) 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 study (22) included patients with septic shock, four studies (14,18,21,23) recruited surgical, medical and trauma patients that were mechanically ventilated in the intensive care unit, one study (20) included patients with acute lung injury and the last study (24) recruited patients with traumatic brain injury. The remaining five studies included patients undergoing different types of elective surgery.
The administered FiO_2 varied substantially among the studies, with oxygen fraction ranging from 0.26 to 0.60 in the low FiO_2 group and from 0.36 to 1.0 in the high FiO_2 group.

Table 2 presents the outcomes of interest reported in the included studies. Eight studies reported on the 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 FiO_2 group, as two studies (22,25) showed almost two-fold higher risk of atelectasis in the high FiO_2, with RR: 1.875 [0.42-8.37] and RR: 2.0 [1.06-3.79], respectively. One study (15) suggested a minor benefit of treatment with low FiO_2, but this was not statistically significant, RR: 1.46 [0.97-2.20]. Another study (24) found RR: 0.91 [0.56-1.50] suggesting a benefit of treatment with high FiO_2, but this was not statistically significant. These studies are illustrated in the forest plot (figure 2), which shows that in general treatment with high FiO_2 was associated with higher risk of atelectasis formation, RR:1.37 [0.95, 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 al* (8) found a 16.8 times greater area of atelectasis in the high FiO_2 group and similarly, the study by *Benoit et al* (26) found a three-fold larger atelectatic surface in the high FiO_2 group. *Suzuki et al* (21) estimated atelectasis as time weighted averages, and also found a beneficial effect of a low FiO_2. In the study by *Ishii et al* (18) additional information on intubated patients were found in an abstract (27) from the same study. They found a higher incidence of atelectasis in the high FiO_2 group, but the total number of patients was not reported.

ARDS

Panwar et al (14) showed an increase of new-onset ARDS in the low FiO_2 group, RR: 0.87 (0.43-1.75), but this was not statistically significant. The study by *Lång et al* (24) found three patients with ARDS in the low FiO_2 group, while no patients with ARDS were identified in the group receiving high FiO_2.

Pneumonia

The study by *Staehr-Rye et al* (19) showed a significant increase in the incidence of pneumonia, RR: 2.83 [2.25-3.56] in the high FiO_2 group. Similarly, *Barrot et al* (23) showed a small, but nonsignificant, tendency to ventilator-associated pneumonias in the high FiO_2 group, RR: 1.26 [0.71-2.22]. The two other studies, *Asfar et al* (22) and *Lång et al* (24), found a nonsignificant tendency for pneumonia in the low FiO_2 group with RR: 0.94 [0.59-1.49] and RR: 0.71 [0.26-1.97], respectively. These studies are illustrated in the forest plot (figure 3), which shows a non-significant tendency that treatment with high FiO_2 was associated with higher risk of pneumonia, RR: 1.32 [0.65, 2.70].

Duration of mechanical ventilation

The two studies reporting the duration of mechanical ventilation pointed in opposite direction. *Lång et al* (24) reported slightly more time spent on mechanical ventilation in the low FiO_2 group, while *Rachmale et al* (20) reported a two-fold increase in time in the high FiO_2 group.

Risk of bias assessment

Risk of bias for randomized 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 (8,14,22). In the study by *Rothen et al* (8) it was unclear if a randomization was performed between the low FiO_2 group and the high FiO_2 group, indicating a high risk of bias.

Lång et al (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-randomized studies were assessed using the New-Castle Ottawa Scale (17). One study (20) scored six stars, two studies (18,19) scored seven stars and one study (21) scored 8 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_2. In some studies the oxygen fraction in the low FiO_2 group was higher than in the high FiO_2 group in other studies.

Regarding atelectasis, seven of the eight studies favored a conservative oxygen strategy with low FiO_2 and an FiO_2 above 0.8 seemed to be associated with higher risk of atelectasis formation.

Strengths and limitations

This study was conducted according to the PRISMA 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 nonpublished 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. 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 studies reporting this outcome. Therefore conclusions should be drawn with caution.

Half of the randomized 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 (8,15,25) used CT-scans and they all considered densities between -100 to +100 Hounsfield as atelectasis. Of these three, one (8) measured areas of atelectasis in cm^2 whereas the two others (15,25) measured if atelectases were present or not. *Ishii et al* (18) 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* (25) did not define specific criteria on when densities were judged as atelectasis or not.

