Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis

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Summary

Background Supplemental oxygen is often administered liberally to acutely ill adults, but the credibility of the evidence for this practice is unclear. We systematically reviewed the efficacy and safety of liberal versus conservative oxygen therapy in acutely ill adults.

Methods In the Improving Oxygen Therapy in Acute-illness (IOTA) systematic review and meta-analysis, we searched the Cochrane Central Register of Controlled Trials, MEDLINE, Embase, HealthSTAR, LILACS, PapersFirst, and the WHO International Clinical Trials Registry from inception to Oct 25, 2017, for randomised controlled trials comparing liberal and conservative oxygen therapy in acutely ill adults (aged ≥18 years). Studies limited to patients with chronic respiratory diseases or psychiatric disease, patients on extracorporeal life support, or patients treated with hyperbaric oxygen therapy or elective surgery were excluded. We screened studies and extracted summary estimates independently and in duplicate. We also extracted individual patient-level data from survival curves. The main outcomes were mortality (in-hospital, at 30 days, and at longest follow-up) and morbidity (disability at longest follow-up, risk of hospital-acquired pneumonia, any hospital-acquired infection, and length of hospital stay) assessed by random-effects meta-analyses. We assessed quality of evidence using the grading of recommendations assessment, development, and evaluation approach. This study is registered with PROSPERO, number CRD42017065697.

Findings 25 randomised controlled trials enrolled 16 037 patients with sepsis, critical illness, stroke, trauma, myocardial infarction, or cardiac arrest, and patients who had emergency surgery. Compared with a conservative oxygen strategy, a liberal oxygen strategy (median baseline saturation of peripheral oxygen [SpO_2] across trials, 96% [range 94–99%, IQR 96–98]) increased mortality in-hospital (relative risk [RR] 1·21, 95% CI 1·03–1·43, I^2=0%, high quality), at 30 days (RR 1·14, 95% CI 1·01–1·29, I^2=0%, high quality), and at longest follow-up (RR 1·10, 95% CI 1·00–1·20, I^2=0%, high quality). Morbidity outcomes were similar between groups. Findings were robust to trial sequential, subgroup, and sensitivity analyses.

Interpretation In acutely ill adults, high-quality evidence shows that liberal oxygen therapy increases mortality without improving other patient-important outcomes. Supplemental oxygen might become unfavourable above an SpO_2 range of 94–96%. These results support the conservative administration of oxygen therapy.

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See **Comment** page 1640

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Introduction

Oxygen was first described as a treatment in acute care in 1885.[1] In contemporary clinical practice, supplemental oxygen is frequently administered to acutely ill patients—approximately 34% of patients in ambulances, 25% of individuals in emergency rooms,[2] and 15% of patients admitted to hospital[3] in the UK. In these settings, 50–84% of patients are exposed to excess oxygen and hyperoxaemia as a result of efforts to prevent or reverse hypoxaemia.[4–6] Furthermore, many health-care providers consider supplemental oxygen a harmless and potentially beneficial therapy, irrespective of the presence or absence of hypoxaemia.[3,7,8]

Although adequate oxygen delivery is essential to treat hypoxaemia,[9] concerns are increasing about the potential deleterious effects of excessive oxygen supplementation, such as absorption atelectasis, acute lung injury, inflammatory cytokine production, central nervous system toxicity, reduced cardiac output, and cerebral and coronary vasoconstriction.[3,10]

Guidelines[3,11–17] on the use of supplemental oxygen for various acute illnesses in adults are contradictory and inconsistent, and no high-quality evidence base exists. Moreover, although a number of randomised controlled trials comparing liberal versus conservative oxygen for various acute conditions have been done, the trial data have not been synthesised. Two previous systematic reviews[18,19] are illustrative: both focused solely on patients with critical illness, but did not identify any relevant randomised controlled trials, and their meta-analyses of

Research in context

Evidence before this study

Supplemental oxygen is administered to millions of acutely unwell patients around the world every day. Although oxygen can save the lives of patients with severe hypoxaemia, mechanistic and observational studies suggest that excessive oxygen exposure is common in current clinical practice and could have adverse consequences.

We searched MEDLINE, Embase, CENTRAL and the WHO International Clinical Trials Registry, without language restrictions, from inception to Oct 25, 2017, for randomised controlled trials comparing liberal versus conservative oxygen therapy in acutely ill adults. We excluded studies limited to patients with chronic respiratory diseases or psychiatric disease, patients on extracorporeal life support, and patients treated with hyperbaric oxygen therapy. Specifically, previous meta-analyses of observational studies in critically ill patients suggested an association between hyperoxia and increased in-hospital mortality after cardiac arrest, traumatic brain injury, and stroke, but were limited by inconsistency, risk of bias, and the absence of randomised controlled trials. Meta-analyses of randomised controlled trials comparing liberal versus conservative oxygen therapy in the acute myocardial infarction (four trials) and perioperative settings (eight trials) yielded low-quality overall estimates for mortality because of inconsistency and imprecision. We also identified one systematic review of randomised controlled trials assessing normobaric oxygen therapy for stroke, but this study is at the protocol stage. No studies have systematically reviewed all the available randomised controlled trials for these various conditions.

Added value of this study

This systematic review and meta-analysis of more than 16 000 patients across a broad range of acute illnesses is the first study to provide high-quality evidence that excessive supplemental oxygen can be life-threatening. To the best of our knowledge, this is the most comprehensive systematic review on this topic to date. We found high-quality evidence that liberal oxygen therapy increased the relative risk of in-hospital mortality and mortality at 30 days and at longest follow-up, without any significant improvement in other patient-important outcomes, such as disability, risk of hospital-acquired pneumonia, risk of hospital-acquired infections, or length of hospital stay. These findings are distinct from the widespread view that liberal oxygen therapy for acute illnesses is harmless.

Implications of all the available evidence

Our findings have several potential implications for health-care providers, policy makers, and researchers. In view of the paucity of robust evidence and comprehensive knowledge syntheses, practice guidelines and medical directives on oxygen therapy for acute illnesses have been inconsistent. Our results provide much needed clarification, reporting high-quality evidence that a liberal oxygen strategy increases mortality among a broad range of acute illnesses. Moreover, the dose-response relationship between oxygen saturation and mortality risk highlights the need to implement upper limits of acceptable oxygen saturation for safe oxygen supplementation in patients under the care of emergency personnel, nurses, allied health, and clinicians. Future research is required to identify the precise oxygen strategies that maximise benefit and minimise harm. In view of the global burden of disease and the routine use of oxygen worldwide, the findings of this meta-analysis have immediate and important implications.

observational data were limited by considerable heterogeneity and risk of bias. Thus, the primary objective of our study was to systematically review randomised controlled trials investigating the efficacy and safety of liberal versus conservative oxygen therapy in acutely ill adults.

Methods

Search strategy and selection criteria

For this systematic review and meta-analysis, we searched the Cochrane Central Register of Controlled Trials, MEDLINE, Embase, HealthSTAR, LILACS, PapersFirst, and the WHO International Clinical Trials Registry, from inception to Oct 25, 2017, without language restrictions, for randomised controlled trials that compared the use of liberal and conservation oxygen therapies in acutely ill adults. Full search terms and search strategy are provided in the appendix. Database searches were supplemented by screening the reference lists of relevant studies and reviews. We also contacted authors for unpublished data, and in all instances of missing or unclear data. We also translated non-English records.

