Supplementary Online Content

Ferreyro BL, Angriman F, Munshi L, et al. Association of noninvasive oxygenation strategies with all-cause mortality in adults with acute hypoxemic respiratory failure: a systematic review and meta-analysis. *JAMA*. Published online June 4, 2020. doi:10.1001/jama.2020.9524

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix 1. Search strategy

General description: The following seven electronic bibliographic databases were searched using a comprehensive search strategy developed by an information specialist: (1) *Ovid MEDLINE*, (2) *Ovid EMBASE*, (3) *PubMed (Non-Medline records only)*, (4) *EBM Reviews - Cochrane Central Register of Controlled Trials,* (5) *CINAHL Complete,* (6) *Web of Science,* (7) *LILACS*. We also searched the *ClinicalTrials.gov*, *WHO International Clinical Trials Registry Platform*, and *International Standard Randomized Controlled Trial Number Registry* for all registered clinical trials and randomized controlled trials.

Search Strategy

The search strategy is structured according to the *Peer Reviewed Electronic Search Strategies (PRESS) 2015 Guidelines* (Refer to Supplementary File 2 for search strategy). All randomized controlled trials were considered if the patient population is > 18 years of age. A validated search filter for randomized controlled trials from the *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0, Section 6.4.11*. were used to screen *Ovid MEDLINE, EMBASE, and PubMed*. A pre-tested search filter for randomized controlled trials from the *Scottish Intercollegiate Guidelines Network* was used to screen *CINAHL Complete* and *Web of Science.* No limits were applied to language, publication year, gender or race.

1) Ovid MEDLINE (Last updated April 28th, 2020)

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to Present> Search Strategy:

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1 Respiratory Insufficiency/ or Respiratory Distress Syndrome, Adult/
2 ((respiratory or respiration or lung or ventilatory) adj2 (depress* or insufficien* or fail* or deficien* or disturb* or dysfunction* or compromis*)).tw,kw,kf.
3 Hypoxia/
4 (acute adj2 (hypoxia or hypox?emi*)).tw,kw,kf.
5 (acute hypox?emic respiratory failure* or AHRF or acute respiratory distress syndrome* or ARDS).tw,kw,kf.
6 Noninvasive ventilation/ or Oxygen inhalation therapy/ or Masks/ or Continuous Positive Airway Pressure/
7 ((non-invasive or non invasive or noninvasive) adj3 (oxygen* or ventilat*)).tw,kw,kf.
8 (continuous positive airway pressure or CPAP or continuous positive pressure ventilation or CPPV or bi level positive airway pressure or bilevel positive airway pressure or bi-level positive airway pressure or BiPaP or NIV).tw,kw,kf.
9 standard oxygen.tw,kw,kf.
10 ((low flow or low-flow or lowflow) adj2 oxygen*).tw,kw,kf.
11 ((mask* or helmet*) adj1 (face or oxygen)).tw,kw,kf.
12 (Ambu Res-cue mask* or Easyfit or Performatrack or Performax or transnasal mask* or facemask* or face-mask*).tw,kw,kf.
13 Cannula/

14 ((high flow or highflow or high-flow) adj1 (nasal cannula* or oxygen cannula*)).tw,kw,kf.
15 (HFNC or HFOC).tw,kw,kf.
16 or/1-5
17 or/6-15
18 16 and 17
19 limit 18 to "all adult (19 plus years)"
20 exp animals/ not humans/
21 19 not 20
22 randomized controlled trial.pt.
23 controlled clinical trial.pt.
24 randomized.ab.
25 placebo.ab.
26 drug therapy.fs.
27 randomly.ab.
28 trial.ab.
29 groups.ab.
30 or/22-29
31 21 and 30

2) Ovid EMBASE (Last updated April 28th, 2020)

Embase Classic+Embase <1947 to 2019 November 22>	
#	Search Statement
1	respiratory failure/ or acute respiratory failure/ or lung insufficiency/
2	((respiratory or respiration or lung or ventilatory) adj2 (depress* or insufficien* or fail* or deficien* or disturb* or dysfunction* or compromis*)).tw,kw.
3	(acute hypox?emic respiratory failure* or AHRF or acute respiratory distress syndrome* or ARDS).tw,kw.
4	hypoxia/
5	(acute adj2 (hypoxia or hypox?emi*)).tw,kw.
6	exp nasal cannula/
7	((high flow or high-flow or highflow) adj1 (nasal cannula* or oxygen cannula*)).tw,kw.
8	(HFNC or HFOC or Optiflow or Opti-flow or Opti flow).tw,kw.
9	noninvasive ventilation/ or positive end expiratory pressure/
10	((non-invasive or non invasive or noninvasive) adj3 (oxygen* or ventilat*)).tw,kw.
11	(continuous positive airway pressure or CPAP or continuous positive pressure ventilation or

	CPPV or bi level positive airway pressure or bilevel positive airway pressure or bi-level positive airway pressure or BiPaP or NIV).tw,kw.
12	oxygen therapy/
13	standard oxygen.tw,kw.
14	((low flow or low-flow or lowflow) adj2 oxygen*).tw,kw.
15	face mask/
16	((mask* or helmet*) adj1 (face or oxygen)).tw,kw.
17	(Ambu Res-cue mask* or Easyfit or Performatrack or Performax or transnasal mask* or facemask* or face-mask*).tw,kw.
18	or/1-5
19	or/6-17
20	18 and 19
21	limit 20 to (adult <18 to 64 years> or aged <65+ years>)
22	exp animals/ not human/
23	21 not 22
24	crossover-procedure/
25	double-blind procedure/
26	randomized controlled trial/
27	single-blind procedure/
28	(random* or factorial* or crossover* or cross over* or cross-over* or placebo* or (doubl* adj blind*) or (singl* adj blind*) or assign* or allocat* or volunteer*).tw,kw.
29	24 or 25 or 26 or 27 or 28
30	23 and 29

3) Cochrane CENTRAL (Last updated April 28th, 2020)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <November 2019>
Search Strategy:
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1 respiratory distress syndrome, adult/ or respiratory insufficiency/
2 ((respiratory or respiration or lung or ventilatory) adj2 (depress* or insufficien* or fail* or deficien* or disturb* or dysfunction* or compromis*)).tw,kw.
3 (acute hypox?emic respiratory failure* or AHRF or acute respiratory distress syndrome* or ARDS).tw,kw.
4 Anoxia/
5 (acute adj2 (hypoxia or hypox?emi*)).tw,kw.
6 noninvasive ventilation/
7 oxygen inhalation therapy/
8 masks/
9 continuous positive airway pressure/
10 ((non-invasive or non invasive or noninvasive) adj3 (oxygen* or ventilat*)).tw,kw.
11 standard oxygen.tw,kw.
12 ((low flow or low-flow or lowflow) adj2 oxygen*).tw,kw.
13 ((mask* or helmet*) adj1 (face or oxygen)).tw,kw.
14 (Ambu Res-cue mask* or Easyfit or Performatrack or Performax or transnasal mask* or facemask* or face-mask*).tw,kw.
15 catheters/
16 ((high flow or high-flow or highflow) adj1 (nasal cannula* or oxygen cannula*)).tw,kw.
17 (HFNC or HFOC or Optiflow or Opti-flow or Opti flow).tw,kw.
18 (continuous positive airway pressure or CPAP or continuous positive pressure ventilation or CPPV or bi level positive airway pressure or bilevel positive airway pressure or bi-level positive airway pressure or BiPaP or NIV).tw,kw.
19 or/1-5
20 or/6-18
21 19 and 20
22 exp animals/ not human/
23 21 not 22

4) EBSCO CINAHL Complete (Last updated April 28th, 2020)

#	Query
S30	S17 AND S29
S29	S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28
S28	TX allocat* random*
S27	(MH "Quantitative Studies")
S26	(MH "Placebos")
S25	TX placebo*
S24	TX random* allocat*
S23	(MH "Random Assignment")
S22	TX randomi* control* trial*
S21	TX (((trebl* n1 blind*) or (trebl* n1 mask*))) OR TX (((tripl* n1 blind*) or (tripl* n1 mask*))) OR TX (((doubl* n1 blind*) or (doubl* n1 mask*))) OR TX (((singl* n1 blind*) or (singl* n1 mask*)))
S20	TX clinic* N1 trial*
S19	PT Clinical trial
S18	(MH "Clinical Trials+")
S17	S15 AND S16
S16	S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14
S15	S1 OR S2 OR S3 OR S4
S14	TI (HFNC or HFOC or Optiflow or Opti-flow or "Opti flow") OR AB (HFNC or HFOC or Optiflow or Opti-flow or "Opti flow")
S13	TI ((("high flow" or highflow or high-flow) N1 (nasal cannula* or oxygen cannula*))) OR AB ((("high flow" or highflow or high-flow) N1 (nasal cannula* or oxygen cannula*)))
S12	(MH "Nasal Cannula")
S11	TI (("Ambu Res-cue mask*" or Easyfit or Performatrack or Performax or "transnasal mask*" or facemask* or face-mask*)) OR AB (("Ambu Res-cue mask*" or Easyfit or Performatrack or Performax or "transnasal mask*" or facemask* or face-mask*))
S10	TI (((mask* or helmet*) N1 (face or oxygen))) OR AB (((mask* or helmet*) N1 (face or oxygen)))
S9	(MH "Oxygen Masks+")
S8	TI ((("low flow" or low-flow or lowflow) N2 oxygen)) OR AB ((("low flow" or low-flow or lowflow) N2 oxygen))
S7	TI ("standard oxygen" or "standard O2") OR AB ("standard oxygen" or "standard O2")
S6	TI (("continuous positive airway pressure" or CPAP or "continuous positive pressure ventilation" or CPPV or "bi level positive airway pressure" or "bilevel

	positive airway pressure" or "bi-level positive airway pressure" or BiPaP or NIV)) OR AB (("continuous positive airway pressure" or CPAP or "continuous positive pressure ventilation" or CPPV or "bi level positive airway pressure" or "bilevel positive airway pressure" or "bi-level positive airway pressure" or BiPaP or NIV))
S5	(MH "Oxygen Therapy+") OR (MH "Continuous Positive Airway Pressure")
S4	TI (("acute hypox?emic respiratory failure*" or AHRF or "acute respiratory distress syndrome*" or ARDS)) OR AB (("acute hypox?emic respiratory failure*" or AHRF or "acute respiratory distress syndrome*" or ARDS))
S3	TI ((acute N2 (hypoxia or hyox?emi*))) OR AB ((acute N2 (hypoxia or hyox?emi*)))
S2	TI (((respiratory or respiration or lung or ventilatory) N2 (depress* or insufficien* or fail* or deficien* or disturb* or dysfunction* or compromis*))) OR AB (((respiratory or respiration or lung or ventilatory) N2 (depress* or insufficien* or fail* or deficien* or disturb* or dysfunction* or compromis*)))
S1	(MH "Respiratory Distress Syndrome, Acute") OR (MH "Respiratory Failure")

5) Web of Science (Last updated April 28th, 2020)

# 15	#13 NOT #14
# 14	TOPIC: (infant* or child* or neonat* or NICU* or newborn* or (newly NEAR/1 born) or premature or pre-mature or "low birth weight" or VLBW or LBW)
# 13	#12 AND #11
# 12	TOPIC: (clinical NEAR/1 trial*) *OR* TOPIC: ((trebl* NEAR/1 blind*) or (trebl* NEAR/1 mask*)) *OR* TOPIC: ((tripl* NEAR/1 blind*) or (tripl* NEAR/1 mask*)) *OR* TOPIC: ((doubl* NEAR/1 blind*) or (doubl* NEAR/1 mask*)) *OR* TOPIC: ((singl* NEAR/1 blind*) or (singl* NEAR/1 mask*)) *OR* TOPIC:("randomi* control* trial*") *OR* TOPIC: ("random* allocat*") *OR* TOPIC: (placebo*) *OR* TOPIC: ("allocat* random*")
# 11	#10 AND #1
# 10	#9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2
# 9	TOPIC: (HFNC or HFOC or Optiflow or Opti-flow or "Opti flow")
# 8	TOPIC: ((("high flow" or highflow or high-flow) NEAR/1 ("nasal cannula*" or "oxygen cannula*")))
# 7	TOPIC: ("Ambu Res-cue mask*" or Easyfit or Performatrack or Performax or "transnasal mask*" or facemask* or face-mask*)
# 6	TOPIC: (((mask* or helmet*) NEAR/1 (face or oxygen)))
# 5	TOPIC: (("low flow" or low-flow or lowflow) NEAR/2 oxygen*)
# 4	TOPIC: ("standard oxygen")
# 3	TOPIC: (("continuous positive airway pressure" or CPAP or "continuous positive pressure ventilation" or CPPV or "bi level positive airway pressure" or "bilevel positive airway pressure" or "bi-level positive airway pressure" or BiPaP or NIV))