Asfar et al (22) and *Suzuki et al* (21) used chest x-rays, without defining atelectasis specifically, as this was decided by the individual physician. *Lång et al* (24) used chest x-rays in the same manner, however they allowed the appliance of positive end-expiratory pressure to minimize atelectasis, which makes it hard to directly compare results with other studies. Only *Suzuki et al* (21) used more than one radiologist to perform the outcome assessment.

In *Panwar et al* (14), 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 (29). *Lång et al* (24) did not report their definition of ARDS.

Regarding pneumonia, the database study of 26841 patients performed by *Staehr-Rye et al* (19) found a significant, almost three-fold 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* (30) 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* (31). 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 *Wetterslev et al* (32), comparing low (FiO_2 0.30-0.40) vs high (FiO_2 0.60-0.90) perioperative inspiratory oxygen fractions, they found no association between perioperative FiO_2 and postoperative surgical site infection and mortality. In another Cochrane review from 2016 performed by *Cabello et al* (33), 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* (4) 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 indicate 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 anesthesia, 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 (1, 34-36). Our study contributes to the current evidence in a different way, by looking at the association between FiO_2 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 maximize benefits and minimize 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 $FiO_2 \leq 0.8$ with regards to formation of atelectasis.

Figure caption

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flow diagram of identification, screening, eligibility and inclusion process (28) on a search for studies comparing low dose oxygen supplementation with high dose oxygen supplementation with pulmonary complications as an outcome.

Figure 2: Forest plot of formation of atelectasis in studies comparing low FiO_2 with high FiO_2.

Figure 3: Forest plot of risk of pneumonia in studies comparing low FiO_2 with high FiO_2.

Ethics approval

Ethics approval was not required as this was a systematic review with no involvement of humans or animals.

Contributorship statement

The idea for the article was formed by LSR. Literature search was performed by MLL and BR. MLL wrote the article. JSB contributed with high subject knowledge and all authors gave substantial contributions to the work. Every author revised the work critically for important intellectual content. Every author made a final approval of the version to be published. Every author agree to be accountable for all aspects of the work.

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Competing interests

None declared.

Data sharing statement

This was a systematic review and researchers can contact the authors to access the material.

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Table 1: Characteristics of studies comparing low FiO_2 with high FiO_2, with lung complications as an outcome. Lung complications were atelectasis, ARDS, pneumonia and duration of mechanical ventilation.

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	Randomized controlled trial	30	0.3	0.8	Atelectasis
Asfar et al (2017) (22)	France	Septic shock	Randomized controlled trial	434	SpO2 between 88 and 95%	1.0	Mortality day-28
Barrot et al (2020) (23)	France	Critical care	Randomized controlled trial	205	SpO_2 between 88 and 92%	$SpO_2 \geq$ 96%	Mortality day-28
Benoît et al (2002) (26)	Switzerland	Elective surgery	Randomized 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	Randomized controlled trial	65	0.4	0.7	Levels of ROS, IL-6 and NSE
Panwar et al (2015) (14)	Australia, NZ & France	Critical care	Randomized 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, obser-vational study	210	Mean = 0.4	Mean = 0.6	Duration of exposure to excessive FiO_2 during the first 48 h of mechanical ventilation
Rothen et al (1995) (8)	Sweden	Elective surgery	Randomized controlled trial	24	0.3	1.0	Atelectasis
Staehr et al (2012) (25)	Denmark	Laparo-tomy for ovarian cancer	Randomized 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