See Online for appendix

Studies were included if they were randomised controlled trials comparing liberal and conservative oxygenation strategies in acutely ill adults (aged ≥18 years), and reported an outcome of interest. Patients were defined as acutely ill if they had any condition requiring non-elective hospital admission and the potential to be exposed to supplemental oxygen. We defined critical illness as admission to an intensive care unit. The treatment arm with the higher oxygen target, measured by any one of the following: fraction of inspired oxygen (FiO_2), arterial partial pressure of oxygen (PaO_2), arterial oxygen saturation (measured by blood analysis), or peripheral oxygen saturation (measured by a pulse oximeter [SpO_2]) was defined as the liberal arm, and the arm with the lower oxygen target (including room air) was defined as the conservative arm.

We excluded studies including patients younger than 18 years and patients who were pregnant, and studies limited to patients with chronic respiratory diseases, psychiatric disease, patients on extracorporeal life support, and patients treated with hyperbaric oxygen therapy or elective surgery. Observational and preclinical studies, and studies solely comparing different oxygen delivery modalities (eg, nasal prongs *vs* facemask), were also excluded.

Two reviewers (DKC and LH-YK), independently and in duplicate, screened titles and abstracts using a pre-piloted standardised data form (Covidence; Veritas Health Innovation, Melbourne, VIC, Australia). Disagreements about inclusion were resolved through consensus.

This study is reported in accordance with the Cochrane Handbook for Systematic Reviews of Interventions,[20] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[21] The study protocol is available online.

Data analysis

Two reviewers (DKC and LH-YK) extracted data independently and in duplicate using a pre-piloted standardised data-form through Covidence (Veritas Health Innovation, Melbourne, VIC, Australia). We considered publications reporting on the same trial at different follow-up timepoints as a single trial for all analyses. We used DigitizeIt software (Braunschweig, Germany) to extract patient-level mortality data from survival curves.

Outcomes of interest[20] were mortality (in-hospital, at 30 days, and at the longest follow-up), and morbidity (disability measured by the modified Rankin Scale at longest follow-up, risk of hospital-acquired pneumonia, risk of any hospital-acquired infection, and hospital length of stay).

Analyses for all outcomes were done on an intention-to-treat basis, and included all patients who were randomly assigned to any treatment arm.[22] Summary measures were pooled using DerSimonian and Laird random-effects models, with the estimate of heterogeneity being taken from the Mantel-Haenszel model. For dichotomous outcomes, we calculated the relative risk (RR) with 95% CI. For continuous outcomes, the mean difference with 95% CI was calculated. For ordinal outcomes, shift analysis using proportional odds models calculated odds ratio (OR) and 95% CI per trial, after validating proportionality assumptions.

We calculated absolute risks by multiplying the RR and its 95% CI with the baseline risk. We used two data sources to estimate baseline risk:[23] the pooled proportion of participants who had an event in the control arm in our meta-analysis[24] and disease-specific estimates from observational studies.[25–31] In view of the potential imprecision of calculated pooled risk estimates secondary to a wide range of included acute illnesses, disease-specific baseline risks were also used.[23]

Sensitivity analyses to test the robustness of the findings included the following: worst-case or various plausible scenarios for missing participants,[32] disregarding excluded participants or participants lost to follow-up post-randomisation,[32] reweighing trials using fixed-effect meta-analysis, excluding unpublished trials, excluding trials with early termination for apparent benefit or harm, adjusting for trials terminated early by reducing their effect size,[33,34] and using the more conservative Knapp-Hartung-Sidik-Jonkman random-effects meta-analytic method.[35] To compare meta-analysis of aggregate mortality outcome data with patient-level time-to-event data, we digitised Kaplan-Meier curves and extracted patient-level data,[36] validated proportional hazards assumptions, fitted a shared frailty Cox regression model with the study as a random-effects variable, and report hazard ratio (HR) with 95% CI.

We used a modified Cochrane Risk of Bias assessment tool[37,38] to examine eligible studies and reviewers (DKC and LH-YK) classified studies at high risk of bias if at least one domain was high risk. To evaluate the quality (certainty) of evidence for each outcome, we used the Grading of Recommendations, Assessment, Development and Evaluation approach,[23] using optimal information size as an objective measure of imprecision. Trial sequential analysis accounts for multiple testing, and evaluates the reliability of a meta-analysis by

For the **study protocol** see http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017065697