# 2	TOPIC: (oxygen* NEAR/3 (non-invasive or "non invasive" or noninvasive)) *OR* TOPIC: (ventilat* NEAR/3 (non-invasive or "non invasive" or noninvasive))
# 1	TOPIC: (((respiratory or respiration or lung or ventilatory) NEAR/2 (depress* or insufficien* or fail* or deficien* or disturb* or dysfunction* or compromis*))) *OR* TOPIC: ((acute NEAR/2 (hypoxia or hypox?emi*))) *OR* TOPIC: ((acute hypox?emic respiratory failure* or AHRF or acute respiratory distress syndrome* or ARDS))

6) PubMed (Last updated April 28th, 2020)

((((((((((respiratory insufficiency[MeSH Terms]) OR respiratory distress syndrome, adult[MeSH Terms]) OR ((((((((respiratory depress*[Title/Abstract] OR respiration depress*[Title/Abstract] OR lung depress*[Title/Abstract] OR ventilatory depress*[Title/Abstract])) OR (respiratory insufficien*[Title/Abstract] OR respiration insufficien*[Title/Abstract] OR lung insufficien*[Title/Abstract] OR ventilatory insufficien*[Title/Abstract])) OR (respiratory fail*[Title/Abstract] OR respiration fail*[Title/Abstract] OR lung fail*[Title/Abstract] OR ventilatory fail*[Title/Abstract])) OR (respiratory deficien*[Title/Abstract] OR respiration deficien*[Title/Abstract] OR lung deficien*[Title/Abstract] OR ventilatory deficien*[Title/Abstract])) OR (respiratory disturb*[Title/Abstract] OR respiration disturb*[Title/Abstract] OR lung disturb*[Title/Abstract] OR ventilatory disturb*[Title/Abstract])) OR (respiratory dysfunction*[Title/Abstract] OR respiration dysfunction*[Title/Abstract] OR lung dysfunction*[Title/Abstract] OR ventilatory dysfunction*[Title/Abstract])) OR (respiratory compromis*[Title/Abstract] OR respiration compromis*[Title/Abstract] OR lung compromis*[Title/Abstract] OR ventilatory compromis*[Title/Abstract]))) OR hypoxia[MeSH Terms]) OR "acute hypoxia"[Title/Abstract]) OR (("acute hypoxemia"[Title/Abstract] OR "acute hypoxemic"[Title/Abstract] OR "acute hypoxaemia"[Title/Abstract] OR "acute hypoxaemic"[Title/Abstract]))))) AND ((((((((((((positive pressure ventilation, non invasive[MeSH Terms]) OR oxygen inhalation therapy[MeSH Terms]) OR masks[MeSH Terms]) OR continuous positive airway pressure[MeSH Terms]) OR ((NIV[Title/Abstract] OR "non-invasive oxygenation"[Title/Abstract] OR "non invasive oxygenation"[Title/Abstract] OR "noninvasive oxygenation"[Title/Abstract] OR "non-invasive ventilation"[Title/Abstract] OR "non invasive ventilation"[Title/Abstract] OR "noninvasive ventilation"[Title/Abstract]))) OR (("continuous positive airway pressure"[Title/Abstract] OR CPAP[Title/Abstract] OR "continuous positive pressure ventilation"[Title/Abstract] OR CPPV[Title/Abstract] OR "bi level positive airway pressure"[Title/Abstract] OR "bilevel positive airway pressure"[Title/Abstract] OR "bi-level positive airway pressure"[Title/Abstract] OR BiPaP[Title/Abstract]))) OR "standard oxygen"[Title/Abstract]) OR ((low flow oxygen*[Title/Abstract] OR low-flow oxygen*[Title/Abstract] OR low flow oxygen*[Title/Abstract]))) OR ((face mask*[Title/Abstract] OR oxygen mask*[Title/Abstract] OR face helmet*[Title/Abstract] OR oxygen helmet*[Title/Abstract]))) OR ((ambu res-cue mask*[Title/Abstract] OR Easyfit[Title/Abstract] OR Performatrack[Title/Abstract] OR Performax[Title/Abstract] OR transnasal mask*[Title/Abstract] OR facemask*[Title/Abstract] OR face-mask*[Title/Abstract]))) OR cannula[MeSH Terms]) OR

((high flow nasal cannula*[Title/Abstract] OR high flow nasal cannula*[Title/Abstract] OR high-flow nasal cannula*[Title/Abstract] OR high flow oxygen cannula*[Title/Abstract] OR high flow oxygen cannula*[Title/Abstract] OR high-flow oxygen cannula*[Title/Abstract])) OR ((HFNC[Title/Abstract] OR HFOC[Title/Abstract] OR Optiflow[Title/Abstract] OR Opti-flow[Title/Abstract] OR "Opti flow"[Title/Abstract]))))) AND (pubmednotmedline[sb] OR publisher[sb] OR inprocess[sb])) AND (((((randomized controlled trial [pt] or controlled clinical trial [pt] or randomized [tiab] or placebo [tiab] or drug therapy [sh] or randomly [tiab] or trial [tiab] or groups [tiab]))))) NOT (((animals [mh] NOT humans [mh])))

Eligibility Criteria for Studies

Inclusion Criteria	Exclusion Criteria
▪ Study design o Randomized clinical trial ▪ Age of patients in study > 18 years ▪ Acute hypoxemic respiratory failure o New onset (< 7 days) o Clinical signs (tachypnea, increased work of breathing) o Radiologic signs (unilateral or bilateral x-ray opacities) o Gas exchange alterations (hypoxemia or requirement of supplemental oxygen) ▪ Setting: ICU, High Dependency Unit, Emergency Department. ▪ Interventions assessed o High flow nasal oxygen o Noninvasive ventilation (oronasal or helmet interface) o Standard oxygen therapy ▪ Mortality and/or intubation assessed	▪ Study design o Observational cohort studies, case control studies. o Cross-over randomized controlled studies ▪ Study participants o 50% or more of the included patients have AE-COPD or CHF o Patients with respiratory failure immediately post extubation o Post-extubation after major cardiovascular/thoracic surgery ▪ No relevant intervention or outcomes o Both mortality and intubation not reported ▪ Animal studies

AE-COPD: acute exacerbation of chronic obstructive pulmonary disease; CHF: congestive heart failure; ICU: intensive care unit.

eAppendix 2. Statistical Analysis

This network meta-analysis was conducted using Bayesian random effects models to derive head-to-head treatment effect estimates comparing all interventions. Main analyses were based on Markov chain Monte Carlo methods using minimally informative prior distribution for treatment effect estimates, and informative prior distributions for heterogeneity estimates derived from external evidence for each of the study outcomes. Specifically, we fitted generalized linear models with a log-link function and a binomial likelihood, with 3 chains, 70000 iterated simulations plus 20000 iterations used for the burn-in period. This was done via the gemtc package available in R which is based on the models proposed by Dias.[1,2] Correction of the treatment associations for multi-arm trials was applied.[3] Model convergence was assessed by means of the Brooks-Gelman-Rubin diagnostic plots. The goodness-of-fit of our final models[4] was assessed by the use of deviance, leverage and deviance information criterion. Also, we compared the mean residual deviance with the number of contributing data points. Pairwise and network risk ratios (RR) with corresponding 95% credible intervals (CIs) where derived using the median and the 2.5th and 97.5th percentile of the posterior distribution respectively. In addition to relative associations, Bayesian analyses were used to produce absolute risk differences and 95% CIs between treatment groups. For these, we assumed an incidence of 30% (mortality) and 40% (intubation) in the standard oxygen group, based on pooled data and from previous literature.[5,6] To take into consideration the uncertainty about this assumption, we sampled the log control group risk for mortality from a normal distribution with mean -1.2039728 and variance 0.1, and for intubation from a normal distribution with mean -.91629073 and variance 0.1. The sampled

log control group risks were then exponentiated and used to derive risk differences from pooled relative risks generated by the network meta-analysis for each outcome.

We calculated the median and the 95% credible intervals of the posterior distribution for the rank of each treatment. We chose to use this approach as it explicitly shows the uncertainty regarding the ranking of interventions. An intervention with a median rank of 1 would be interpreted as having the most beneficial effect.[7] Heterogeneity in treatment effects between studies was quantified using the posterior distribution of τ^2 alongside 95% credible intervals. Incoherence between direct and indirect comparisons was estimated using the node-splitting approach contrasting estimates from both direct and indirect evidence.[8,9]

Use of informative priors

For heterogeneity

For all-cause mortality, the parameters of the predictive log-normal distribution for heterogeneity used as prior information were μ=-3.50 and σ=1.26. For endotracheal intubation (device related success/failure) the parameters were μ=-1.69 and σ=1.68. μ and σ are the mean and standard deviation on the log scale, respectively. The intervention comparison type considered was non-pharmacological versus non-pharmacological.[7] These distributions have been suggested by empirical evidence from previous literature and account for the nature of each of these outcomes.[10] It should be noted that the informative prior distributions for heterogeneity were derived from Turner et al for meta-analyses conducted in the log-odds scale, and our meta-analyses are conducted in the log-relative risk scale. To our knowledge, there are no established prior distributions for heterogeneity for meta-analyses based on the log-relative

risk scale. The expectation is that the prior distributions proposed by Turner et al are wide enough to cover plausible values for both scales. Furthermore, if the event is common (i.e.: more than 10%) the OR tends to be more extreme than the RR. One could thus argue that a prior based on the log OR is conservative (i.e. tends to assume larger heterogeneity) if used for a log RR analysis. Finally, to test the robustness of our analysis, we also conducted a sensitivity analysis using vague priors for the between-trial standard deviation of log-relative risk.

For treatment effects

As further sensitivity analyses, we used previous literature in order to modify the priors of effect estimates using skeptical priors for the effect of face mask non-invasive ventilation versus standard oxygen and optimistic priors for the effect of high flow nasal oxygen versus face mask noninvasive ventilation. We performed this sensitivity analysis to better account for a subgroup of clinicians who may have greater confidence in high flow nasal canula in comparison to face mask noninvasive ventilation. We defined priors based on a combination of 1) relative effect estimates for comparisons between face mask noninvasive ventilation and standard oxygen in a large observational study (skeptical, Bellani, 2016[5]), 2) a randomized clinical trial comparing high flow nasal oxygen with noninvasive ventilation (optimistic, Frat, 2015[6]) and 3) a previous study using a Bayesian approach to estimate the effectiveness of therapies in patients with acute respiratory failure (Goligher, 2018[11]). To incorporate such priors into the gemtc analysis, we directly modified the JAGS code including the prior distribution for the effects of interest (face-mask noninvasive ventilation vs. high flow nasal cannula and SOT) as a normal distribution defined by the median log(RR) and the corresponding precision for strongly

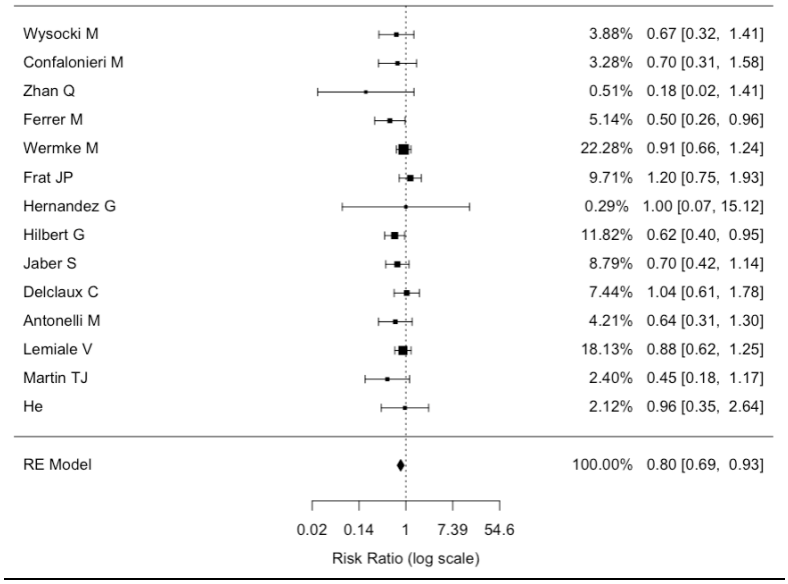
enthusiastic or skeptical priors (following the work in Goligher, 2018[11]). Specifically, the median RR for the facemask / standard oxygen contrast was 1.5 and for the facemask / high flow was 1.6. For both distributions we assumed a SD for the ln(RR) of 0.25.