Abbreviations: AUC: area under the curve

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 (15)	9 (64%)	15 (94%)	1.46 (0.97-2.2)
Asfar et al (22)	13 (6%)	26 (12%)	2.0 (1.06-3.79)
Benoit et al (26)	2.5% of total surface	7% of total surface	-
Ishii et al (18)	64% of patients	76.8% of patients	-
Lång et al (24)	14 (52%)	18 (47%)	0.914 (0.56-1.5)
Rothen et al (8)	0.25 cm^2 ± 0.4	4.2 cm^2 ± 5.6	-
Staehr et al (25)	2 (13.3%)	5 (25%)	1.88 (0.42-8.37)
Suzuki et al (21)	TWA AS = 1.5 (0.7-2)	TWA AS = 2 (1.2-2.2)	-
ARDS			
Lång et al (24)	3 (11%)	0 (0%)	-
Panwar et al (14)	11 (32%)	11 (28%)	0.87 (0.43-1.75)
Pneumonia			
Asfar et al (22)	32 (15%)	30 (14%)	0.94 (0.59-1.49)
Barrot et al (23)	17 (17.2%)	22 (21.6%)	1.26 (0.71-2.22)
Lång et al (24)	6 (22.2%)	6 (15.8%)	0.71 (0.26-1.97)
Staehr-Rye et al (19)	104 (0.7%)	227 (1.9%)	2.83 (2.25-3.56)
Duration of mechanical ventilation			
Lång et al (24)	6.3 days (4.7-10)	5 days (2.5-7.5)	-
Rachmale et al (20)	2.8 days (1-6)	6 days (3-10.5)	-

Continuous data is presented as mean (SD) or median (IQR). Relative risk (RR) is presented with high dose oxygen in the numerator.
Abbreviations: RR: relative risk, CI: confidence interval, TWA AS: time weighted average atelectasis, SD: standard deviation, IQR: interquartile range

Table 3: Risk of bias assessment for randomized controlled trials comparing low dose oxygen supplementation with high dose oxygen supplementation. 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).

	Akca et al	Asfar et al	Barrot et al	Benoit et al	Lång et al	Panwar et al	Rothen et al	Staehr et al
Random sequence generation								
Allocation concealment								
Blinding of participants and personal								
Blinding of outcome assessment								
Incomplete outcome data								
Selective reporting								
Other bias								

Green = low risk of bias, yellow = unclear risk of bias, red = high risk of bias

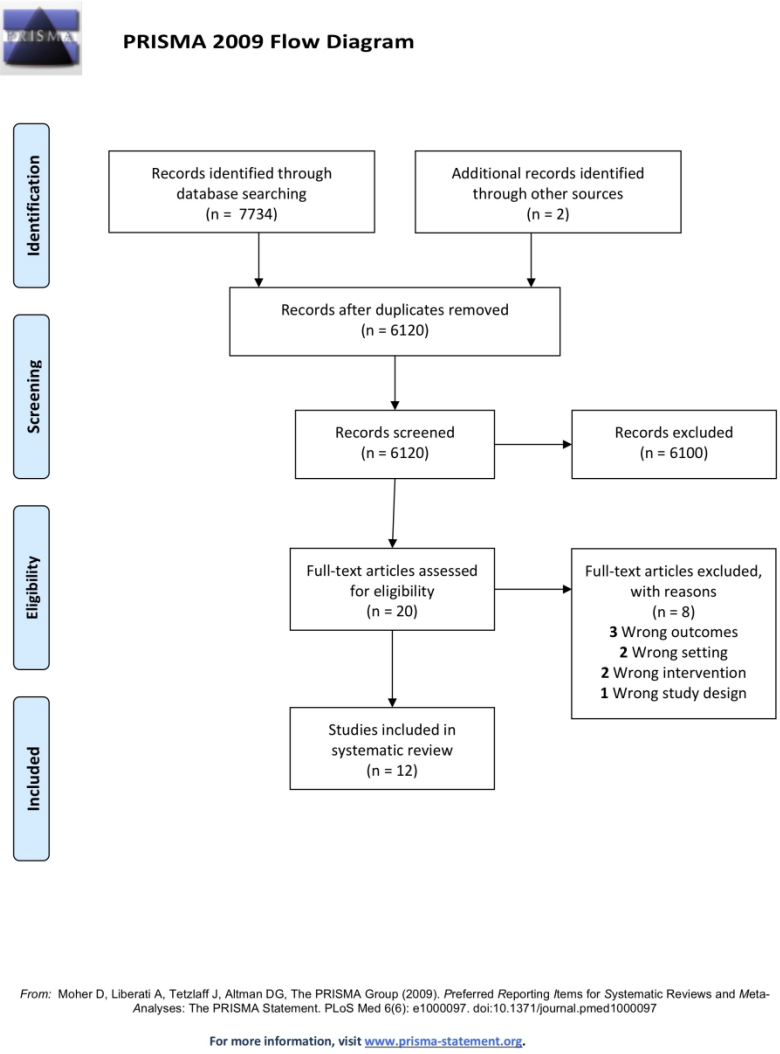

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flow diagram of identification, screening, eligibility and inclusion process (28) on a search for studies comparing low dose oxygen supplementation with high dose oxygen supplementation with pulmonary complications as an outcome.

