Supplementary file

Nasal versus Oronasal Masks for Home Non-Invasive Ventilation in patients with chronic hypercapnia.

A systematic review and individual participant data meta-analysis

M. Lebret, A. Léotard, JL. Pépin, W. Windisch, E. Ekkernkamp, M. Pallero, MÁ. Sánchez-Quiroga, N. Hart, J. Kelly, M. Patout, GC. Funk, ML. Duiverman, JF. Masa, A. Simonds, P. B Murphy, PJ. Wijkstra, M. Dreher, J. Storre, C. Khouri and JC. Borel

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Search equation for Medline:

("Noninvasive Ventilation"[Mesh] OR NIV OR nppv OR nipp OR nippv OR noninvasive positive pressure ventilation) AND ("Respiratory Insufficiency"[Mesh] OR "Pulmonary Disease, Chronic Obstructive"[Mesh] OR "Respiratory failure" OR "Obesity Hypoventilation Syndrome"[Mesh] OR copd OR OHS) AND ("Randomized Controlled Trial"[Publication Type] OR randomised trial OR randomized trial OR controlled trial)

Publication dates: from 1994/01/01

Search equation for CENTRAL:

#1 MeSH descriptor: [Noninvasive Ventilation] explode all trees
#2 NIV
#3 NPPV
#4 NiPPV
#5 NiPP
#6 noninvasive positive pressure ventilation
#7 MeSH descriptor: [Respiratory Insufficiency] explode all trees
#8 MeSH descriptor: [Pulmonary Disease, Chronic Obstructive] explode all trees
#9 MeSH descriptor: [Obesity Hypoventilation Syndrome] explode all trees
#10 Respiratory failure
#11 COPD
#12 OHS
#13 MeSH descriptor: [Randomized Controlled Trial] explode all trees
#14 Randomised trial
#15 Randomized trial
#16 Controlled trial
#17 (#1 OR #2 OR #3 OR #4 OR #5 OR #6) AND (#7 OR #8 #9 OR #10 OR #11 OR #12) AND (#13 OR #14 OR #15 OR #16)

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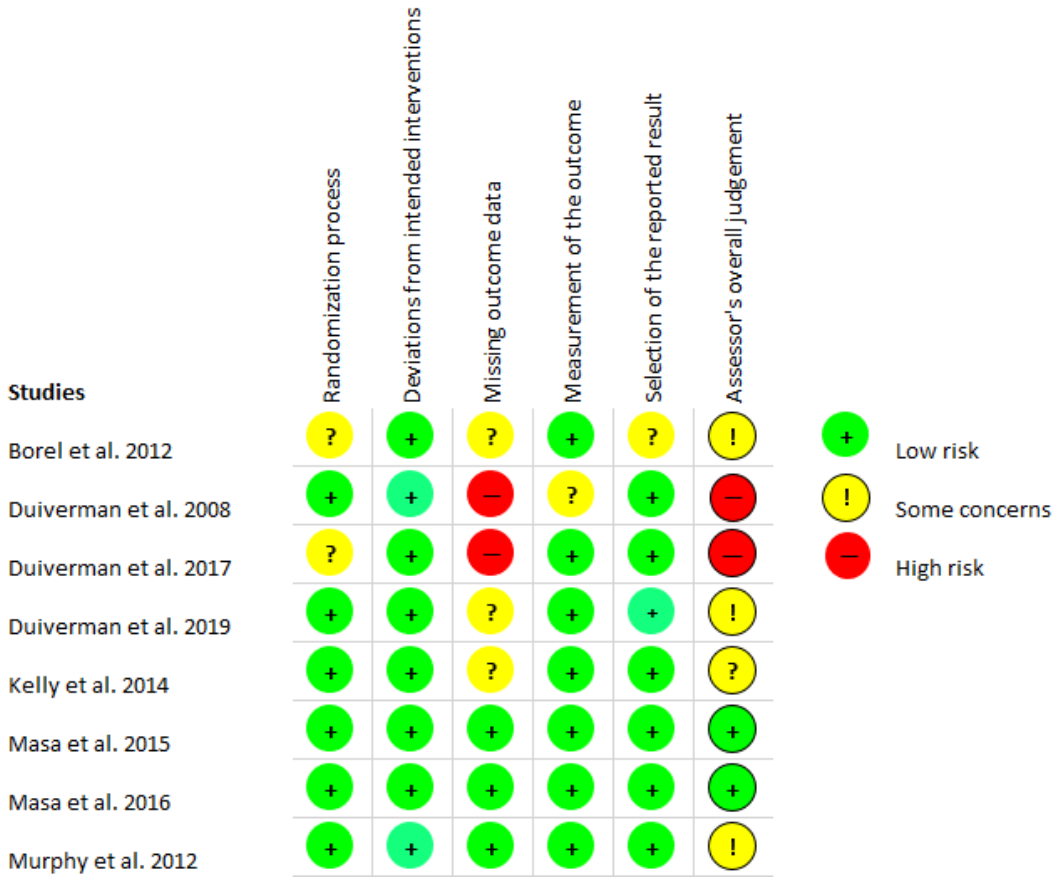
Detailed risk of bias analysis