We performed all analyses in R v3.6 (packages gemtc, coda, pcnetmeta and rjags) using Just Another Gibbs Sampler (JAGS) version 4.3.0 and OpenBUGS.

eFigure 1. Initial pairwise meta-analysis for all comparisons

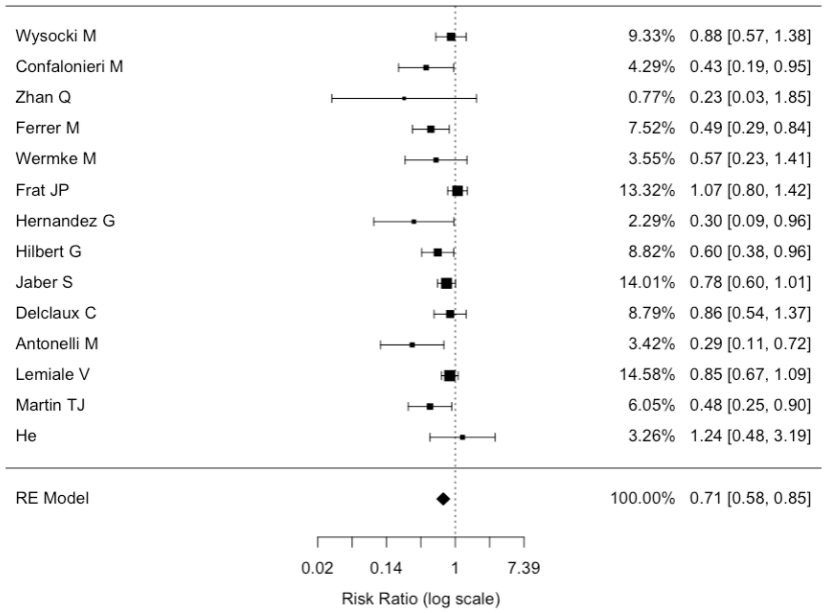
Comparison 1 – Face mask non-invasive ventilation vs. standard oxygen.

Mortality



	estimate	ci.lb	ci.ub
tau^2	0.0000	0.0000	0.1719
tau	0.0000	0.0000	0.4146
I^2(%)	0.0000	0.0000	67.2159
H^2	1.0000	1.0000	3.0503

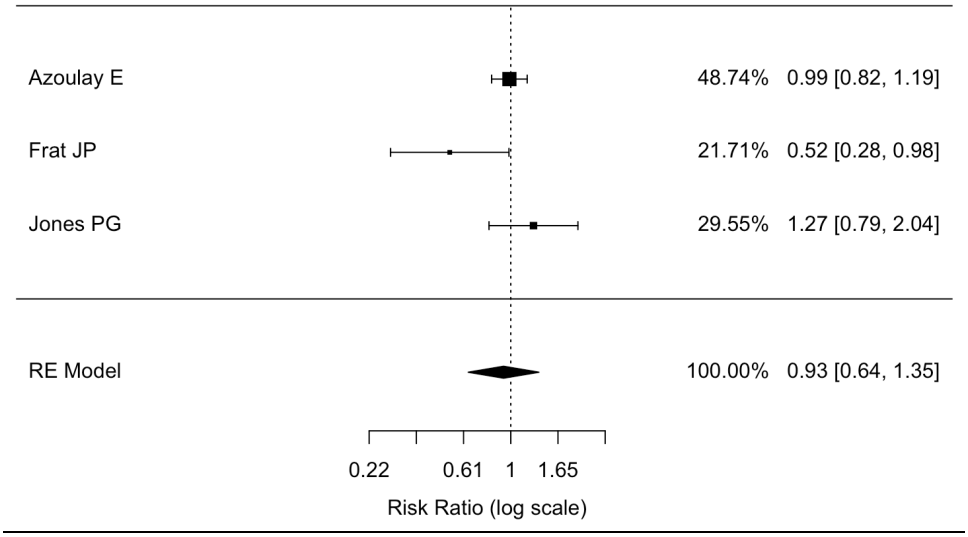
Intubation



	estimate	ci.lb	ci.ub
tau^2	0.0479	0.0000	0.4162
tau	0.2188	0.0000	0.6451
I^2(%)	45.8126	0.0000	88.0193
H^2	1.8454	1.0000	8.3468

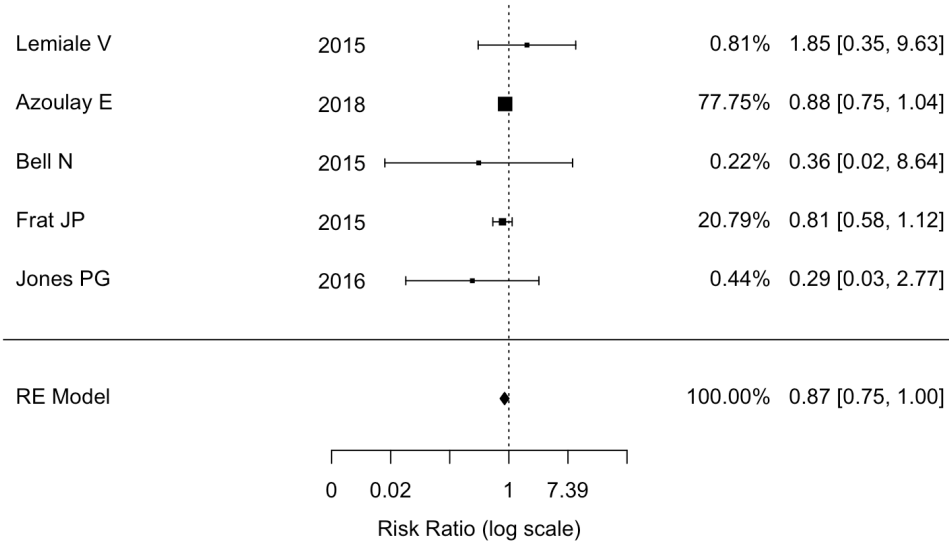
Comparison 2 – High flow nasal oxygen vs. standard oxygen

Mortality



	estimate	ci.lb	ci.ub
tau^2	0.0655	0.0000	8.1478
tau	0.2560	0.0000	2.8544
I^2(%)	60.0292	0.0000	99.4673
H^2	2.5018	1.0000	187.7325

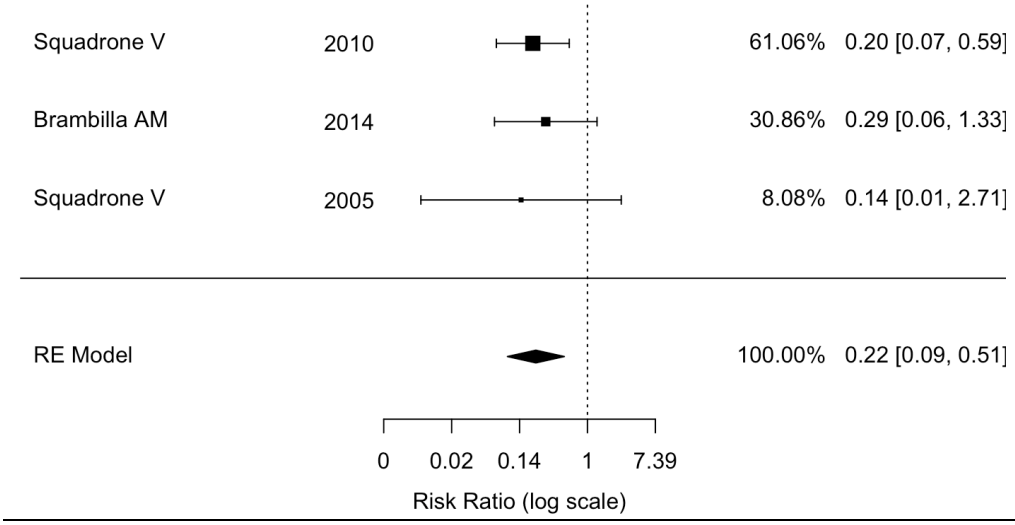
Intubation



	estimate	ci.lb	ci.ub
tau^2	0.0000	0.0000	3.4056
tau	0.0000	0.0000	1.8454
I^2(%)	0.0000	0.0000	98.1190
H^2	1.0000	1.0000	53.1630

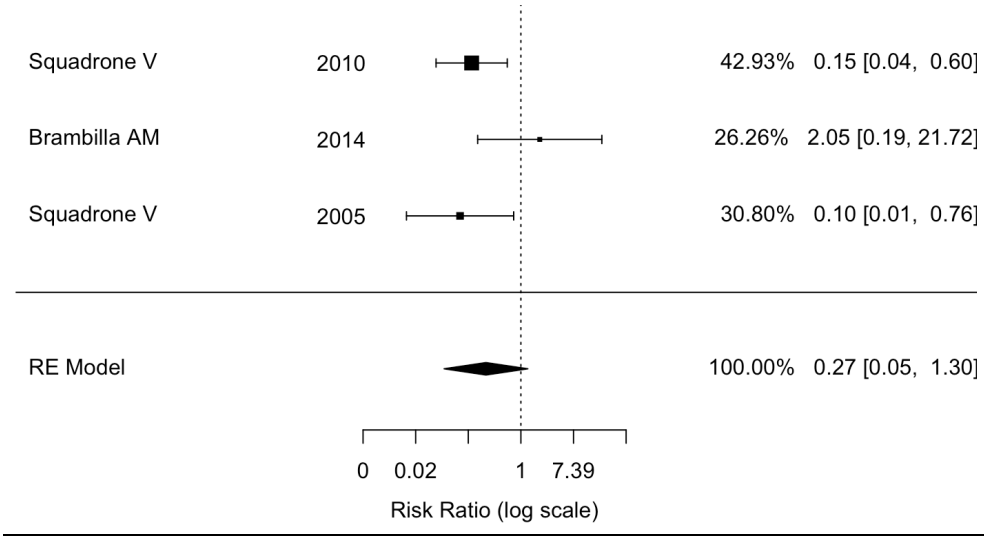
Comparison 3 – Helmet non-invasive ventilation vs. standard oxygen

Mortality



	estimate	ci.lb	ci.ub
tau^2	0.0000	0.0000	3.8806
tau	0.0000	0.0000	1.9699
I^2(%)	0.0000	0.0000	84.7698
H^2	1.0000	1.0000	6.5659