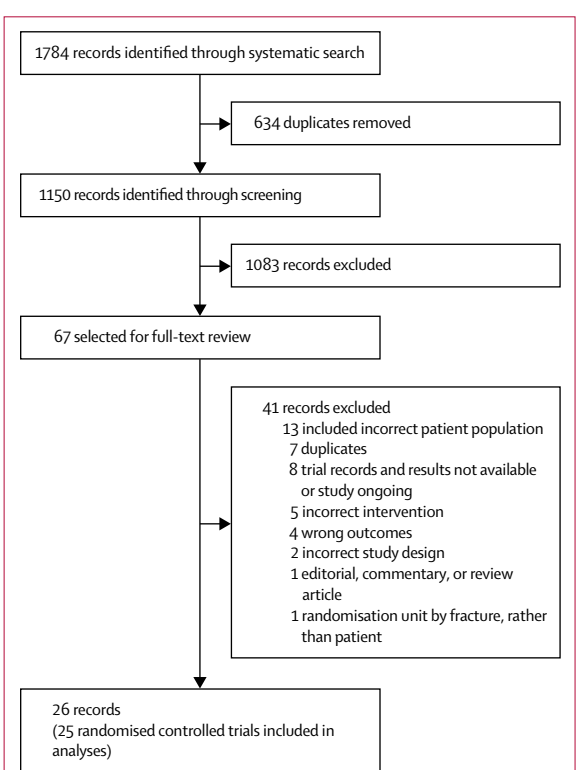


Figure 1: **Study selection**

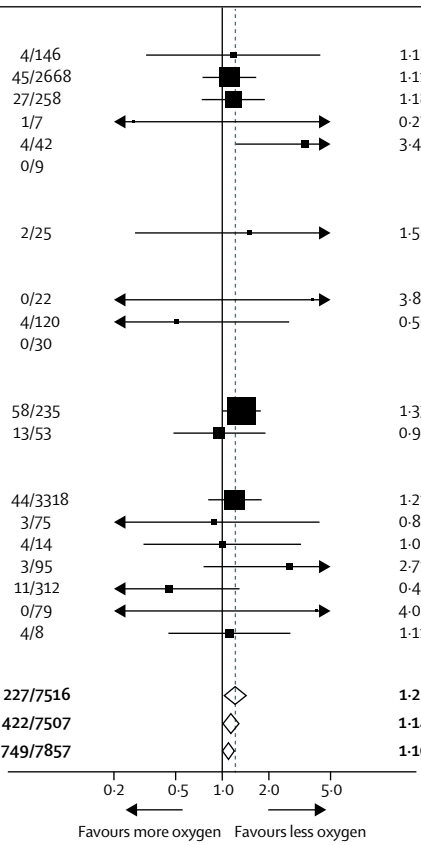
	Setting	Country	Intervention assignments				Participants					Liberal group, mean baseline SpO_2* (%)	Conservative group mean baseline SpO_2* (%)
			Liberal group FiO_2*	Conservative group FiO_2	Delivery method	Intended duration, h	Sample size, n	Mean age, years	Men, n (%)*	Women, n (%)*	Follow-up duration		
Ali et al (2014)[44,66]†‡	Stroke	UK	0·30	0·21	NP	72	301	72·3 (11·6)	141 (47%)	160 (53%)	6 months	96·1% (1·9)	96·1% (2·0)
Asfar et al (2017)[45]†‡	Septic shock	France	1·00	§	IMV	24	442	67·0¶	282 (64%)	160 (36%)	90 days	99·0% (3·0)	97·0% (3·0)
Butler et al (1987)[46]*	Limb ischaemia	UK	0·28	0·21	FM	48	39	69·0¶	24 (62%)	15 (38%)	1 year	..	..
Girardis et al (2016)[47]*†‡	Critical care	Italy	0·39	0·36	IMV	144	480	64·0¶	272 (57%)	208 (43%)	60 days	..	..
Hofmann et al (2017)[48]†	Myocardial infarction	Sweden	0·50	0·21	FM	12	6629	68·0 (11·8)‖	4606 (69%)	2023 (31%)	1 year	97·0% (2·2)‖	97·0% (2·2)‖
Khoshnood et al (2015)[49]†‡	Myocardial infarction	Sweden	0·74	0·21	FM	1	160	66·0¶	106 (66%)	54 (34%)	6 months	98·0% (1·7)	97·7% (1·6)
Kuisma et al (2006)[50]†‡	Cardiac arrest	Finland	1·00	0·33	IMV	1	32	63·1¶	26 (81%)	6 (19%)	In-hospital	..	..
NCT00414726†‡	Stroke	USA	1·00	0·21	FM	8	85	73·7 (14·0)	41 (48%)	44 (52%)	3 months	..	..
Mazdeh et al (2015)[51]†	Stroke	Iran	0·50	0·21	FM	12	52	..	28 (54%)	24 (46%)	6 months	..	..
NCT02687217	Acute appendicitis	India	0·50	0·21	FM	3	60	..	46 (77%)	14 (23%)	14 days	..	..
Padma et al (2010)[52]†	Stroke	India	0·55	0·21	FM	12	40	55·8 (13·2)	..	..	3 months	..	..
Panwar et al (2016)[53]	Critical care	Australia, New Zealand, France	0·36	0·26	IMV	90	104	62·4¶	65 (62%)	39 (38%)	90 days	96·0% (3·0)	95·0% (3·0)
NCT02378545†‡	Sepsis	UK	1·00	0·21	FM	4	50	64·2¶	20 (40%)	30 (60%)	90 days	94·8% (2·8)	94·7% (3·8)
Ranchord et al (2012)[54]†‡	Myocardial infarction	New Zealand, UK	0·50	**	FM	6	148	61·1	101 (68%)	47 (32%)	30 days	..	..
Rawles et al (1976)[55]*	Myocardial infarction	UK	0·50	0·21	FM	24	200	55·8¶	160 (80%)	40 (20%)	In-hospital	..	..
Rønning et al (1999)[56]	Stroke	Norway	0·30	0·21	NP	24	550	76·4¶	292 (53%)	258 (47%)	1 year	..	..
Schietroma et al (2016)[57]*†‡	Perforated viscus	Italy	0·80	0·30	IMV	7	239	58·1¶	105 (44%)	134 (56%)	15 days	..	..
Singhal et al (2005)[58]*	Stroke	USA	1·00	0·21	FM	8	16	68·5¶	7 (44%)	9 (56%)	3 months	..	..
Roffe et al (2017)[59]†‡	Stroke	UK	0·30	0·21	NP	72	5336	72·0 (13·0)	2932 (55%)	2404 (45%)	90 days	96·6% (1·7)	96·7% (1·7)
Stub et al (2012)[60]†‡	Myocardial infarction	Australia		0·21	FM	1	624	63·0 (13·3)¶	482 (77%)	142 (23%)	6 months	98·0% (1·5)‖	98·0% (1·5)‖
Ukholkina et al (2005)[61]†‡	Myocardial infarction	Russia	0·38	0·21	NP	3	137	54·6 ¶	115 (84%)	22 (16%)	In-hospital	94·0% (5·3)	93·4% (6·2)
Young et al (2014)[62]†‡	Cardiac arrest	New Zealand	1·00	††	IMV	72	17	66·2 (17·1)	16 (94%)	1 (6%)	8 months	95·8% (3·1)‖	‡‡
Bickel et al (2011)[63]*	Acute appendicitis	Israel	0·80	0·30	IMV	3	210	28·1¶	152 (72%)	58 (28%)	14 days	..	..
Taher et al (2016)[64]	Traumatic brain injury	Iran	0·80	0·50	IMV	6	68	42·7¶	48 (70%)	20 (30%)	6 months	..	..
Shi et al (2017)[65]†‡	Stroke	China	0·69	0·21	FM	4	18	59·8¶	13 (72%)	5 (28%)	In-hospital	..	..

Data are n (%), mean (SD), or mean percentage (SD), unless stated otherwise. FiO_2=fraction of inspired oxygen. SpO_2=arterial saturation of peripheral oxygen. NP=nasal prongs. IMV=invasive mechanical ventilation. FM=face mask. *Estimated values. †Received responses from investigators. ‡Received clarification or unpublished data included from investigators. §Titrated to SaO_2 88–95%. ¶Mean of both treatment groups groups, thus the SD for the entire study population was not available. ‖Median. **Titrated to SpO_2 93–96%. ††Titrated to SaO_2 90–94%. ‡‡Not reliably recorded.

Table: **Characteristics of included studies**

A

	Setting	Liberal (n/N)	Conservative (n/N)	RR (95% CI)	% weight
Neurological (stroke–traumatic brain injury)					
Ali et al (2014)[44,66]	Stroke	5/155	4/146	1·18 (0·32–4·30)	1·6
Roffe et al (2017)[59]	Stroke	50/2668	45/2668	1·11 (0·75–1·66)	16·6
Ronning et al (1999)[56]	Stroke	36/292	27/258	1·18 (0·74–1·89)	11·9
Singhal et al (2005)[58]	Stroke (ischaemic)	0/9	1/7	0·27 (0·01–5·70)	0·3
NCT00414726	Stroke (ischaemic)	14/43	4/42	3·42 (1·22–9·54)	2·5
Shi et al (2017)[65]	Stroke (ischaemic)	0/9	0/9	(Excluded)	0
Sepsis					
NCT02378545 (2015)	Sepsis	3/25	2/25	1·50 (0·27–8·22)	0·9
Emergency surgery					
Butler et al (1987)[46]	Limb ischaemia	1/17	0/22	3·83 (0·17–88·62)	0·3
Schietroma et al (2016)[57]	Perforated peptic ulcer	2/119	4/120	0·50 (0·09–2·70)	0·9
NCT02687217	Acute appendicitis	0/30	0/30	(Excluded)	0
Critical care (mixed medical-surgical)					
Girardis et al (2016)[47]	Critical illness	80/243	58/235	1·33 (1·00–1·78)	32·1
Panwar et al (2016)[53]	Critical illness	12/51	13/53	0·96 (0·48–1·90)	5·6
Cardiac (myocardial infarction–cardiac arrest)					
Hofmann et al (2017)[48]	Myocardial infarction	53/3311	44/3318	1·21 (0·81–1·80)	16·8
Khoshnood et al (2015)[49]	Myocardial infarction (STEMI)	3/85	3/75	0·88 (0·18–4·24)	1·1
Kuisma et al (2006)[50]	Cardiac arrest	4/14	4/14	1·00 (0·31–3·23)	1·9
Rawles et al (1976)[55]	Myocardial infarction	9/105	3/95	2·71 (0·76–9·73)	1·6
Stub et al (2012)[60]	Myocardial infarction (STEMI)	5/312	11/312	0·45 (0·16–1·29)	2·4
Ukholkina et al (2005)[61]	Myocardial infarction	1/58	0/79	4·07 (0·17–98·10)	0·6
Young et al (2014)[62]	Cardiac arrest	5/9	4/8	1·11 (0·45–2·75)	3·2
$p_{interaction}$=0·97					
In-hospital mortality, overall (I^2=0%, p=0·020)		**283/7555**	**227/7516**	**1·21 (1·03–1·43)**	**100**
30-day mortality, overall (I^2=0%, p=0·033)		**484/7546**	**422/7507**	**1·14 (1·01–1·28)**	**100**
Mortality at longest follow-up, overall (I^2=0%, p=0·044)		**828/7897**	**749/7857**	**1·10 (1·00–1·20)**	**100**