215x279mm (300 x 300 DPI)

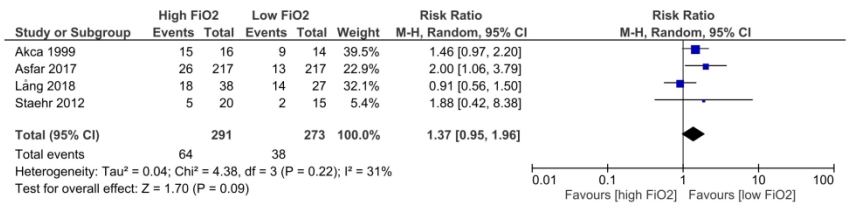

Figure 2: Forest plot of formation of atelectasis in studies comparing low FiO2 with high FiO2.

209x278mm (300 x 300 DPI)

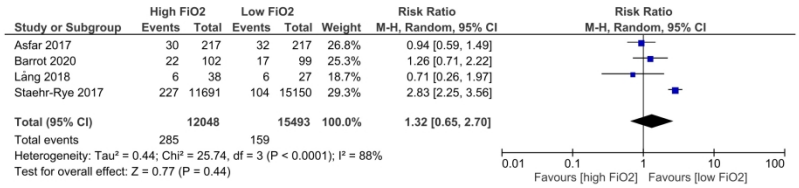

Figure 3: Forest plot of risk of pneumonia in studies comparing low FiO2 with high FiO2.

209x297mm (300 x 300 DPI)

PRISMA 2009 Checklist (Adapted for KIN 4400)

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a literature review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings;	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known about your topic.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Eligibility criteria	5	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	6	Describe all information sources (e.g., databases with dates of coverage) in the search and date last searched.	5
Search	7	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	8	State the process for selecting studies (i.e., screening, eligibility).	6
Risk of bias in individual studies	9	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level).	6
Risk of bias across studies	10	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
RESULTS			
Study selection	11	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	12	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8

PRISMA 2009 Checklist (Adapted for KIN 4400)

Section/topic	#	Checklist item	Reported on page #
Synthesis of results of individual studies	13	For all outcomes considered (benefits or harms), present, for each study: (a) summary of results and (b) relationship to other studies under review (e.g. agreements or disagreements in methods, sampling, data collection or findings).	8
DISCUSSION			
Summary of evidence	14	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	15	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10
CONCLUSION			
Conclusions	16	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13

Adapted from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA statement. *PLoS Medicine*, 6(6), e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

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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 (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 nonsignificant increased risk of atelectasis if an oxygen fraction of 0.8 or above was used, Relative Risk (RR):1.37 [0.95, 1.96]. One study showed an almost three-fold higher risk of pneumonia in the high oxygen fraction group (RR 2.83 [2.25-3.56]). 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 regards to formation of atelectases.

PROSPERO registration number CRD42020154242

Strengths and limitations of this study

- The use of predefined Population, Intervention, Comparison, Outcome and Study design to asses studies for eligibility.
- The use of a wide search string in two databases.
- Two independent reviewers screening and including studies, assessing risk of bias and extracting data.
- There is a risk of publication bias that arises due to the possibility of missing unpublished studies.
- It is possible that our search did not identify all relevant studies.

Introduction

Oxygen is a molecule vital for life, as it is the cornerstone in cellular respiration in all aerobic organisms. In trauma care, during anesthesia and in the management of respiratory failure, an oxygen fraction 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 mortality (3–6) 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 inspired oxygen fraction FiO_2 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) and was registered in PROSPERO, the international prospective register of systematic reviews (13) (CRD42020154242).