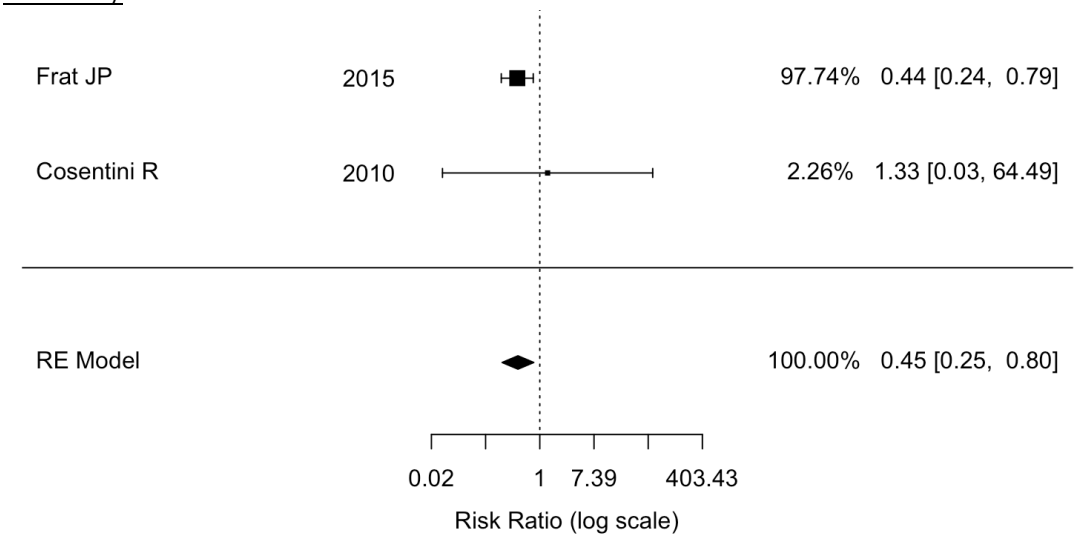
Intubation



	estimate	ci.lb	ci.ub
tau^2	1.0567	0.0000	>100.0000
tau	1.0280	0.0000	>10.0000
I^2(%)	53.3904	0.0000	>99.0859
H^2	2.1455	1.0000	>109.4018

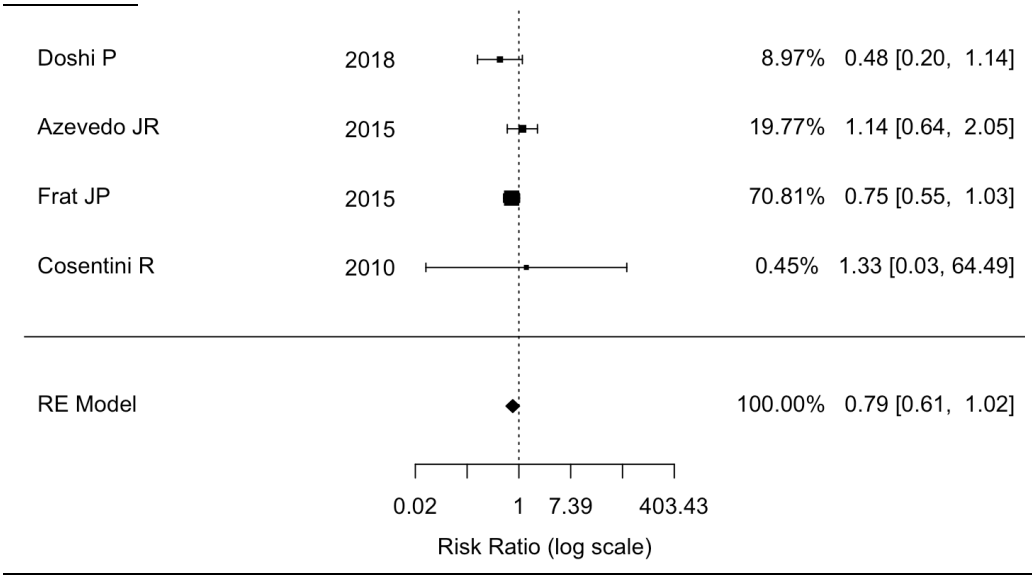
Comparison 4 – High flow nasal oxygen vs. face mask non-invasive ventilation[1]

Mortality



	estimate	ci.lb	ci.ub
tau^2	0.0000	0.0000	>100.0000
tau	0.0000	0.0000	>10.0000
I^2(%)	0.0000	0.0000	>98.0357
H^2	1.0000	1.0000	>50.9086

Intubation

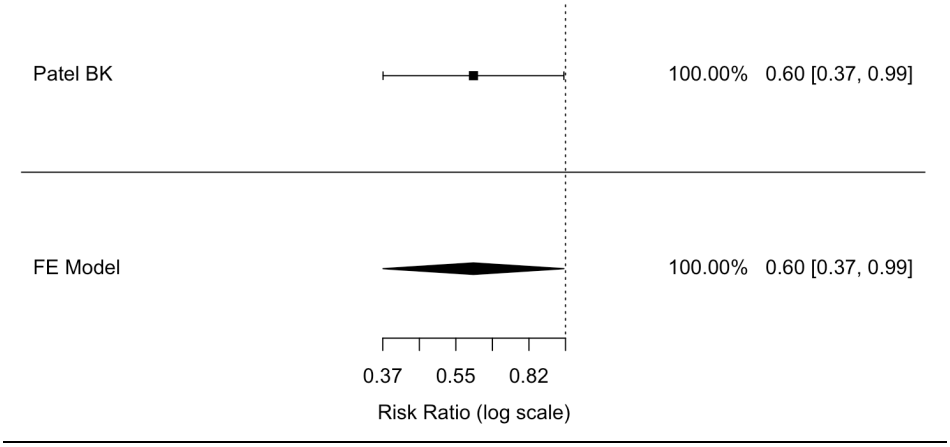


	estimate	ci.lb	ci.ub
tau^2	0.0000	0.0000	2.1037
tau	0.0000	0.0000	1.4504
I^2(%)	0.0000	0.0000	94.7728
H^2	1.0000	1.0000	19.1305

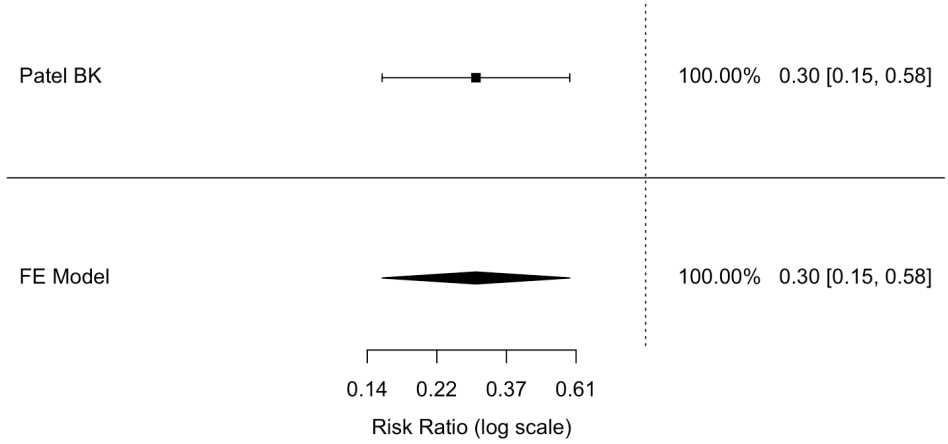
1. The study by Cosentini included by adding 0.5 to the 0 events in both groups. This study was not included in the network metanalysis.

Comparison 5 – Helmet non-invasive ventilation vs. face mask non-invasive ventilation

Mortality



Intubation



eTable 1. Individual study risk of bias for all-cause mortality

Name (year)	Randomization generation	Allocation concealment	Blinding	Incomplete data	Selective reporting	Other	Overall risk of bias
Wysocki (1995)	LOW	LOW	PL	LOW	LOW	LOW	LOW
Confalonieri (1999)	LOW	LOW	PL	LOW	LOW	LOW	LOW
Squadrone (2010)	LOW	LOW	PL	LOW	LOW	LOW	LOW
Brambilla (2014)	PL	PL	PL	LOW	LOW	LOW	UNCLEAR
Zhan (2012)	LOW	LOW	PL	LOW	LOW	LOW	LOW
Ferrer (1999)	LOW	LOW	PL	LOW	LOW	LOW	LOW
Azoulay (2018)	LOW	LOW	PL	LOW	LOW	LOW	LOW
Wermcke (2011)	LOW	LOW	PL	PL	LOW	LOW	UNCLEAR
Frat (2015)	LOW	LOW	PL	LOW	LOW	LOW	LOW
Hernandez (2010)	LOW	LOW	PL	LOW	LOW	LOW	LOW
Hilbert (2001)	LOW	LOW	PL	LOW	LOW	LOW	LOW
Jaber (2016)	LOW	LOW	PL	LOW	LOW	LOW	LOW
Delclaux (2000)	LOW	LOW	PL	LOW	LOW	LOW	LOW
Squadrone (2005)	LOW	LOW	PL	LOW	LOW	LOW	LOW
Antonelli (2000)	LOW	LOW	PL	LOW	LOW	LOW	LOW
Jones (2016)	LOW	LOW	PL	PH	LOW	LOW	HIGH
Lemiale (2015)	LOW	LOW	PL	LOW	LOW	LOW	LOW
Martin (2000)	PL	PL	PL	LOW	LOW	LOW	UNCLEAR
Cosentini (2010)	LOW	LOW	UNCLEAR	LOW	LOW	LOW	LOW
Patel (2016)	LOW	LOW	PL	LOW	LOW	LOW	LOW
He (2019)	LOW	LOW	PL	LOW	HIGH	LOW	HIGH

PL: probably low, PH: probably high

eFigure 2. Estimated association of different noninvasive oxygenation strategies with all-cause mortality (overall and all comparisons)

Comparison	Network Relative Risk (95% Credible Interval)	Network Risk difference (95% Credible Interval)	Number of trials and participants in direct comparison	Quality of Evidence[a]
Helmet vs. Standard Oxygen	0.40 (0.24 – 0.63)	-0.19 (-0.37 to -0.09)	3 trials, 330 patients	Low
Face mask vs. Standard Oxygen	0.83 (0.68 – 0.99)	-0.06 (-0.15 to -0.01)	14 trials, 1725 patients	Moderate
High-flow nasal oxygen vs. Standard Oxygen	0.87 (0.62 – 1.15)	-0.04 (-0.15 to 0.04)	3 trials, 1279 patients	Moderate
Helmet vs. High-flow nasal oxygen	0.46 (0.26 – 0.80)	-0.15 (-0.34 to -0.05)	No head to head comparison	Low
Helmet vs. Face Mask	0.48 (0.29 – 0.76)	-0.13 (-0.27 to -0.05)	1 trial, 83 patients	Low
Face mask vs. High-flow nasal oxygen	0.95 (0.69 – 1.37)	-0.02 (-0.14 to 0.07)	1 trial, 216 patients	Low

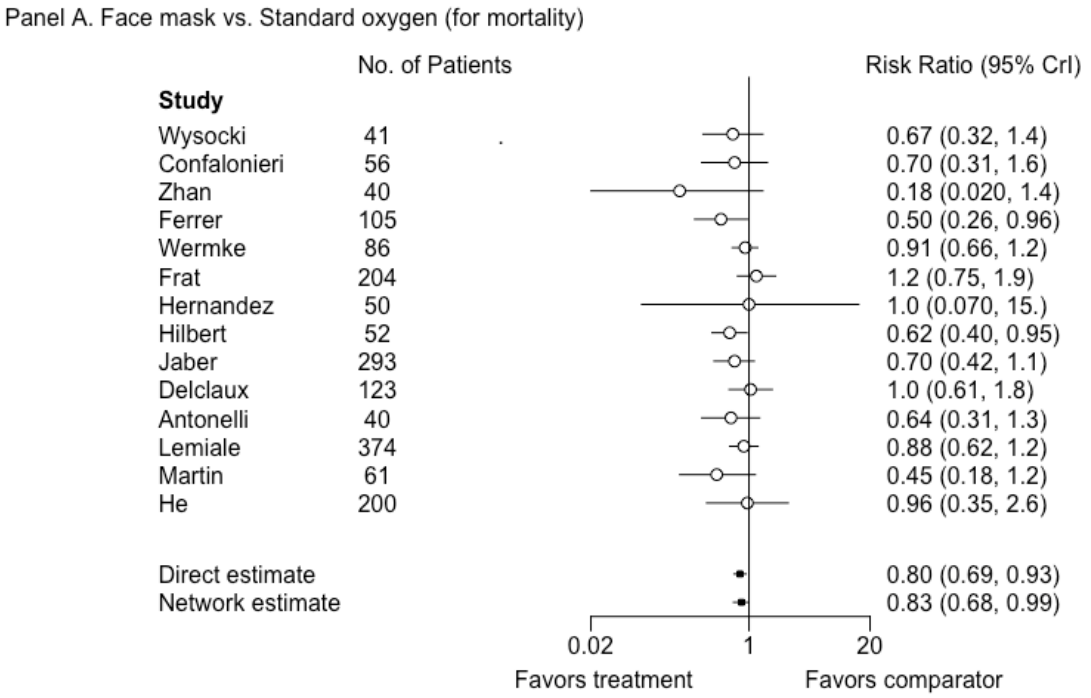
a. Based on GRADE criteria

Tau: 0.17 (95%CrI: 0.056 - 0.23)

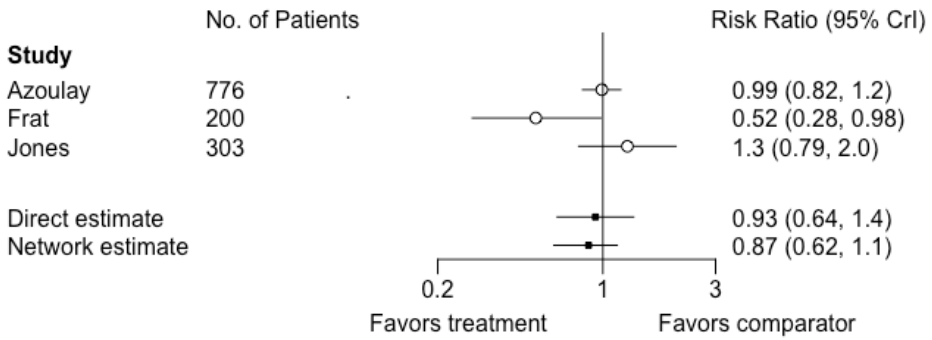
Tau2: 0.0284 (95%CrI: 0.00317 – 0.0508); I2=12%.