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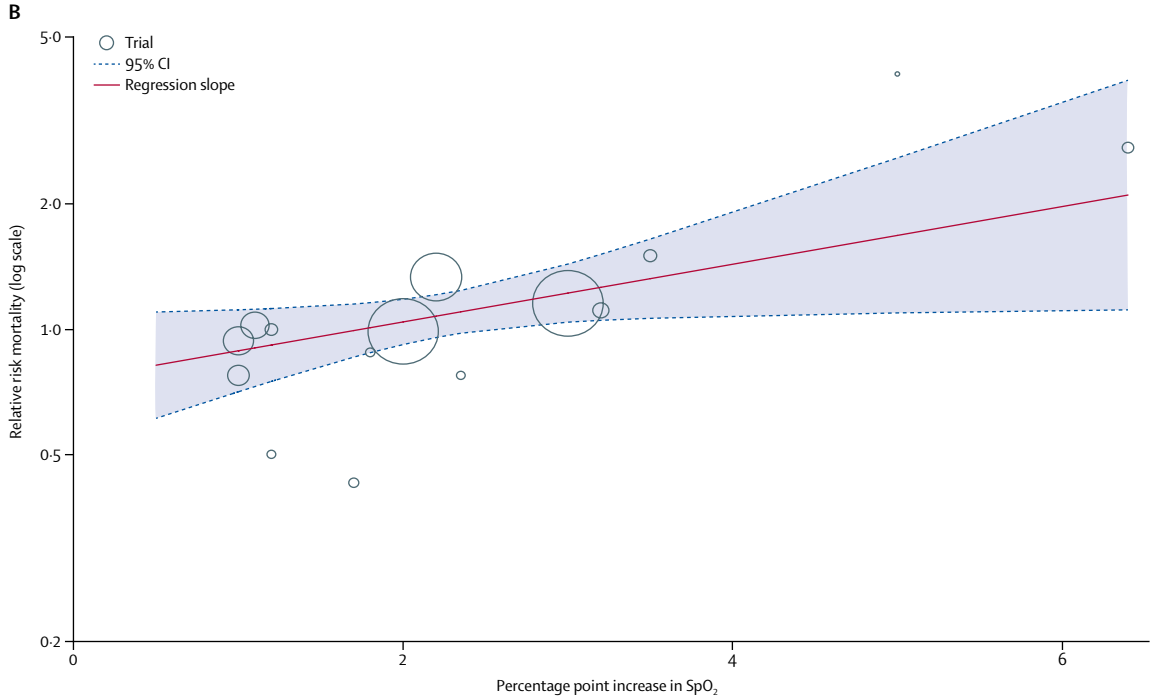

Figure 2: **Mortality outcomes with liberal versus conservative oxygen therapy**
(A) Forest plot of in-hospital mortality with superimposed summary estimates at 30 days and longest follow-up. (B) Meta-regression of effect of increasing SpO_2 on RR of in-hospital mortality. Size of data markers indicates their weight in the respective analysis. n=deaths. N=group size. RR=relative risk. STEMI=ST-elevation myocardial infarction. SpO_2=peripheral oxygen saturation.

Outcome of interest	Participants, n	Relative effect (95% CI)	Population baseline risk	Anticipated absolute effects (per 1000 individuals)			Evidence quality	Overall findings
				Conservative oxygen therapy	Liberal oxygen therapy (95% CI)	Risk difference (95% CI)		
In-hospital mortality (n=19)	15071	RR 1·21 (1·03–1·43)	Study population of included trials	51*	62 (53 to 73)	11 more (two to 22 more)	High†‡§	Liberal oxygen therapy increases mortality. This effect decreases over time after exposure. For every 1% increase in SpO_2, the relative risk of in-hospital mortality is associated with a 25% increase. For every 1% increase in SpO_2, the relative risk of mortality at longest follow-up is associated with a 17% increase. Overall, these results are consistent with a sensitivity analysis using patient-level survival (time-to-event) data: 1 year mortality HR 1·11 (95% CI 1·00–1·24). Assuming a baseline risk of the included trials, the mean number needed to harm resulting in one death using a liberal approach is approximately 71 (95% CI 37–1000).
			Stroke	69[30]	83 (71 to 99)	14 more (two to 30 more)		
			Sepsis	89[29]	108 (92 to 127)	19 more (three to 38 more)		
			Critical illness	190[31]	230 (196 to 272)	40 more (six to 82 more)		
			Emergency surgery	38[25]	46 (39 to 55)	8 more (one to 17 more)		
			Acute coronary syndrome (all)	49[28]	59 (50 to 70)	10 more (one to 21 more)		
30-day mortality (n=14)	15053	RR 1·14 (1·01–1·28)	Study population of included trials	97*	111 (98 to 124)	14 more (one to 27 more)	High†‡§¶	
			Stroke	126[30]	144 (127 to 161)	18 more (one to 35 more)		
			Sepsis	125[29]	143 (126 to 160)	18 more (one to 35 more)		
			Critical illness	164[31]	187 (166 to 210)	23 more (two to 46 more)		
			Emergency surgery	57[26]	65 (58 to 73)	8 more (one to 16 more)		
			Acute coronary syndrome (all)	67[28]	76 (68 to 86)	9 more (one to 19 more)		
Mortality at longest follow-up (n=23)	15754	RR 1·10 (1·00–1·20)	Study population of included trials	118*	130 (118 to 142)	12 more (zero to 24 more)	High†‡§	
			Stroke	236[30]	260 (236 to 283)	24 more (zero to 47 more)		
			Sepsis	230[29]	253 (230 to 276)	23 more (zero to 46 more)		
			Critical illness	217[31]	239 (217 to 260)	22 more (zero to 43 more)		
			Emergency surgery	110[27]	121 (110 to 132)	11 more (zero to 22 more)		
			Acute coronary syndrome (all)	91[28]	100 (91 to 109)	9 more (zero to 18 more)		
Probability of patients' mRS score increasing by one (n=5)	5523	OR 1·02 (0·93–1·12)	Low risk of bias estimate	NA	NA	NA	Moderate‖**††	Liberal oxygen therapy does not reduce the risk of worsening disability after acute stroke.
		OR 0·94 (0·62–1·41)	Overall estimate					
Proportion of patients with mRS score>2 (n=5)	5840	RR 1·00 (0·92–1·09)	Study population of included trials	524	524 (482 to 571)	0 fewer (42 fewer to 47 more)	High§	Liberal oxygen therapy does not reduce the risk of worsening disability after acute stroke.
Proportion of patients with mRS score >4 (n=4)	5772	RR 1·00 (0·87–1·15)	Study population of included trials	213	213 (185 to 245)	0 fewer (28 fewer to 32 more)	High§	Liberal oxygen therapy does not reduce the risk of worsening disability after acute stroke.