Eligibility criteria

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

Inclusion criteria:

- **P**opulation: intubated patients ≥ 18 years

- **I**ntervention and **C**omparison: low inspiratory oxygen fraction (FiO_2) (as defined by author) vs high FiO_2 (as defined by authors)
- **O**utcome: atelectasis, pneumonia, ARDS and duration of mechanical ventilation (as defined by authors)
- **S**tudy 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 6th of August 2019. The search was updated the 6th of July 2020. Modifications were made to fit Embase.

We identified one additional record (14) by obtaining the full-text article of an abstract identified through the search string. Another record (15) was identified by screening the reference list of an article.

Selection process

Two independent reviewers (MLL, BR) screened all titles and abstracts yielded by the search against the inclusion criteria using Covidence (an online program 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, 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-randomized 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, categorized into three domains: selection of the study group, comparability of cohorts, and evaluation of the outcome of interest.

For randomized 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 was calculated where possible and a forest plot was used to illustrate the results. Relative risks with 95% confidence intervals, 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 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 (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 summarized in table 1. Eight of the 12 included studies were randomized controlled trials. Among the four remaining there were two retrospective observational studies (18,19) 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 study (22) included patients with septic shock, four studies (14,18,21,23) recruited surgical, medical and trauma patients that were mechanically ventilated in the intensive care unit, one study (20) included patients with acute lung injury and the last study (24) recruited patients with traumatic brain injury. The remaining five studies included patients undergoing different types of elective surgery.
The administered FiO_2 varied substantially among the studies, with oxygen fraction ranging from 0.26 to 0.60 in the low FiO_2 group and from 0.36 to 1.0 in the high FiO_2 group.

Table 2 presents the outcomes of interest reported in the included studies. Eight studies reported on the 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 FiO_2 group, as two studies (22,25) showed almost two-fold higher risk of atelectasis in the high FiO_2, with RR: 1.875 [0.42-8.37] and RR: 2.0 [1.06-3.79], respectively. One study (15) suggested a minor benefit of treatment with low FiO_2, but this was not statistically significant, RR: 1.46 [0.97-2.20]. Another study (24) found RR: 0.91 [0.56-1.50] suggesting a benefit of treatment with high FiO_2, but this was not statistically significant. These studies are illustrated in the forest plot (figure 2), which shows that in general treatment with high FiO_2 was associated with higher risk of atelectasis formation, RR:1.37 [0.95, 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 al* (8) found a 16.8 times greater area of atelectasis in the high FiO_2 group and similarly, the study by *Benoit et al* (26) found a three-fold larger atelectatic surface in the high FiO_2 group. *Suzuki et al* (21) estimated atelectasis as time weighted averages, and also found a beneficial effect of a low FiO_2. In the study by *Ishii et al* (18) additional information on intubated patients were found in an abstract (27) from the same study. They found a higher incidence of atelectasis in the high FiO_2 group, but the total number of patients was not reported.

ARDS

Panwar et al (14) showed an increase of new-onset ARDS in the low FiO_2 group, RR: 0.87 (0.43-1.75), but this was not statistically significant. The study by *Lång et al* (24) found three patients with ARDS in the low FiO_2 group, while no patients with ARDS were identified in the group receiving high FiO_2.

Pneumonia

The study by *Staehr-Rye et al* (19) showed a significant increase in the incidence of pneumonia, RR: 2.83 [2.25-3.56] in the high FiO_2 group. Similarly, *Barrot et al* (23) showed a small, but nonsignificant, tendency to ventilator-associated pneumonias in the high FiO_2 group, RR: 1.26 [0.71-2.22]. The two other studies, *Asfar et al* (22) and *Lång et al* (24), found a nonsignificant tendency for pneumonia in the low FiO_2 group with RR: 0.94 [0.59-1.49] and RR: 0.71 [0.26-1.97], respectively. These studies are illustrated in the forest plot (figure 3), which shows a non-significant tendency that treatment with high FiO_2 was associated with higher risk of pneumonia, RR: 1.32 [0.65, 2.70].

Duration of mechanical ventilation

The two studies reporting the duration of mechanical ventilation pointed in opposite direction. *Lång et al* (24) reported slightly more time spent on mechanical ventilation in the low FiO_2 group, while *Rachmale et al* (20) reported a two-fold increase in time in the high FiO_2 group.