e-figure 1. Detailed risk of bias analysis using the revised tool for assessing risk of bias in randomized trials.

Baseline characteristics of the IPD in each study included in the meta-analysis

e-table 1. Baseline characteristics of the IPD in each study included in the meta-analysis

Study	Type of mask used, No(%)	Female, No(%)	Age, mean (SD), y	BMI [a], mean (SD)	FEV1, mean (SD), L	FVC, mean (SD), L	PaCO2, mean (SD), mmHg	PaO2, mean (SD), mmHg
Borel et al. (2012)	Nasal, 4(31)	9 (53)	57·3 (10·7)	39·7 (6·44)	2·23 (0·72)	2·82 (0·96)	47·9 (4·21)	73·8 (8·97)
	Oronasal, 9(69)							
Diuverman et al. (2019)	Nasal, 4(7)	40 (60)	63·3 (7·80)	25·3 (5·09)	0·59 (0·19)	2·05 (0·62)	55·4 (7·56)	52·7 (11·6)
	Oronasal, 57(93)							
Kelly et al. (2014)	Nasal, 2(18)	5 (45)	50·7 (13·1)	45·4 (14·6)	1·52 (0·84)	2·24 (0·93)	50·4 (5·31)	62·7 (11·0)
	Oronasal, 9(82)							
Diuverman et al. (2017)	Nasal, 4(29)	9 (64)	68·4 (8·42)	25·4 (5·75)	0·76 (0·37)	2·97 (0·92)	53·5 (8·02)	64·8 (9·57)
	Oronasal, 10(71)							
Diuverman et al. (2008)	Nasal, 11(35)	13 (41)	63·3 (9·85)	27·1 (6·41)	0·83 (0·37)	2·74 (0·82)	51·0 (4·79)	59·2 (8·42)
	Oronasal, 20(65)							
Masa et al. (2015)	Nasal, 5(7)	46 (65)	63·8 (10·5)	43·1 (6·63)	2·30 (0·76)	2·83 (0·94)	50·9 (4·32)	61·6 (8·71)
	Oronasal, 66(93)							
Masa et al. (2016)	Nasal, 7(19)	27 (75)	64·8 (10·4)	41·0 (5·45)	2·14 (0·70)	2·66 (0·89)	50·6 (4·26)	64·4 (10·5)
	Oronasal, 32(82)							
Murphy et al. (2012)	Nasal, 4(8)	23 (46)	54·8 (10·6)	50·8 (7·98)	1·70 (0·71)	2·13 (0·85)	51·8 (5·49)	65·8 (11·4)
	Oronasal, 46(92)							
Overall	Nasal, 41(14)	164 (57)[b]	61·8 (10·7)	27·1 (8·9)	1·6 (0·9)	2·2 (8)	50·9 (6·4)	61·2 (11·7)
	Oronasal, 249(86)							

a - Calculated as weight in kilograms divided by height in meters squared.
b - 3 patients had missing data
PaCO2: Partial pressure of carbon dioxide; PaO2: Partial pressure of oxygen; FVC: Forced Vital Capacity; FEV1; Forced Expiratory Volume in the first second; BMI: Body Mass Index; SD: Standard Deviation

Grading of Recommendations, Assessment, Development and Evaluations (GRADE)

We GRADEd each interaction estimates according to the following criteria.

(1) Study limitations: we estimated the risk of bias as low, moderate, or high for each study using the Cochrane RoB2. We rated the body of evidence at the outcome level according to the risk of bias.

(2) Inconsistency: we downgraded for inconsistency if substantial heterogeneity (I^2>50%) or if CI of effect size did not overlap.