(Figure 3 continues on next page)

Outcome of interest	Participants, n	Relative effect (95% CI)	Population baseline risk	Anticipated absolute effects (per 1000 individuals)			Evidence quality	Overall findings
				Conservative oxygen therapy	Liberal oxygen therapy (95% CI)	Risk difference		
Hospital-acquired infections in patients admitted with medical diagnoses (n=7)	7283	RR 1·04 (0·93–1·16)	Study population of included trials, medical diagnoses	127	132 (118 to 147)	5 more (nine fewer to 20 more)	High§	Liberal oxygen therapy does not reduce the risk of hospital-acquired infection among patients with medical conditions.
Hospital-acquired infections in patients admitted for emergency surgery (n=2)	449	RR 0·50 (0·36–0·69)	Study population of included trials, surgical diagnoses	321	161 (115 to 221)	160 fewer (205 fewer to 99 fewer)	Low‡‡§§¶¶	Uncertain if liberal oxygen therapy reduces infection after urgent or emergent surgery. Future trials are likely to considerably change the estimates presented.
Hospital-acquired pneumonia (n=4)	1785	RR 1·00 (0·74–1·35)	Study population of included trials	86	86 (63 to 116)	0 fewer (22 fewer to 30 more)	Moderate††	Liberal oxygen therapy might not reduce hospital-acquired pneumonia, but trial sequential analysis suggests that this is not yet definitive.
Length of hospital stay (n=12)	2448	...	Study population of included trials	The mean length of stay in hospital was 10·5 days	...	Mean difference 0·25 days fewer (0·68 fewer to 0·18 more)	Low††||||	Whether liberal oxygen therapy reduces length of stay in hospital remains unclear. Future trials will likely considerably change the estimates presented.

Figure 3: **Summary of findings comparing liberal oxygen therapy with conservative oxygen therapy for acutely-ill adults**
Risk in the intervention group is based on the assumed risk in the comparison group and the relative effect of the intervention. Quality of evidence was assessed according to the grading of recommendations assessment, development, and evaulation approach (high quality, moderate quality, low quality, and very low quality). RR=risk ratio. SpO_2=arterial saturation of peripheral oxygen. HR=hazard ratio. mRS=modified Rankin scale. OR=odds ratio. NA=not applicable. *Meta-analysed across included studies as baseline risk. †Although the lower limit of the 95% CI was between 1 and 1·03 (ie, no effect to very small harm), we did not rate down for imprecision because the clinical decision would not change when the most likely effect and upper CI are considered. ‡Meta-regression showed a dose-response relationship between increases in oxygen saturation and mortality. The effect of liberal oxygen therapy on mortality was also time-dependent (waning in effect size after exposure). §Trial sequential analysis confirmed that the required information size was met. ¶Visual inspection of funnel plots suggested the absence of some small studies reporting increased mortality with liberal oxygen supplementation at 30 days, but this was not substantiated by Egger's test. ||We did not rate down for risk of bias. **We did not rate down for inconsistency because heterogeneity was explained by the studies at high risk of bias (ie, one study of traumatic brain injury was compared with the other four trials in stroke). ††Rated down by one level for imprecision because the 95% CI included both important benefit and harm. ‡‡Down rated for risk of bias because both trials were terminated early for apparent benefit, with very few events per trial (20 and 92 events). §§Rated down for imprecision (did not meet optimal information size). ¶¶Although the treatment effect was potentially large (RR 0·50), the limitations identified in the other domains decreased the confidence in this estimate and therefore, we did not rate up for large effect.||||Down rated for inconsistency as a result of widely variable point estimates with little to no overlap in confidence intervals, combined with high statistical heterogeneity (I^2=58%), which was not explained by subgroup analyses.

examining for sufficient data to avoid type I (false-positive) and type II (false-negative) errors. Trial sequential analysis was done using TSA software (version 0.9.5.9 Beta;[39] Copenhagen Trial Unit, Copenhagen, Denmark), Lan-DeMets implementation of the O'Brien-Fleming monitoring boundaries,[40] adjustment for heterogeneity, and an optimal information size set to a two-sided alpha of 0·05, beta 0·80, relative risk reduction of 20%, and the pooled control-group event rate across the included studies.

Prespecified subgroup analyses for the main outcomes included stratification by study population, risk of bias, oxygen delivery method, and dose and duration of oxygen exposure. Subgroup analyses of the dose and duration of oxygen exposure was by random effects univariate meta-regression using restricted maximum likelihood, with statistical significance calculated using 10 000 Monte-Carlo random permutations.[41] We also stratified on the basis of whether trials excluded patients with baseline hypoxaemia or not.

We calculated heterogeneity between studies using χ^2 (threshold p=0·10), which was quantified using the I^2 statistic. For unclarified missing data, we did case analyses, including worst, complete-case, and most plausible scenarios.[32] Because all analyses were insensitive to varied assumptions, we present primary analyses using intention to treat. Missing data were accounted for using the event rate of the control group for each study, a conservative and plausible assumption.[32] In some instances, we estimated mean values and SDs from medians and IQR,[20] in-hospital mortality from length of stay, and SpO_2 from PaO_2.[42] Publication bias was assessed visually by inspecting funnel plots and statistically by the Egger test.[43]

We did all statistical analyses using STATA (version 14.3; College Station, TX, USA) and RevMan (version 5.3; The Nordic Cochrane Centre, Copenhagen, Denmark). GRADEpro GDT (McMaster University, Hamilton, ON, Canada) was used to create the summary of findings table. Unless otherwise specified, a two-sided p value of

0·05 or less was considered to indicate a statistically significant difference.

This study is registered with PROSPERO, number CRD42017065697.