Helmet: helmet noninvasive ventilation, Face mask: face mask noninvasive ventilation.

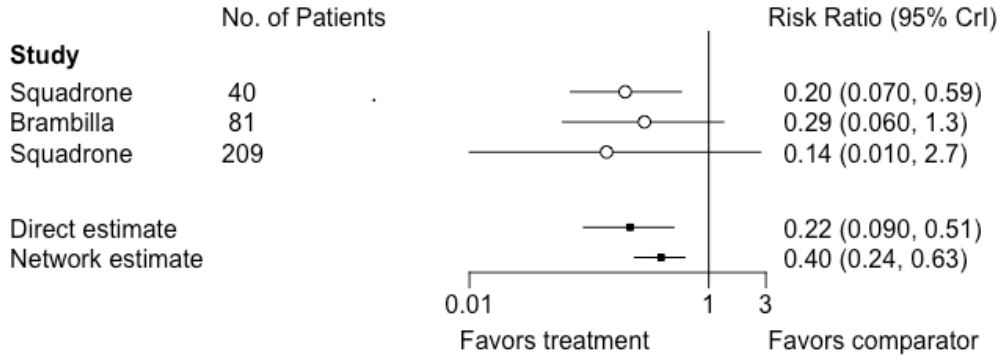
Cumulative incidence of mortality in standard oxygen arm: 30%.



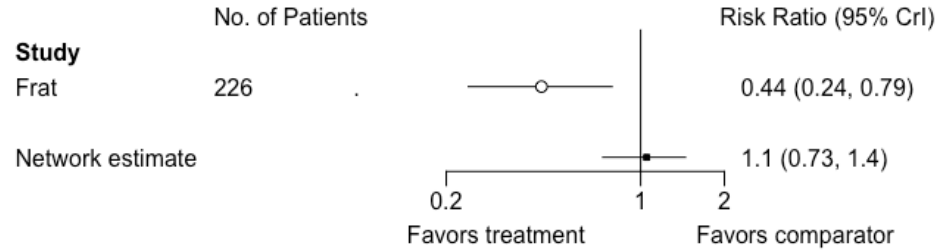
Panel B. High flow vs. Standard Oxygen (for mortality)



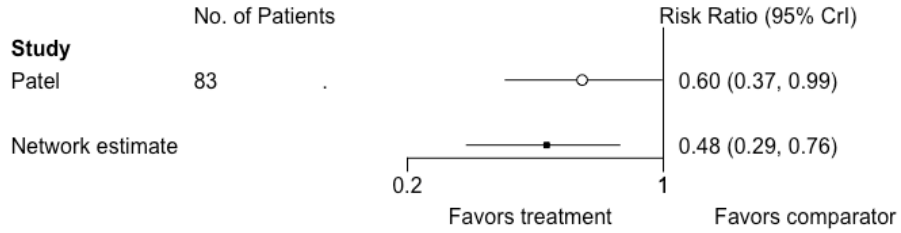
Panel C. Helmet vs. Standard Oxygen (for mortality)



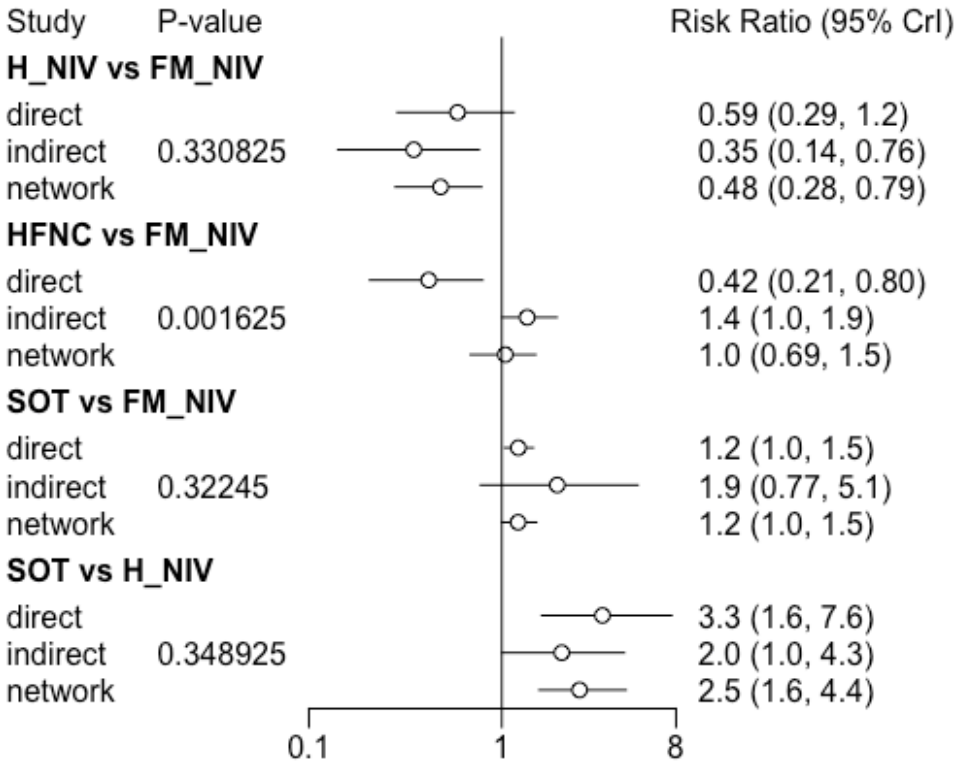
Panel D. High flow vs. Face mask (for mortality)



Panel E. Helmet vs. Face mask (for mortality)



eFigure 3. Results of incoherence assessment for all-cause mortality[1]



H_NIV: helmet noninvasive ventilation, FM_NIV: face mask noninvasive ventilation, HFNC: high-flow nasal oxygen, SOT: standard oxygen therapy.

1. The node split analysis does not include the comparison between high flow nasal oxygen and standard oxygen given that there was not enough indirect evidence to derive a precise estimate for the outcome of mortality.

eFigure 4. Rank probabilities for each treatment strategy to decrease the risk of all-cause mortality.

	Rank 1	Rank 2	Rank 3	Rank 4
FM_NIV	0.1	61.2	37.2	1.5
H_NIV	99.6	0.4	0.0	0.0
HFNC	0.4	38.0	46.9	14.6
SOT	0.0	0.4	15.8	83.9

H_NIV: helmet noninvasive ventilation, FM_NIV: face mask noninvasive ventilation
HFNC: high-flow nasal oxygen, SOT: standard oxygen therapy.

eTable 2. Summary of evidence grading for all comparison and primary and secondary outcome.

		All-cause mortality			Intubation		
		Direct	Indirect	NMA	Direct	Indirect	NMA
Helmet	SOT	Low	Low	Low	Low	Low	Low
Helmet	FM	Low	Low	Low	Low	Low	Low
Helmet	HFNC	N/A	Low	Low	N/A	Low	Low
FM	SOT	Moderate	Low	Moderate	Low	Moderate	Moderate
HFNC	SOT	Low	Moderate	Moderate	Moderate	Low	Moderate
HFNC	FM	High	Low	Low[1]	Moderate	Low	Low[1]

N/A: not available (e.g., no direct comparison). Helmet: helmet noninvasive ventilation, FM: face mask noninvasive ventilation, SOT: standard oxygen therapy, HFNC: high-flow nasal oxygen.

1. Due to incoherence

eTable 3. Individual study risk of bias for endotracheal intubation

Name (year)	Randomization generation	Allocation concealment	Blinding	Incomplete data	Selective reporting	Other	Overall risk of bias
Wysocki (1995)	LOW	LOW	HIGH	LOW	LOW	LOW	UNCLEAR
Confalonieri (1999)	LOW	LOW	HIGH	LOW	LOW	LOW	UNCLEAR
Squadrone (2010)	LOW	LOW	HIGH	LOW	LOW	LOW	UNCLEAR
Brambilla (2014)	PL	PL	HIGH	LOW	LOW	LOW	HIGH
Doshi (2018)	LOW	LOW	HIGH	PL	LOW	LOW	HIGH
Zhan (2012)	LOW	LOW	HIGH	LOW	LOW	LOW	UNCLEAR
Lemiale (2015)	LOW	LOW	HIGH	LOW	LOW	LOW	UNCLEAR
Azevedo (2015)	PL	PL	HIGH	PH	PL	PL	HIGH
Ferrer (1999)	LOW	LOW	HIGH	LOW	LOW	LOW	UNCLEAR
Azoulay (2018)	LOW	LOW	HIGH	LOW	LOW	LOW	UNCLEAR
Bell (2015)	LOW	LOW	HIGH	LOW	LOW	LOW	UNCLEAR
Wermcke (2011)	LOW	LOW	HIGH	PL	LOW	LOW	HIGH
Frat (2015)	LOW	LOW	HIGH	LOW	LOW	LOW	UNCLEAR
Hernandez (2010)	LOW	LOW	HIGH	LOW	LOW	LOW	UNCLEAR
Hilbert (2001)	LOW	LOW	HIGH	LOW	LOW	LOW	UNCLEAR
Jaber (2016)	LOW	LOW	HIGH	LOW	LOW	LOW	UNCLEAR
Delclaux (2000)	LOW	LOW	HIGH	LOW	LOW	LOW	UNCLEAR
Squadrone (2005)	LOW	LOW	HIGH	LOW	LOW	LOW	UNCLEAR
Antonelli (2000)	LOW	LOW	HIGH	LOW	LOW	LOW	UNCLEAR
Jones (2016)	LOW	LOW	HIGH	PH	LOW	LOW	HIGH
Lemiale (2015)	LOW	LOW	HIGH	LOW	LOW	LOW	UNCLEAR
Martin (2000)	PL	PL	HIGH	LOW	LOW	LOW	HIGH
Patel (2016)	LOW	LOW	HIGH	LOW	LOW	LOW	UNCLEAR
Cosentini (2010)	LOW	LOW	HIGH	LOW	LOW	LOW	UNCLEAR
He (2019)	LOW	LOW	HIGH	LOW	HIGH	LOW	HIGH

PL: probably low, PH: probably high

eFigure 5. Estimated association of different comparisons with endotracheal intubation risk at longest available follow-up up to 30 days