(3) Indirectness: we downgraded for indirectness if trial characteristics (duration of follow-up, design) or etiology/population differed significantly.

(4) Imprecision: we downgraded for impression if CI of the overall results were superior to minimal differences (non-inferiority margins), that we defined for each outcome and if the optimal information size was not reached.

(5) Publication bias: we systematically downgraded for publication bias given that we did not get access to all selected data in this individual patient meta-analysis

	Number of studies	Number of patients	Heterogeneity	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence
PaC02	8	266	50%	No serious risk of bias (High certainty)	No serious inconsistency (High certainty)	Serious indirectness (Low certainty)	Serious imprecision IOS=544 (Low certainty)	Strongly suspected (Low certainty)	VERY LOW ○○○⊗
Pa02	7	255	71%	No serious risk of bias (High certainty)	No serious inconsistency (Low certainty)	Serious indirectness (Low certainty)	Serious imprecision IOS=544 (Low certainty)	Strongly suspected (Low certainty)	VERY LOW ○○○⊗
Compliance	8	262	4%	No serious risk of bias (High certainty)	No serious inconsistency (High certainty)	Serious indirectness (Low certainty)	Serious imprecision IOS=544 (Low certainty)	Strongly suspected (Low certainty)	VERY LOW ○○○⊗
EPAP	8	269	0%	No serious risk of bias (High certainty)	No serious inconsistency (High certainty)	Serious indirectness (Low certainty)	Serious imprecision IOS=544 (Low certainty)	Strongly suspected (Low certainty)	VERY LOW ○○○⊗
IPAP	8	238	24%	No serious risk of bias (High certainty)	No serious inconsistency (High certainty)	Serious indirectness (Low certainty)	Serious imprecision IOS=544 (Low certainty)	Strongly suspected (Low certainty)	VERY LOW ○○○⊗

e-table 2 GRADE assessment of overall and subgroup analysis. *Optimal Information Size (OIS); EPAP: Expiratory Positive Airway Pressure; IPAP: Inspiratory Positive Airway Pressure; PaCO2: partial pressure of CO2; PaO2: partial pressure of O2.*

Summary of mixed model results

Outcome	Model	N (subjects, studies)	Mean difference oronasal minus nasal (95% CI)	p-value
PaCO2	Crude model	266· 8	1·34 (-2·07· 4·76)	0·46
	Adjusted model	252· 8	0·61 (-2·15· 3·38)	0·68
PaO2	Crude model	255· 7	-0·89 (-5·28· 3·50)	0·70
	Adjusted model	242· 7	-0·00 (-4·59· 4·58)	1·00
Compliance	Crude model	262· 8	0·39 (-0·59· 1·37)	0·44
	Adjusted model	257· 8	0·29 (-0·74· 1·32)	0·58
EPAP	Crude model	269· 8	0·02 (-0·67· 0·71)	0·95
	Adjusted model	220· 7	-0·36 (-1·08· 0·36)	0·33
IPAP	Crude model	238· 8	1·87 (0·44· 3·30)	**0·01**
	Adjusted model	220· 7	1·42 (-0·04· 2·88)	0·06

e-table 3. Summary of mixed model results. *EPAP: Expiratory Positive Airway Pressure; IPAP: Inspiratory Positive Airway Pressure; PaCO2: partial pressure of CO2; PaO2: partial pressure of O2.*

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Interaction between type of mask and the underlying pathology

Outcome	Model	Population	N (subjects-studies)	Mean difference oronasal minus nasal (95% CI)	p-value
PaCO2	Interaction mask*pathology	Whole population	252- 8	-5·19 (-9·65· -0·72)	0·06
		OHS	167- 5	-1.03 (-4.36, 2.29)	0.56
		COPD	85- 4	3.29 (0.22, 6.35)	0.08
PaO2	Interaction mask*pathology	Whole population	242- 7	7·32 (-0·52· 15·15)	0·12
		OHS	159- 4	2.97 (-2.92, 8.87)	0.39
		COPD	83- 3	-4.36 (-10.26, 1.54)	0.23
Compliance	Interaction mask*pathology	Whole population	257- 8	0·93 (-1·47· 3·34)	0·48
		OHS	172- 5	0.67 (-0.69, 2.03)	0.34
		COPD	85- 4	-0.50 (-2.05, 1.05)	0.61
EPAP	Interaction mask*pathology	Whole population	220- 7	-0·22 (-1·64· 1·20)	0·76
		OHS	137- 4	-0.46 (-1.57, 0.65)	0.42
		COPD	83- 3	-0.25 (-1.07, 0.56)	0.54
IPAP	Interaction mask*pathology	Whole population	220- 7	-1·15 (-4·02· 1·72)	0·43
		OHS	137- 4	0.67 (-1.26, 2.59)	0.50
		COPD	83- 3	2.31 (-0.01, 4.63)	0.06