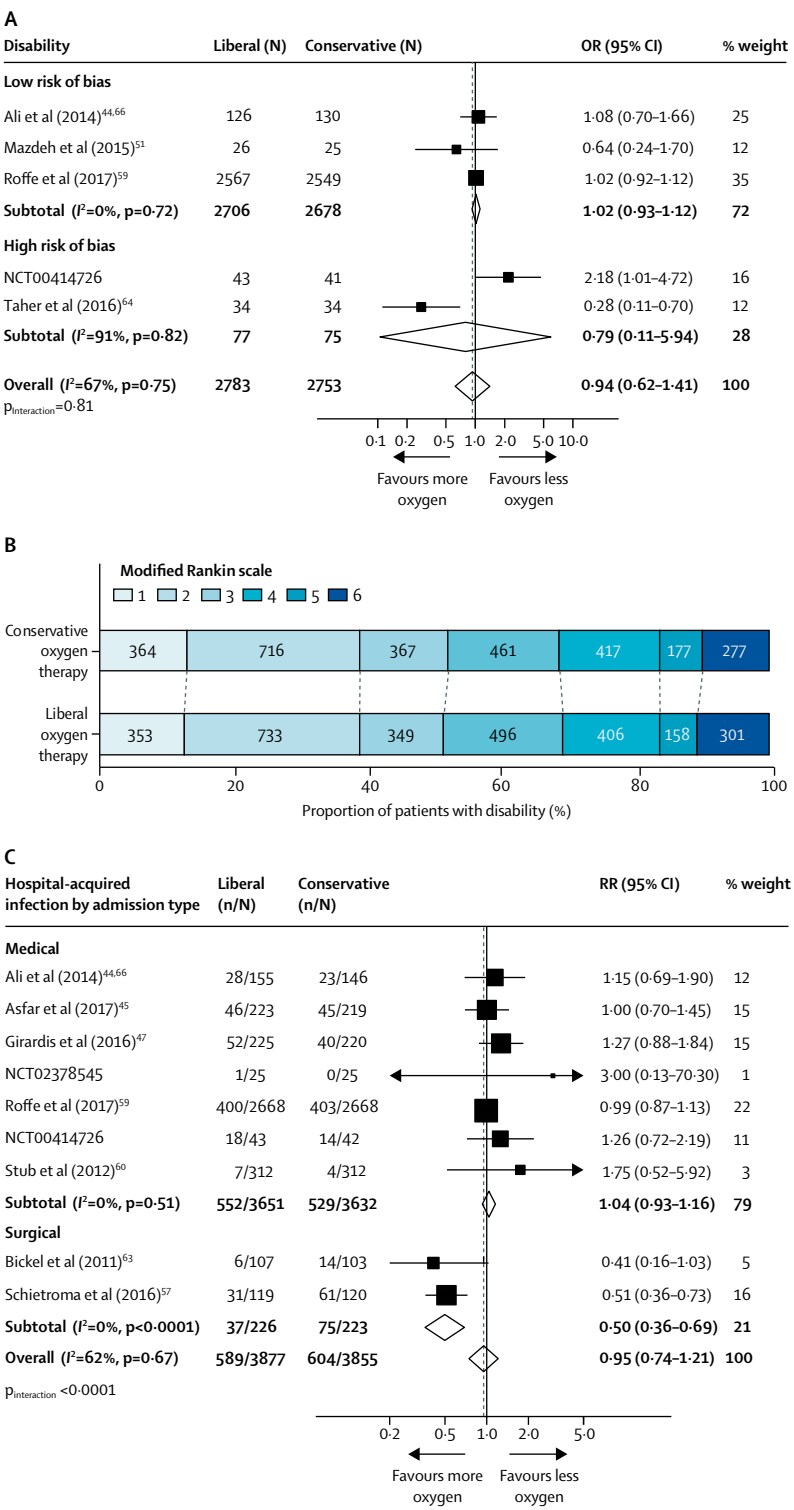

Figure 4: **Morbidity outcomes with liberal versus conservative oxygen therapy**
(A) Forest plot of disability. The data used to calculate the number of events per trial are shown in the appendix. (B) Shift analysis of the probability of patients' scores increasing by one on the modified Rankin Scale. Numbers in coloured boxes indicate number of patients in each category. (C) Forest plot of hospital-acquired infections. Size of data markers indicates weight in analysis. OR=odds ratio. n=number of events. N=group size. RR=relative risk.

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Our search strategy identified 1784 records. Once duplicates had been removed, 1150 unique records were screened, of which 67 full-texts were assessed for eligibility. This process yielded 25 randomised controlled trials, reported in 26 publications[44–66] (figure 1). 23 requests for unpublished results or data clarification (no contact information was available for two randomised controlled trials), yielded 17 responses with 14 data items reporting on 14 trials, including three unpublished trials (NCT00414726, NCT02687217, and NCT02378545). We considered two publications[44,66] reporting on the same trial at two different follow-up timepoints as a single trial for all analyses. We excluded one trial[67] because the randomisation unit was per fracture—ie, patients could be randomly assigned multiple times to different treatment groups by being randomly assigned at the time of each fracture repair—rather than per individual patient, and individual-patient data were not available upon request.

The trials included 16 037 patients (median 137 patients, range 16–6629 patients; IQR 50–301) with critical illness,[45,47,53] trauma,[64] sepsis (NCT02378545),[45] stroke (NCT00414726),[44,51,52,56,58,65] myocardial infarction,[48,49,54,55,60,61] or cardiac arrest,[50,62] and patients who had emergency surgery (NCT02687217)[46,57,63] (table). 43% of patients with critical illness and sepsis were admitted to hospital for a surgical diagnosis. 12 of 25 trials (n=13 389) excluded patients with hypoxaemia at baseline, whereas all other trials only excluded patients if baseline hypoxamia was severe (ie, ratio of PaO_2 to fraction of inspired oxygen [FiO_2] <100). Across the included trials, the median age of participants was 64 years (range 28–76 years; IQR 59–68), of whom 64% (range 40–94%; IQR 54–73) were men and 36% were women (range 6–60%; IQR 27–46). Median follow-up duration across studies was 3 months (range 14 days to 12 months; IQR 2–6 months). Liberal oxygen supplementation constituted a median FiO_2 of 0·52 (range 0·28–1·00; IQR 0·39–0·85) for a median duration of 8 h (range 1–144 h; IQR 4–24) compared with conservative supplementation (median FiO_2 0·21, range 0·21–0·50; IQR 0·21–0·25). Room air or oxygen were delivered by nasal prongs in four trials,[44,56,61,66] facemask in 13 trials (NCT00414726),[46,48,49,51–55,58,60,65] and

invasive mechanical ventilation in eight trials.[45,47,50,53,57,62–64] In ten studies (NCT02378545)[44,45,48,49,53,59–62,66] reporting SpO_2, the median baseline SpO_2 was 96·4% (range 94·0–99·0%; IQR 95·8–97·8) in the liberal group and 96·7% (range 93·4–98·0%; IQR 95·0–97·0) in the conservative group. 18 trials were deemed to be at low risk of bias and seven were at high risk of bias (appendix) because of early termination as a result of interim analyses showing apparent benefit or harm (NCT00414726),[45,57,58,63] quasi-randomisation,[56] or missing outcome data.[64]

Mortality data were available from 23 trials (n=15754).[44–62,65] A liberal oxygen strategy increased the risk of death compared with a conservative strategy in hospital (19 randomised controlled trials, n=15071, RR 1·21 [95% CI 1·03–1·43], p=0·020, I^2=0, high quality), at 30 days (14 randomised controlled trials, n=15053, RR 1·14 [1·01–1·28], p=0·033, I^2=0, high quality), and at longest reported follow-up (median 3 months; 23 randomised controlled trials, n=15755, RR 1·10 [1·00–1·20], p=0·044, I^2=0, high quality; figure 2; appendix). Meta-regression showed that as SpO_2 increased, liberal oxygen therapy was associated with a higher RR of in-hospital mortality (14 randomised controlled trials, slope 1·25 [95% CI 1·00–1·57], p=0·0080, figure 2B) and a higher RR of mortality at longest follow-up (15 randomised controlled trials, slope 1·17 [1·01–1·36], p=0·0052; appendix). No statistically significant association was identified between SpO_2 and 30-day mortality (nine randomised controlled trials, slope 1·08 [95% CI 0·89–1·35], p=0·25) or FiO_2 and mortality at any timepoint (slope 1·11–1·80, p=0·28–0·81; appendix). Subgroup analyses revealed no significant interactions with study settings (intensive care unit RR 1·20 [95% CI 0·93–1·55] *vs* non-intensive care unit RR 1·24 [0·97–1·59], $p_{interaction}$=0·86), risk of bias, delivery method (invasive mechanical ventilation RR 1·22 [95% CI 0·95–1·56] *vs* non-invasive mechanical ventilation RR 1·21 [0·97–1·51], $p_{interaction}$=0·95), duration of oxygen exposure, or whether trials excluded patients with hypoxaemia at baseline (appendix) for the main outcome. Visual inspection of funnel plots suggested the absence of some small studies reporting increased mortality with liberal oxygen supplementation at 30 days, but this was not supported by the Egger test (p=0·55; appendix). The magnitude of absolute risk increase in mortality with liberal oxygen therapy varied across the study populations (figure 3). Using the pooled proportion of individuals who had an event across the included trials as the estimate of baseline risk, liberal oxygen supplementation increased the absolute risk of in-hospital mortality by 1·1% (95% CI 0·2–2·2), 30-day mortality by 1·4% (0·1–2·7), and mortality at longest-follow-up by 1·2% (0–2·4, figure 3).