Risk of bias assessment

Risk of bias for randomized 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 (8,14,22). In the study by *Rothen et al* (8) it was unclear if a randomization was performed between the low FiO_2 group and the high FiO_2 group, indicating a high risk of bias.

Lång et al (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-randomized studies were assessed using the New-Castle Ottawa Scale (17). One study (20) scored six stars, two studies (18,19) scored seven stars and one study (21) scored 8 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_2. In some studies the oxygen fraction in the low FiO_2 group was higher than in the high FiO_2 group in other studies.

Regarding atelectasis, seven of the eight studies favored a conservative oxygen strategy with low FiO_2 and an FiO_2 above 0.8 seemed to be associated with higher risk of atelectasis formation. Looking at figure 2, there is a relative risk of 1.37, which suggests a clinically relevant difference with less atelectasis with a lower oxygen fraction. However, the confidence interval 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 PRISMA 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 nonpublished 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 studies reporting this outcome. Therefore conclusions should be drawn with caution.
Half of the randomized 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 (8,15,25) used CT-scans and they all considered densities between -100 to +100 Hounsfield as atelectasis. Of these three, one (8) measured areas of atelectasis in cm^2 whereas the two others (15,25) measured if atelectases were present or not. *Ishii et al* (18) 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* (25) did not define specific criteria on when densities were judged as atelectasis or not.
Asfar et al (22) and *Suzuki et al* (21) used chest x-rays, without defining atelectasis specifically, as this was decided by the individual physician. *Lång et al* (24) used chest x-rays in the same manner, however they allowed the appliance of positive end-expiratory pressure to minimize atelectasis, which makes it hard to directly compare results with other studies. Only *Suzuki et al* (21) used more than one radiologist to perform the outcome assessment.

In *Panwar et al* (14), 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 (29). *Lång et al* (24) did not report their definition of ARDS.

Regarding pneumonia, the database study of 26841 patients performed by *Staehr-Rye et al* (19) found a significant, almost three-fold 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* (30) 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* (31). 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 *Wetterslev et al* (32), comparing low (FiO_2 0.30-0.40) vs high (FiO_2 0.60-0.90) perioperative inspiratory oxygen fractions, they found no association between perioperative FiO_2 and postoperative surgical site infection and mortality. In another Cochrane review from 2016 performed by *Cabello et al* (33), 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* (4) 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 indicate 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 anesthesia, 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 (1, 34-36). Our study contributes to the current evidence in a different way, by looking at the association between FiO_2 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 maximize benefits and minimize 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 $FiO_2 \leq 0.8$ with regards to formation of atelectasis.

Figure caption

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flow diagram of identification, screening, eligibility and inclusion process (28) on a search for studies comparing low dose oxygen supplementation with high dose oxygen supplementation with pulmonary complications as an outcome.

Figure 2: Forest plot of formation of atelectasis in studies comparing low FiO_2 with high FiO_2. Abbreviations: M.H. Random: Maentel-Haentzel Random effects model.

Figure 3: Forest plot of risk of pneumonia in studies comparing low FiO_2 with high FiO_2. Abbreviations: M.H. Random: Maentel-Haentzel Random effects model.

Ethics approval

Ethics approval was not required as this was a systematic review with no involvement of humans or animals.

Contributorship statement

The idea for the article was formed by LSR. Literature search was performed by MLL and BR. MLL wrote the article. JSB contributed with high subject knowledge and all authors gave substantial contributions to the work. Every author revised the work critically for important intellectual content. Every author made a final approval of the version to be published. Every author agree to be accountable for all aspects of the work.

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Competing interests

None declared.

Data sharing statement

This was a systematic review and researchers can contact the authors to access the material.

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Table 1: Characteristics of studies comparing low FiO_2 with high FiO_2, with lung complications as an outcome. Lung complications were atelectasis, ARDS, pneumonia and duration of mechanical ventilation.