e-table 4. Interaction between type of mask and the underlying pathology and marginal means in mixed effect models according to the underlying pathology and the type of mask. *EPAP: Expiratory Positive Airway Pressure; IPAP: Inspiratory Positive Airway Pressure; PaCO2: partial pressure of CO2; PaO2: partial pressure of O2*

Sensitivity analysis according to risk of bias

Outcome	*N (subjects-studies)*	*Mean difference oronasal minus nasal (95% CI)*	*p-value*
PaCO2	216- 6	0.49 (-3.71, 4.71)	0.82
PaO2	206- 5	1.26 (-4.54, 7.07)	0.69
Compliance	221- 6	0.63 (-0.67, 1.94)	0.34
EPAP	188- 6	-0.47 (-1.39, 0.44)	0.31
IPAP	188- 6	1.16 (-0.49, 2.82)	0.17

e-table 5 sensitivity analysis including moderate to low risk of bias trials

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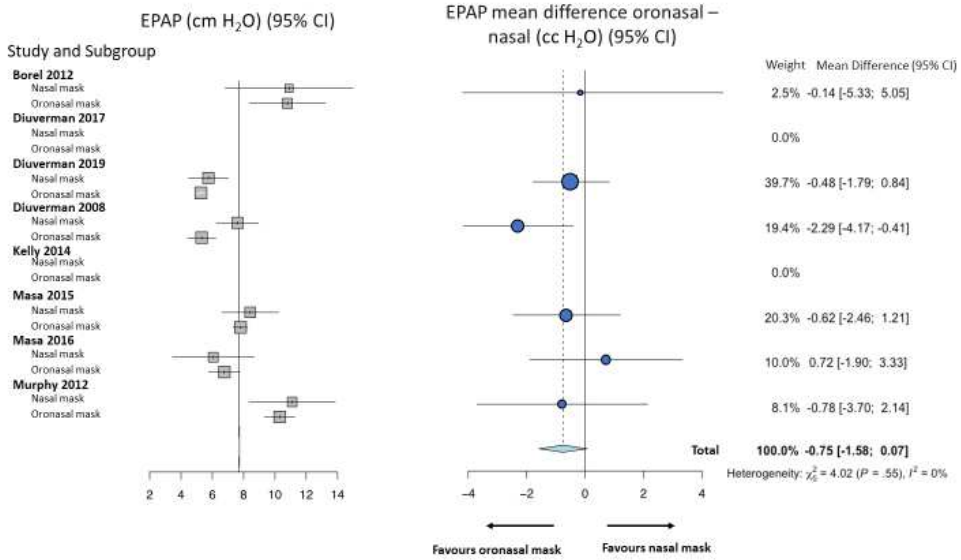
Interaction between type of mask and the duration of follow-up