Disability was reported in participants with stroke (NCT00414726)[44,51,59] or traumatic brain injury.[64] Two randomised controlled trials were at high risk of bias because outcome data was incomplete,[64] or the trials had early termination as a result of interim analyses showing apparent benefit or harm (NCT00414726).

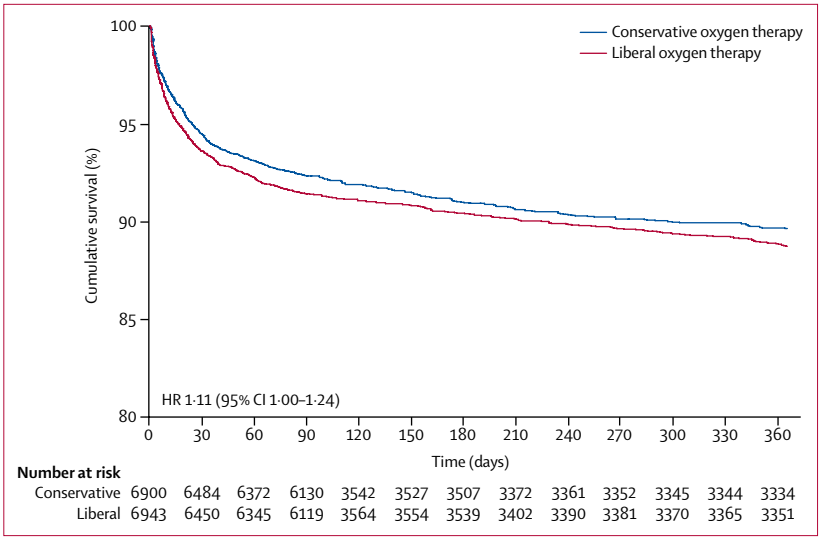

Figure 5: **Kaplan-Meier analysis of cumulative survival for liberal versus conservative oxygen therapy**
We extracted patient-level data from eight randomised controlled trials with various follow-up durations for this analysis: in the study by Panwar and colleagues[53] patient follow-up was 60 days, in the study by Ali and coworkers[44] patients were followed up for 6 months, and in the studies by Hofmann and colleagues[48] and Rønning and coworkers[56] patients were followed up for 1 year. In all other studies, patient follow-up was 90 days. HR=hazard ratio.

Ordered logistic regression showed no significant between-group differences at 3 to 6 months (five randomised controlled trials, n=5536, OR 0·94, [95% CI 0·62–1·41], p=0·75, I^2=67%, low quality), with heterogeneity explained by the two studies at high risk of bias (three low risk of bias randomised controlled trials, n=5384, OR 1·02 [0·93–1·12], p=0·72, I^2=0%, high quality, figure 4A). Dichotomisation of the modified Rankin Scale at cutoffs of 2, 3, or 4 also showed no meaningful differences between the groups (figure 4B; appendix). Interaction tests revealed no subgroup differences (appendix).

The risk of hospital-acquired infections (NCT00414726, NCT02378545)[44,45,47,57,59,60,63] were not statistically different between groups (nine randomised controlled trials, n=7732, RR 0·95 [95% CI 0·74–1·21], p=0·67, I^2=62%, moderate quality; figure 4C). Heterogeneity was explainable by admission type ($p_{interaction}$<0·0001); patients who had emergency surgery had fewer hospital-acquired infections when treated with liberal oxygen therapy (two randomised controlled trials,[57,63] n=449, RR 0·50 [95% CI 0·36–0·69], p<0·0001, low quality) than patients treated with conservative therapy. This effect was not seen in patients admitted with medical diagnoses (seven randomised controlled trials, n=7283, RR 1·04 [95% CI 0·94–1·16], p=0·51, high quality). Both trials in emergency surgery[57,63] were at high risk of bias.

No significant between-group differences were identified in the risk of hospital-acquired pneumonia[45,47,57,60] (four randomised controlled trials, n=1785, RR 1·00 [95% CI 0·74–1·35], p=0·71, I^2=0, moderate quality), or length of hospital stay (NCT00414726, NCT02687217, and NCT02378545)[47,53,55–57,60,62–64] (12 randomised controlled trials, n=2448, mean difference –0·25 days [95% CI –0·68

to 0·18], p=0·26, I^2=58%, low quality; appendix). No subgroup differences were identified for hospital-acquired pneumonia or length of hospital stay (appendix).

For mortality outcomes, trial sequential analysis confirmed that the required information size was met (appendix). Trial sequential analysis confirmed futility of the intervention for disability, and hospital-acquired infections in the medical subgroup. Trial sequential analysis showed that the required information size was not reached to conclusively determine the effect of the intervention on hospital-acquired pneumonia, length of hospital stay, and hospital-acquired infections in the surgical subgroup.

Sensitivity analyses did not change the overall findings (appendix). Mortality analyses were consistent with a sensitivity analysis using survival data to 1 year (eight randomised controlled trials,[44,45,47,48,53,56,59,62] n=13 843, HR 1·11 [95% CI 1·00–1·24], p=0·050, figure 5).

Discussion

This systematic review and meta-analysis of more than 16 000 acutely ill adults provides high-quality evidence that liberal supplemental oxygen is harmful. Patients treated liberally with oxygen had a dose-dependent increased risk of short-term and long-term mortality, but no significant difference in disability, hospital-acquired pneumonia, or length of hospital stay. We found high-quality evidence that liberal oxygen did not reduce the risk of hospital-acquired infections in patients admitted to hospital with medical diagnoses, and low-quality evidence that it might reduce infections in patients admitted for emergency surgery.