Comparison	Network Relative Risk (95% Credible Interval)	Network Risk difference (95% Credible Interval)	Number of trials and participants in direct comparison	Quality of Evidence[a]
Helmet vs. Standard Oxygen	0.26 (0.14 – 0.46)	-0.32 (-0.60 to -0.16)	3 trials, 330 patients	Low
Face mask vs. Standard Oxygen	0.76 (0.62 – 0.90)	-0.12 (-0.25 to -0.05)	14 trials, 1725 patients	Moderate
High-flow nasal oxygen vs. Standard Oxygen	0.76 (0.55 – 0.99)	-0.11 (-0.27 to -0.01)	5 trials, 1479 patients	Moderate
Helmet vs. High-flow nasal oxygen	0.35 (0.18 – 0.66)	-0.20 (-0.43 to -0.08)	No head to head comparison	Low
Helmet vs. Face mask	0.35 (0.19 – 0.61)	-0.20 (-0.40 to -0.09)	1 trial, 83 patients	Low
Face mask vs. High-flow nasal oxygen	1.01 (0.74 – 1.38)	0.00 (-0.13 to 0.10)	3 trials, 450 patients	Low

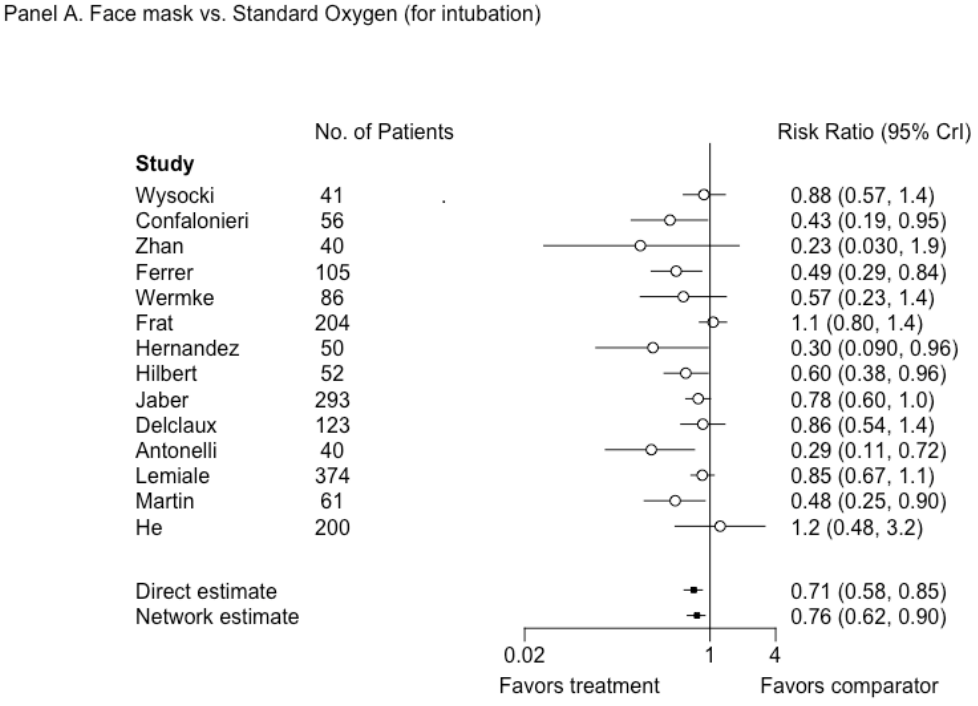
a. Based on GRADE criteria

Tau: 0.21 (95%CrI: 0.07 - 0.27)

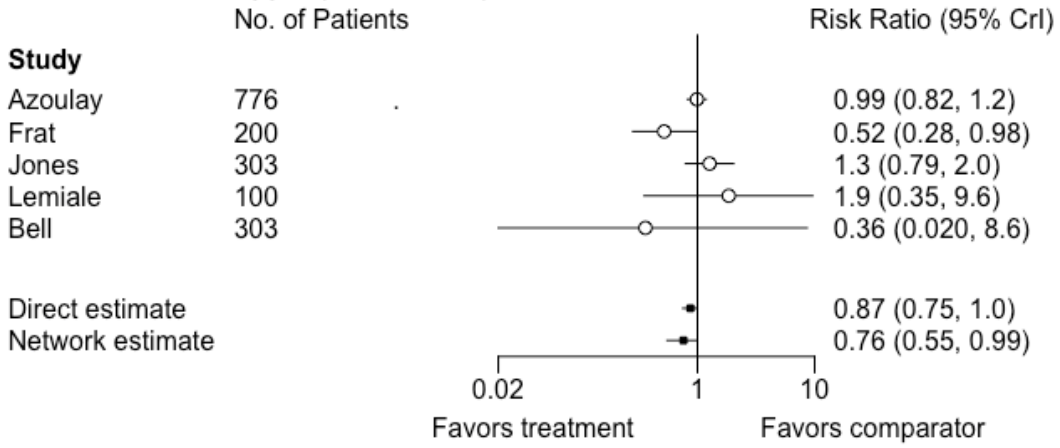
Tau2: 0.0437 (95% CrI: 0.00554 – 0.0743), I2=15%.

Helmet: helmet noninvasive ventilation, Face mask: face mask noninvasive ventilation.

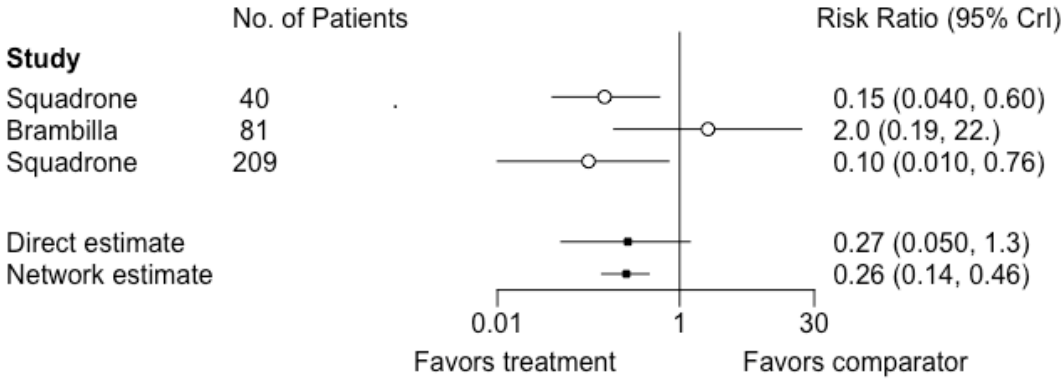
Cumulative incidence of intubation in standard oxygen arm: 40%



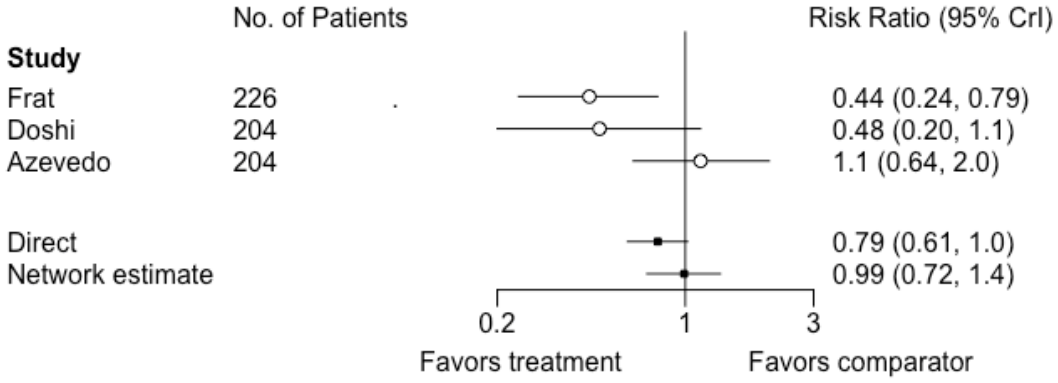
Panel B. High flow vs. Standard Oxygen (for intubation)



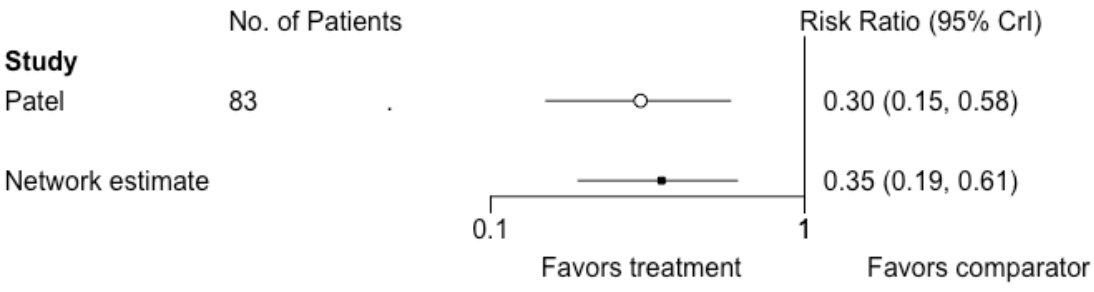
Panel C. Helmet vs. Standard Oxygen (for intubation)



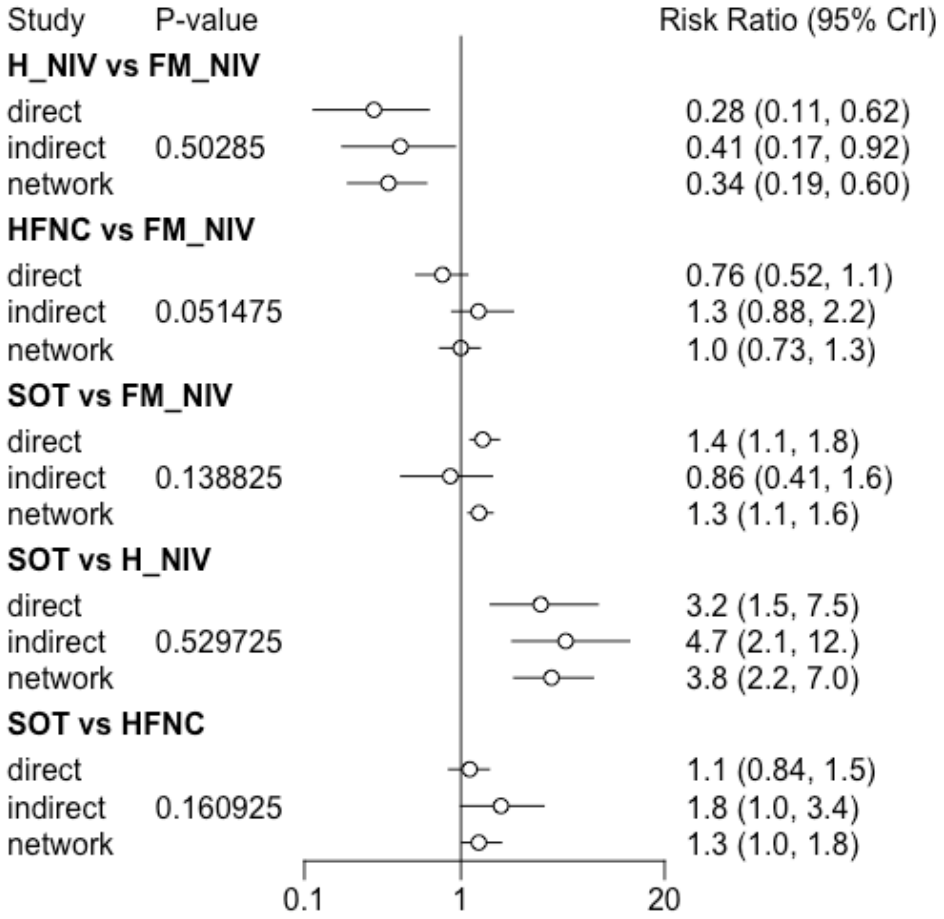
Panel D. High flow vs. Face mask (for intubation)



Panel E. Helmet vs. Face mask (for intubation)