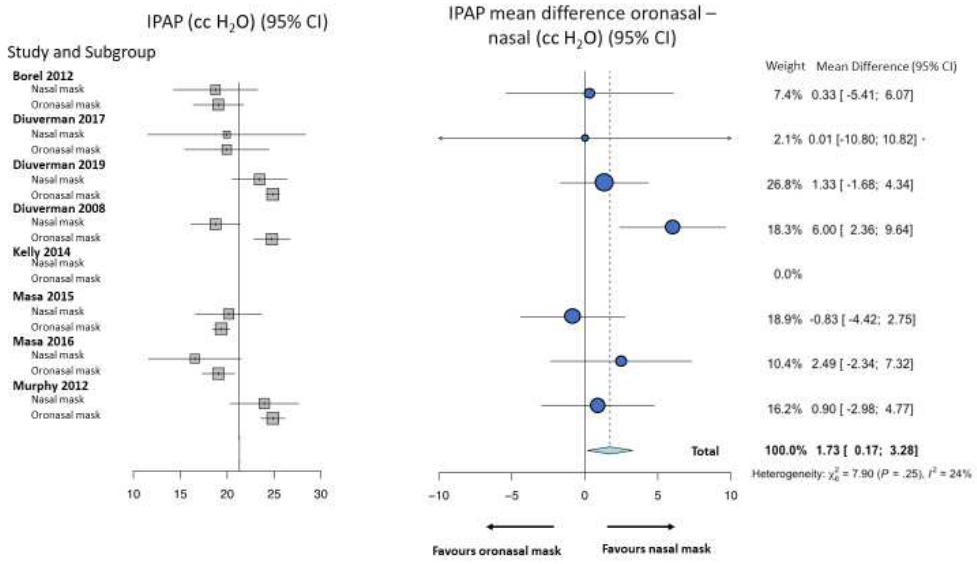
Outcome	*Model*	*N (subjects-studies)*	*Mean difference oronasal minus nasal (95% CI)*	*p-value*
PaCO2	Interaction mask* duration of follow-up	252- 8	10.81 (-6.68, 28.31)	0.25
PaO2	Interaction mask* duration of follow-up	242- 7	-21.02 (-50.13, 8.10)	0.20
Compliance	Interaction mask* duration of follow-up	257- 8	-4.07 (-11.76, 3.61)	0.32
PEP	Interaction mask* duration of follow-up	220- 7	-0.28 (-5.14, 4.58)	0.91
PIP	Interaction mask* duration of follow-up	220- 7	2.47 (-7.24, 12.19)	0.62

e-table 6. Interaction between type of mask and the duration of follow-up. *EPAP: Expiratory Positive Airway Pressure; IPAP: Inspiratory Positive Airway Pressure; PaCO2: partial pressure of CO2; PaO2: partial pressure of O2.*

Two step meta-analysis for EPAP and IPAP

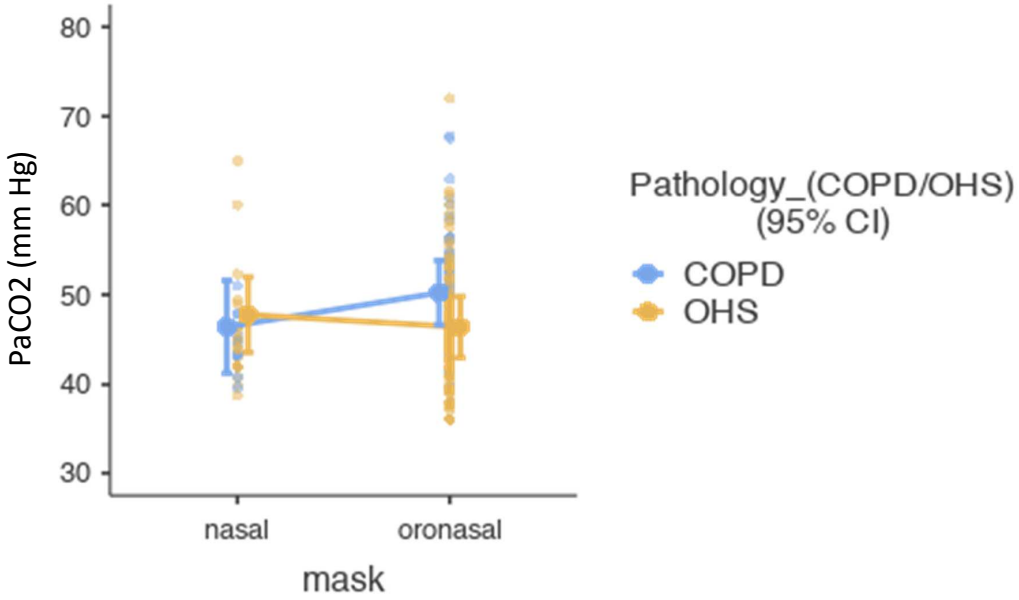


e-figure 2: Summary results of the two step meta-analysis using fixed effect model for Expiratory Positive Airway Pressure (EPAP). The results for each type of mask in each study are displayed on the left forest plot and the interactions between mask-type and the effect on the outcomes at the end of the studies are displayed on the right forest plot. Results are presented using mean differences and 95% CI. Squares are used to depict effects and circles to depict the interaction effects, with sizing in proportion to the inverse of the variance of the estimates.