Our systematic review and meta-analysis demonstrates a biologically plausible association between liberal oxygen therapy and increased mortality. Animal and human mechanistic studies[3,10] have shown that excessive oxygen (ie, hyperoxia) can promote vasoconstriction, inflammation, and oxidative stress on pulmonary, cardiovascular, and neurological systems. The sigmoidal shape of the oxyhaemoglobin dissociation curve indicates that even small changes in SpO_2 could be harmful because they lead to large increases in PaO_2.[3] Individual randomised controlled trials have suggested an increased risk of respiratory failure,[68] new shock episodes,[47] recurrent myocardial infarction, arrhythmia,[60] and other cardiovascular adverse events (NCT00414726) as potential mechanisms of harm with liberal oxygen therapy. In clinical practice, liberal oxygen therapy might decrease vigilance and delay recognition of deteriorating patients because excessive supplemental oxygen might lead to falsely reassuring SpO_2 values.[3,11] Overall, our findings are consistent with meta-analyses of observational studies[18,19] demonstrating an increased mortality risk in critically ill adults with liberal oxygen strategies, and with meta-analyses of randomised controlled trials[69,70] showing increased mortality risk with 100% oxygen supplementation during neonatal resuscitation. Additional research is required to determine the mechanisms of harm with liberal oxygen therapy.

Establishing the optimum range of oxygen saturation that minimises the competing risks of hypoxaemia and hyperoxaemia in acutely ill patients is important. However, the notion that an upper threshold of oxygen saturation exists whereby the risk-benefit ratio of supplemental oxygen becomes unfavourable is absent from many guidelines.[12–17] Our data supports the existence of such a threshold. Across the trials included in our study, the baseline median SpO_2 in the liberal oxygen arm was 96·4% (range 94·0–99·0%). When this group was exposed to liberal oxygenation, an increase in mortality risk was observed, which was dose-dependent on the magnitude of increase in SpO_2. Our data provide exploratory evidence suggesting that this threshold spans the SpO_2 range of 94% to 96% (ie, the lower 95% CI limit and median baseline SpO_2 in the liberal oxygen groups). These data support the 2015 Thoracic Society of Australia and New Zealand's recommendations[11] for oxygen titration to a maximum SpO_2 of 96%. More broadly, our findings parallel other fields of study in which overly aggressive treatment of physiological parameters promotes harm—eg, in transfusion thresholds[71] and in glucose management in patients who are critically ill.[72] Future research is required to precisely define the oxygen therapy strategies that maximise benefits and minimise harms.

Although hyperoxia has been proposed to have potential benefits by rescuing threatened neurons after brain injury or in the ischaemic penumbra of stroke,[73,74] we did not observe an improvement in disability with liberal use of oxygen. Trial sequential analysis showed the required information size was met to confirm futility of liberal oxygen therapy for these outcomes. However, since trial sequential analysis was primarily driven by a single large randomised controlled trial,[59] we cannot exclude a small beneficial effect of liberal oxygen therapy.

Hyperoxia has also been proposed to decrease surgical-site infections by promoting the release of reactive oxygen species from neutrophils at incision sites.[75] The Centers for Disease Control[16] and WHO[17] strongly recommend administration of increased FIO_2 during surgery and in the immediate postoperative period to reduce the risk of surgical-site infections, on the basis of moderate-quality evidence and primarily studies of elective or mixed acuity (elective and non-elective) surgery. Consistent with this, we observed a subgroup effect whereby liberal oxygen therapy was associated with low-quality evidence of a decreased risk of infection among patients admitted to hospital for emergency surgery, but not for patients admitted with medical diagnoses. Our data raise questions regarding the optimum balance between benefit and risk of hyperoxygenation in surgical settings. The findings of the largest surgical-site infections trial, PROXI,[68,76] are illustrative. This Danish multicentre trial randomly assigned 1400 patients requiring acute or elective laparotomy to liberal versus conservative oxygen therapy

and found similar rates of surgical-site infections (RR 0·95 [95% CI 0·77–1·18]) between the groups, but an increase in mortality with liberal oxygen therapy at 30 days[68] (RR 1·54 [0·84–2·68]) and after a median follow-up of 2·3 years[76] (RR 1·27 [1·03–1·56]); however, PROXI's elective surgery population precluded it from our analysis. Overall, these findings show that high-quality estimates of the effect of liberal oxygen therapy in patients who have surgery, especially emergency surgeries, are urgently needed to clarify how the potential benefits of a reduction in surgical-site infections balance against the potential harms of an increased risk of mortality.

Strengths of our systematic review include its comprehensive and up-to-date search, which included three unpublished trials, broad eligibility criteria that enhance generalisability, and methodological rigour. Our analyses of mortality outcomes included more than 15 000 participants, were consistent across trials, had low risk of bias overall, were robust despite multiple sensitivity analyses, and were supported by patient-level survival data, trial sequential analysis, and meta-regression.

Limitations of this review include the variation in study settings and definitions of liberal and conservative oxygen therapy. For example, some trials used a fixed dose of oxygen (eg, F_IO_2 1·0), whereas others titrated oxygen saturation to a particular target (eg >96%). Although these differences might have contributed to imprecision in the estimates of mortality, there was consistency across other trial characteristics, treatment effect point estimates (I^2=0), and subgroups. Indeed, despite variable follow-up durations, mortality outcomes were consistent whether analysed as dichotomous outcomes or time-to-event survival data. Furthermore, variability in the intervention enabled us to identify a dose-response relationship whereby increasingly liberal oxygen therapy was associated with increasing mortality risk. Although this finding lends confidence to our principal outcomes and provides strong support for the need to establish upper thresholds of safe oxygen therapy, it is important to note that the estimates of the dose-response are derived from trial-level summary estimates, rather than patient-level data. Thus, the meta-regression point estimates should be considered as qualitative and exploratory, rather than definitive estimates of the dose-response relationship. Most included trials reported all-cause mortality, but not cause-specific mortality or uniform morbidity outcomes. Consequently, trial sequential analysis indicated that the information size was sufficient for all-cause mortality. However, because only a small number of studies reported cause-specific mortality or uniform morbidity outcomes, we were unable to identify the precise mechanisms of harm of hyperoxia. Although some included trials were terminated early on the basis of interim statistical analyses for apparent benefit or harm, our estimates are robust for multiple reasons:[33,34] non-truncated randomised controlled trials outnumbered truncated randomised controlled trials and the funnel plots were symmetrical, no substantial differences[34] were identfied between truncated and non-truncated randomised controlled trials (ratio of RRs were greater than 0·7 with no subgroup effect), and our conclusions were not materially altered despite multiple sensitivity analyses in which these trials were excluded, down-weighted, or had their effect size penalised.[34] Although we did not observe statistically significant heterogeneity in pre-specified subgroup pairs, some subgroups were relatively small and we cannot fully exclude the possibility of subgroup differences.

This systematic review and meta-analysis provides high-quality evidence that hyperoxia is life-threatening. This is a distinct viewpoint from the current notion that at worst, liberal oxygen is not beneficial for acute illnesses.[77] Although the increased mortality risk with liberal oxygen therapy was too small to be conclusively detected in any single randomised controlled trial included in our systematic review, as a whole, the mean number needed to harm resulting in one death using a liberal approach is approximately 71 (95% CI 37–1000). The magnitude of this effect is of major global public health importance[78] in view of the ubiquitous use of oxygen in acutely ill adults.

Contributors

NZ, DKC, and JDN originally conceived the study. LH-YK and DKC wrote the first draft. LH-YK, DKC, NZ, JDN, and WA acquired the data and screened records. LH-YK and DKC extracted data and assessed risk of bias. DKC designed the literature search and did the statistical analyses. PJY provided data. WA oversaw study implementation. All authors provided critical conceptual input, interpreted the data analysis, and critically revised the manuscript.

Declaration of interests

PJY is a principal investigator of an ongoing trial (ACTRN12615000957594) evaluating oxygen saturation targets for critically ill patients. All other authors declare no competing interests.

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