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	Randomized controlled trial	30	0.3	0.8	Atelectasis
Asfar et al (2017) (22)	France	Septic shock	Randomized controlled trial	434	SpO2 between 88 and 95%	1.0	Mortality day-28
Barrot et al (2020) (23)	France	Critical care	Randomized controlled trial	205	SpO_2 between 88 and 92%	$SpO_2 \geq$ 96%	Mortality day-28
Benoît et al (2002) (26)	Switzerland	Elective surgery	Randomized 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	Randomized controlled trial	65	0.4	0.7	Levels of ROS, IL-6 and NSE
Panwar et al (2015) (14)	Australia, NZ & France	Critical care	Randomized 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, obser-vational study	210	Mean = 0.4	Mean = 0.6	Duration of exposure to excessive FiO_2 during the first 48 h of mechanical ventilation
Rothen et al (1995) (8)	Sweden	Elective surgery	Randomized controlled trial	24	0.3	1.0	Atelectasis
Staehr et al (2012) (25)	Denmark	Laparo-tomy for ovarian cancer	Randomized 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

Abbreviations: AUC: area under the curve

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 (15)	9 (64%)	15 (94%)	1.46 (0.97-2.2)
Asfar et al (22)	13 (6%)	26 (12%)	2.0 (1.06-3.79)
Benoit et al (26)	2.5% of total surface	7% of total surface	-
Ishii et al (18)	64% of patients	76.8% of patients	-
Lång et al (24)	14 (52%)	18 (47%)	0.914 (0.56-1.5)
Rothen et al (8)	0.25 cm^2 ± 0.4	4.2 cm^2 ± 5.6	-
Staehr et al (25)	2 (13.3%)	5 (25%)	1.88 (0.42-8.37)
Suzuki et al (21)	TWA AS = 1.5 (0.7-2)	TWA AS = 2 (1.2-2.2)	-
ARDS			
Lång et al (24)	3 (11%)	0 (0%)	-
Panwar et al (14)	11 (32%)	11 (28%)	0.87 (0.43-1.75)
Pneumonia			
Asfar et al (22)	32 (15%)	30 (14%)	0.94 (0.59-1.49)
Barrot et al (23)	17 (17.2%)	22 (21.6%)	1.26 (0.71-2.22)
Lång et al (24)	6 (22.2%)	6 (15.8%)	0.71 (0.26-1.97)
Staehr-Rye et al (19)	104 (0.7%)	227 (1.9%)	2.83 (2.25-3.56)
Duration of mechanical ventilation			
Lång et al (24)	6.3 days (4.7-10)	5 days (2.5-7.5)	-
Rachmale et al (20)	2.8 days (1-6)	6 days (3-10.5)	-

Continuous data is presented as mean (SD) or median (IQR). Relative risk (RR) is presented with high dose oxygen in the numerator.
Abbreviations: RR: relative risk, CI: confidence interval, TWA AS: time weighted average atelectasis, SD: standard deviation, IQR: interquartile range

Table 3: Risk of bias assessment for randomized controlled trials comparing low dose oxygen supplementation with high dose oxygen supplementation. 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).

	Akca et al	Asfar et al	Barrot et al	Benoit et al	Lång et al	Panwar et al	Rothen et al	Staehr et al
Random sequence generation								
Allocation concealment								
Blinding of participants and personal								
Blinding of outcome assessment								
Incomplete outcome data								
Selective reporting								
Other bias								