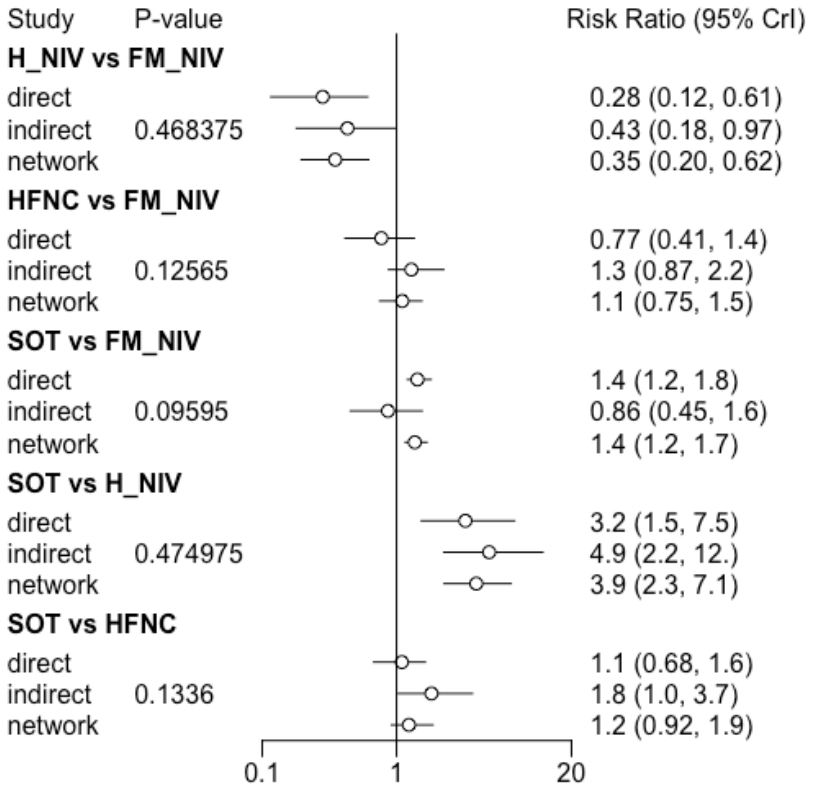
eFigure 6. Results of incoherence assessment for endotracheal intubation (node-splitting models)



H_NIV: helmet noninvasive ventilation, FM_NIV: face mask noninvasive ventilation, HFNC: high-flow nasal oxygen, SOT: standard oxygen therapy.

eFigure 7. Potential sources of incoherence

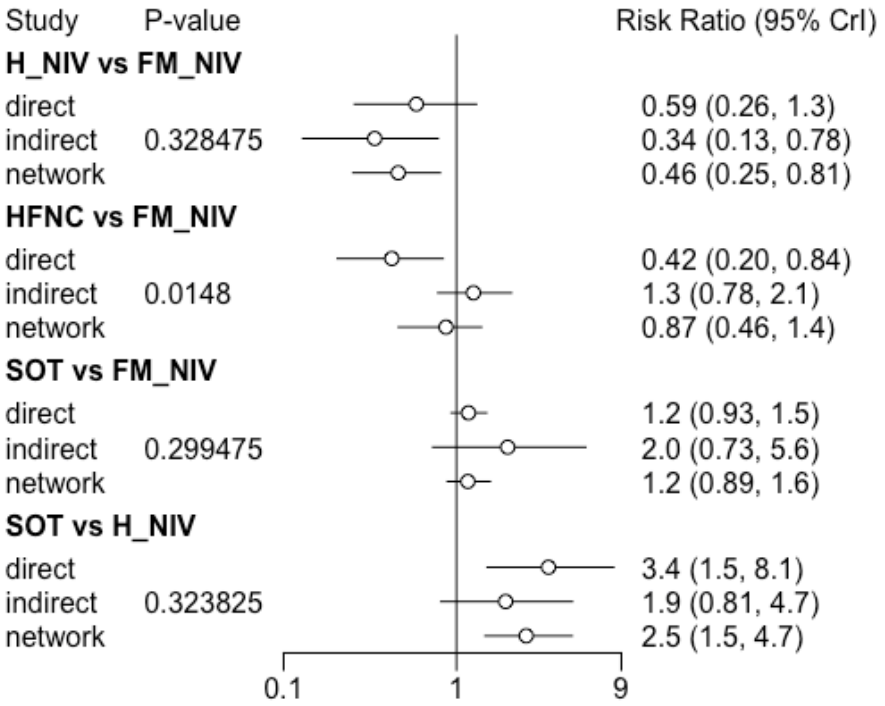
Node-splitting analysis (for intubation)[1] excluding the study by Frat et. al.



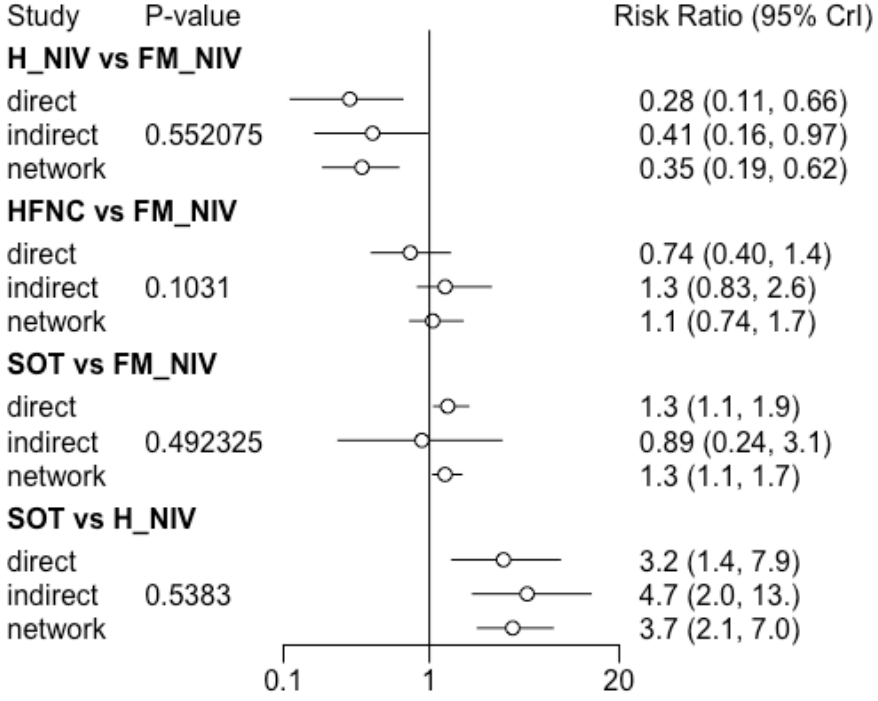
1. Not done for all-cause mortality since no other FM_NIV HFNC direct comparisons available.
H_NIV: helmet noninvasive ventilation, FM_NIV: face mask noninvasive ventilation, HFNC: high-flow nasal oxygen, SOT: standard oxygen therapy.
Model fit - DIC: 82.2, Residual Deviance: 52.8, 46 data points.

Node-splitting analysis (for intubation and mortality) excluding studies with at least one patient with COPD or CHF.

Mortality

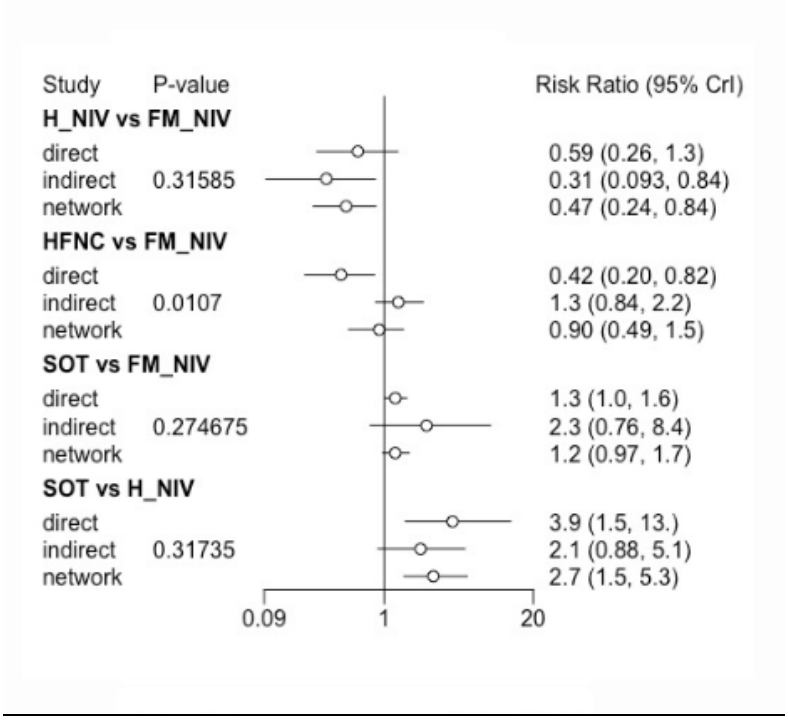


Intubation

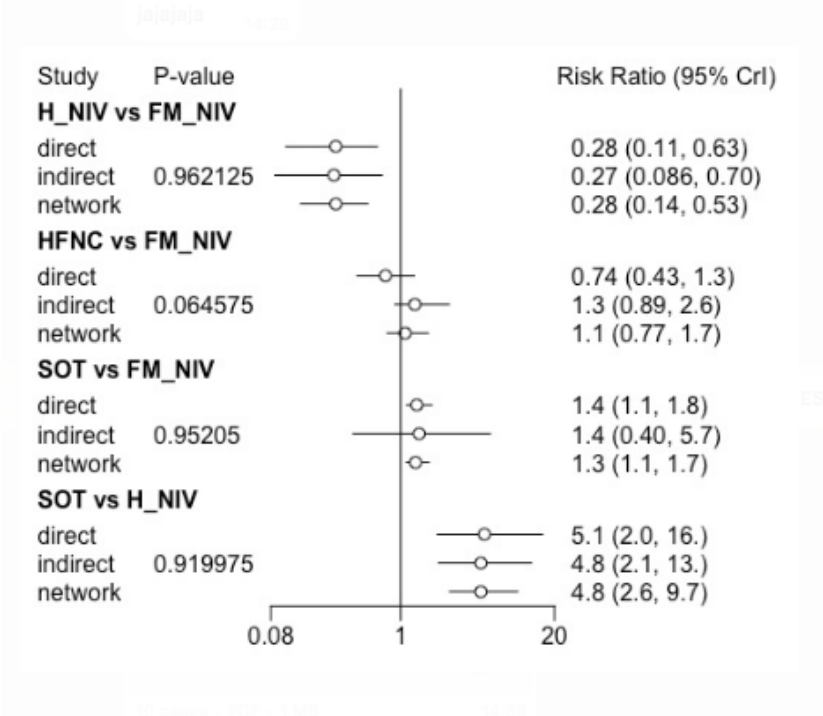


Node-splitting analysis (for intubation and mortality) excluding studies with high risk of bias.