Green = low risk of bias, yellow = unclear risk of bias, red = high risk of bias

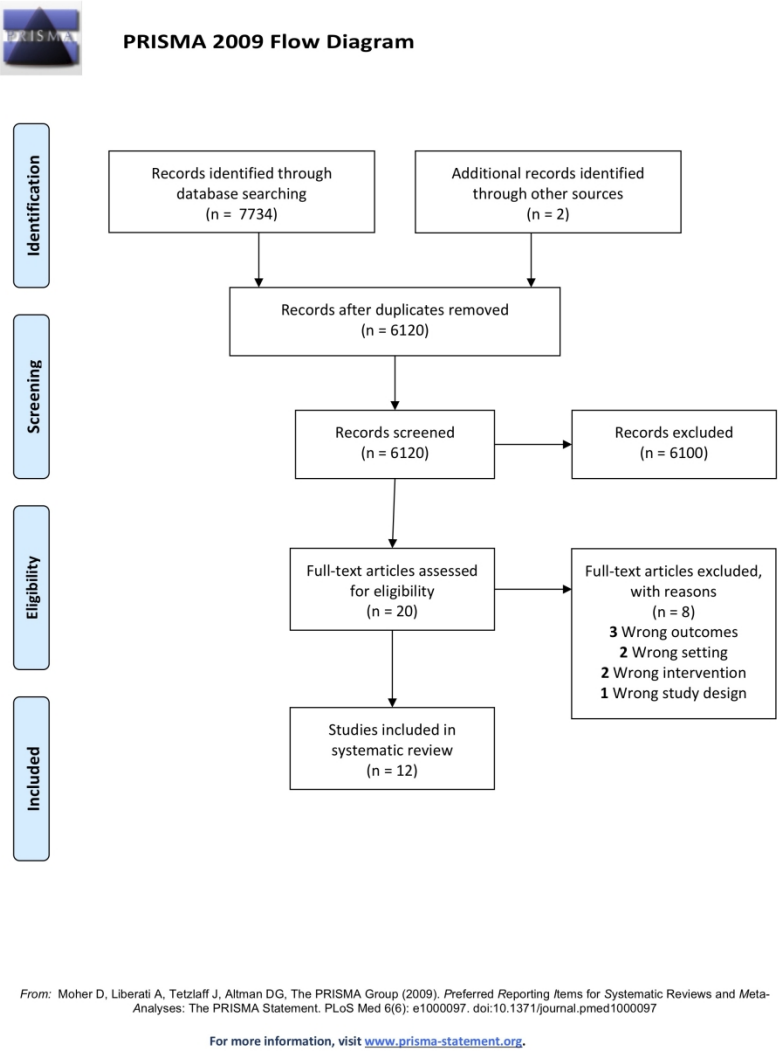

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flow diagram of identification, screening, eligibility and inclusion process (28) on a search for studies comparing low dose oxygen supplementation with high dose oxygen supplementation with pulmonary complications as an outcome.

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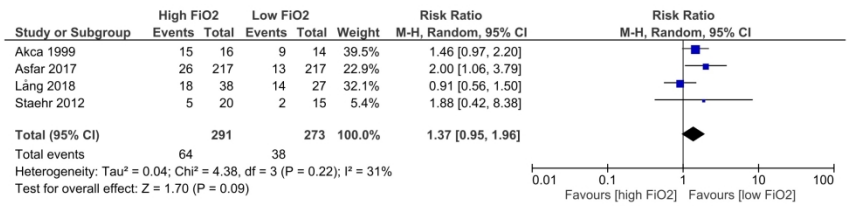

Figure 2: Forest plot of formation of atelectasis in studies comparing low FiO2 with high FiO2. Abbreviations: M.H. Random: Maentel-Haentzel Random effects model.

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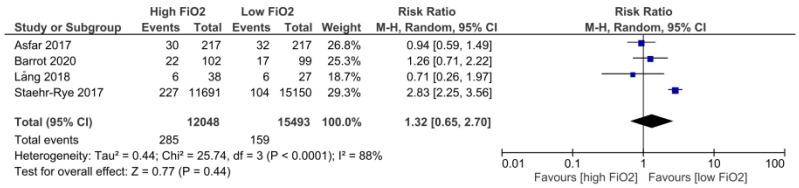

Figure 3: Forest plot of risk of pneumonia in studies comparing low FiO2 with high FiO2. Abbreviations: M.H. Random: Maentel-Haentzel Random effects model.

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PRISMA 2009 Checklist (Adapted for KIN 4400)

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a literature review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings;	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known about your topic.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Eligibility criteria	5	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	6	Describe all information sources (e.g., databases with dates of coverage) in the search and date last searched.	5
Search	7	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	8	State the process for selecting studies (i.e., screening, eligibility).	6
Risk of bias in individual studies	9	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level).	6
Risk of bias across studies	10	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
RESULTS			
Study selection	11	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	12	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8

PRISMA 2009 Checklist (Adapted for KIN 4400)

Section/topic	#	Checklist item	Reported on page #
Synthesis of results of individual studies	13	For all outcomes considered (benefits or harms), present, for each study: (a) summary of results and (b) relationship to other studies under review (e.g. agreements or disagreements in methods, sampling, data collection or findings).	8
DISCUSSION			
Summary of evidence	14	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	15	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10
CONCLUSION			
Conclusions	16	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13

Adapted from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA statement. *PLoS Medicine*, 6(6), e1000097. doi:10.1371/journal.pmed1000097

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