Mortality



Intubation

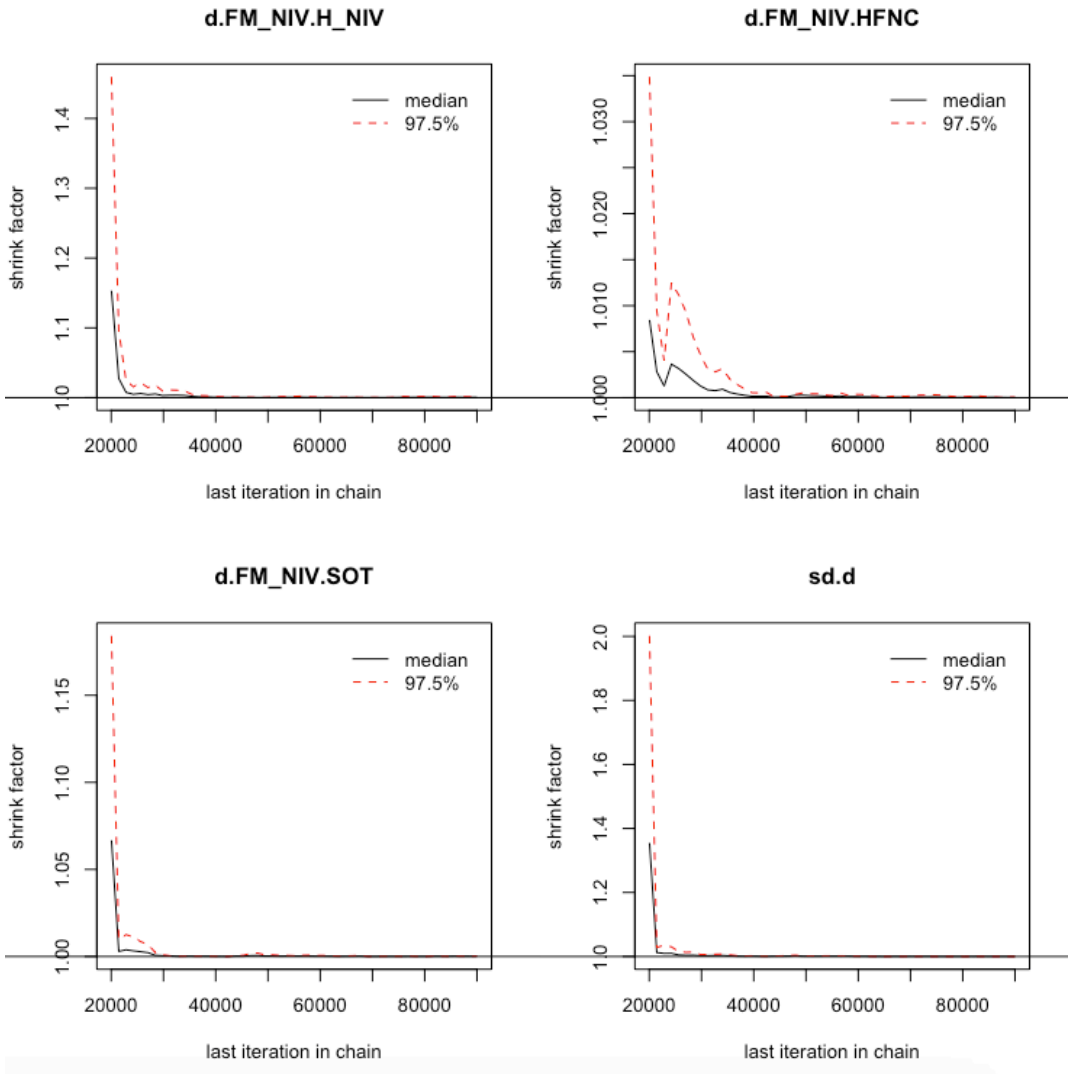


eFigure 8. Rank probabilities for each treatment strategy to decrease the risk of endotracheal intubation.

	Rank 1	Rank 2	Rank 3	Rank 4
FM_NIV	0.0	48.3	51.6	0.1
H_NIV	99.9	0.1	0.0	0.0
HFNC	0.1	51.6	45.9	2.4
SOT	0.0	0.0	2.5	97.5

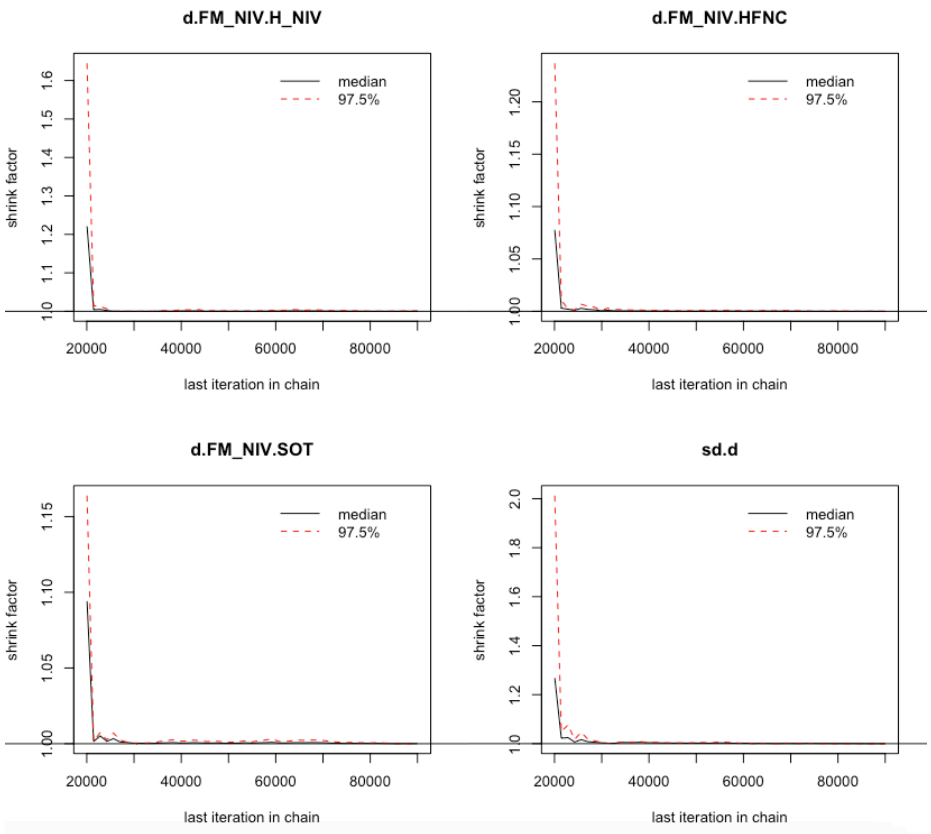
H_NIV: helmet noninvasive ventilation, FM_NIV: face mask noninvasive ventilation
HFNC: high-flow nasal oxygen, SOT: standard oxygen therapy.

eFigure 9. Gelman plots for model convergence for all-cause mortality



H_NIV: helmet noninvasive ventilation, FM_NIV: face mask noninvasive ventilation, HFNC: high-flow nasal oxygen, SOT: standard oxygen therapy.

eFigure 10. Gelman plots for model convergence for endotracheal intubation



H_NIV: helmet noninvasive ventilation, FM_NIV: face mask noninvasive ventilation, HFNC: high-flow nasal oxygen, SOT: standard oxygen therapy.

eTable 4. Assessment of model fit for primary and secondary outcome

Mortality

Model fit characteristic	
Residual deviance	45.2
Leverage	26.3
Deviance information criterion	71.5
Number of data points	41

Intubation

Model fit characteristic	
Residual deviance	56.5
Leverage	32.1
Deviance information criterion	88.6
Number of data points	49

eTable 5. Median length of stay by treatment group[1]

Treatment group	ICU length of stay, days (95% Credible Interval)	Hospital length of stay, days (95% Credible Interval)
Standard oxygen	8.3 (6.1 – 10.6)	18.8 (14.3 – 23.3)
High-flow nasal oxygen	7.5 (2.5 – 15.2)	16.6 (8.5 – 22.2)
Face mask noninvasive ventilation	7.0 (4.5 – 10.2)	16.5 (11.4 – 20.6)
Helmet noninvasive ventilation	7.2 (2.0 – 14.0)	15.6 (11.5 – 21.1)

1. No significant difference was observed between groups. Based on a network metanalysis for continuous outcomes using pcnetmeta package.

ICU LOS data available for: Antonelli, Azoulay, Confalonieri, Cosentini, Doshi, Ferrer, Hernandez, Hilbert, Jaber, Lemiale 2015, Patel, Squadrone 2005, Wysocki, Zhan.

Hospital LOS data available for: Azoulay, Brambilla, Confalonieri, Cosentini, Doshi, Ferrer, Hernandez, Jaber, Jones, Lemiale 2015, Patel, Squadrone 2005, Zhan.

ICU: intensive care unit.

eTable 6. Summary of sensitivity analysis for the association of all interventions (versus standard oxygen) with all-cause mortality

Type of Analysis	Helmet vs SOT	Face Mask vs SOT	High-flow vs SOT
All patients – Main analysis	0.40 (0.24-0.63)	0.83 (0.68-0.99)	0.87 (0.62-1.15)
Non-informative priors for tau	0.39 (0.22-0.64)	0.82 (0.66-1.00)	0.86 (0.58-1.18)
Immunocompromised patients	0.38 (0.22-0.61)	0.78 (0.61-0.97)	0.99 (0.67-1.46)
Mean P/F Ratio < 200	0.47 (0.25-0.88)	0.83 (0.65-1.04)	0.76 (0.47-1.08)
Excluding studies with CHF/AECOPD patients	0.40 (0.24-0.65)	0.86 (0.68-1.09)	0.77 (0.48-1.08)
Excluding studies with postoperative patients	0.40 (0.24-0.65)	0.84 (0.68-1.01)	0.86 (0.61-1.15)
In-hospital mortality	0.37 (0.21-0.61)	0.83 (0.67-1.03)	0.86 (0.59-1.16)
Including studies with low risk of bias	0.38 (0.21-0.65)	0.81 (0.64-0.99)	0.76 (0.47-1.07)

Face mask: face mask non-invasive ventilation, Helmet: helmet non-invasive ventilation, high flow: high-flow nasal oxygen, SOT: standard oxygen therapy, P/F ratio: PaO2 / FiO2 ratio, CHF: congestive heart failure, AECOPD: acute exacerbation of chronic obstructive pulmonary disease.

eTable 7. Summary of sensitivity analysis for the association of all interventions (versus standard oxygen) with endotracheal intubation

Type of Analysis	Helmet vs SOT	Face Mask vs SOT	High-flow vs SOT
All patients – Main analysis	0.26 (0.14-0.46)	0.76 (0.62-0.90)	0.76 (0.55-0.99)
Non-informative priors for tau	0.26 (0.14-0.46)	0.77 (0.62-0.90)	0.77 (0.55-0.99)
Immunocompromised patients	0.20 (0.10-0.38)	0.70 (0.49-0.93)	0.95 (0.59-1.84)
Mean P/F Ratio < 200	0.30 (0.13-0.73)	0.72 (0.55-0.90)	0.81 (0.54-1.28)
Excluding studies with CHF/AECOPD patients	0.26 (0.14-0.47)	0.77 (0.60-0.95)	0.82 (0.58-1.21)
Excluding studies with postoperative patients	0.27 (0.14-0.52)	0.74 (0.59-0.90)	0.74 (0.52-1.01)
Including studies with low risk of bias	0.21 (0.10-0.39)	0.74 (0.58-0.90)	0.81 (0.57-1.18)

Face mask: face mask non-invasive ventilation, Helmet: helmet non-invasive ventilation, High flow: high-flow nasal oxygen, SOT: standard oxygen therapy, P/F ratio: PaO2 / FiO2 ratio, CHF: congestive heart failure, AECOPD: acute exacerbation of chronic obstructive pulmonary disease.

eTable 8 Sensitivity analysis with informative priors[1] for all-cause mortality.

	Non-informative priors (main analysis)	*Informative priors[2]*
Comparison	Relative Risk (95% Credible Interval)	Relative Risk (95% Credible Interval)
Face mask vs. Helmet	2.09 (1.32 – 3.44)	2.24 (1.34 – 4.05)
Face mask vs. High flow nasal cannula	0.95 (0.69 – 1.37)	1.23 (0.91 – 1.82)
Face mask vs. Standard Oxygen	0.83 (0.68 – 0.99)	0.93 (0.77 – 1.14)
Helmet vs. High flow nasal cannula	0.46 (0.26 – 0.80)	0.55 (0.30– 1.04)
Helmet vs. Standard Oxygen	0.40 (0.24 – 0.63)	0.41 (0.23 – 0.70)
High flow nasal cannula vs. Standard Oxygen	0.87 (0.62 – 1.15)	0.76 (0.52 – 1.01)

1. Based on data from Bellami et al, Frat et al, Golligher et al.
2. Strongly optimistic for high-flow nasal oxygen and pessimistic for face mask noninvasive ventilation.

eTable 9. Sensitivity analysis with informative priors[1] for intubation.

	Non-informative priors (main analysis)	*Informative priors*[2]
Comparison	Relative Risk (95% Credible Interval)	Relative Risk (95% Credible Interval)
Face mask vs. Helmet	2.92 (1.64 – 5.35)	3.06 (1.74 – 5.62)
Face mask vs. High flow nasal cannula	1.01 (0.74 – 1.38)	1.16 (0.92 – 1.61)
Face mask vs. Standard Oxygen	0.76 (0.62 – 0.90)	0.84 (0.71 – 1.01)
Helmet vs. High flow nasal cannula	0.35 (0.18 – 0.66)	0.38 (0.20 – 0.74)
Helmet vs. Standard Oxygen	0.26 (0.14 – 0.46)	0.27 (0.15 – 0.49)
High flow nasal cannula vs. Standard Oxygen	0.76 (0.55 – 0.99)	0.72 (0.52 – 0.91)

1. Based on data from Bellami et al, Frat et al, Golligher et al.
2. Strongly optimistic for high-flow nasal oxygen and pessimistic for face mask noninvasive ventilation.

eReferences

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