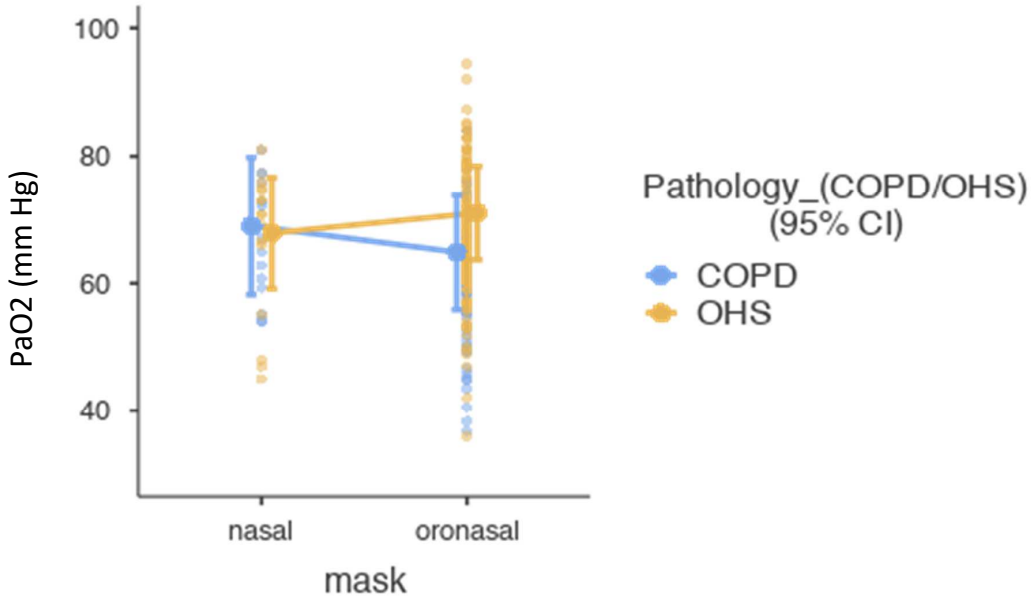


e-figure 3. Summary results of the two step meta-analysis using fixed effect model for Inspiratory Positive Airway Pressure (IPAP). The results for each type of mask in each study are displayed on the left forest plot and the interactions between the type of mask and the effect on the outcomes at the end of the studies are displayed on the right forest plot. Results are presented using mean differences and 95% CI. Squares are used to depict effects and circles to depict the interaction effects, with sizing in proportion to the inverse of the variance of the estimates.

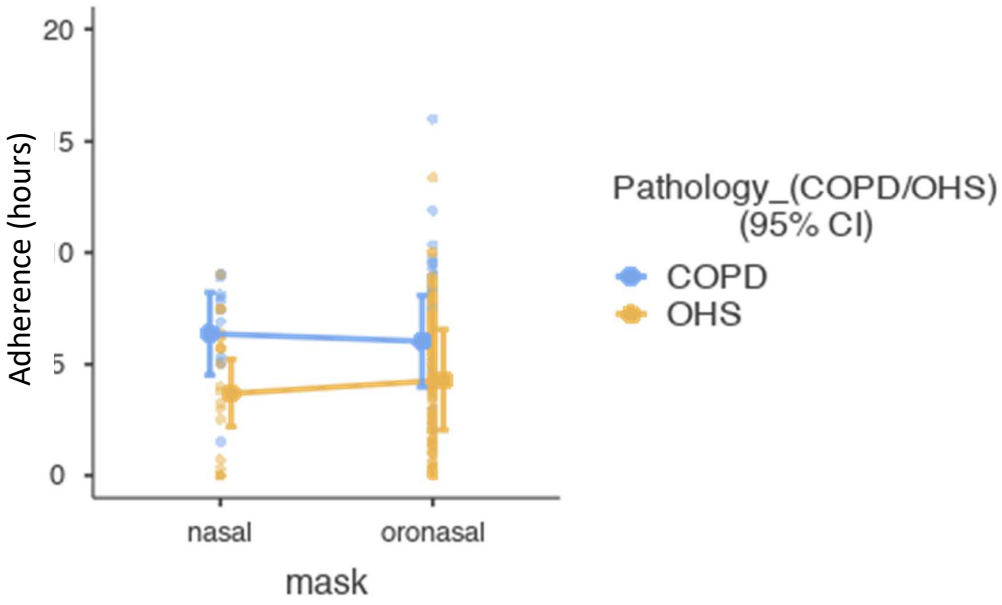
Interaction between mask-type and underlying pathology using marginal means



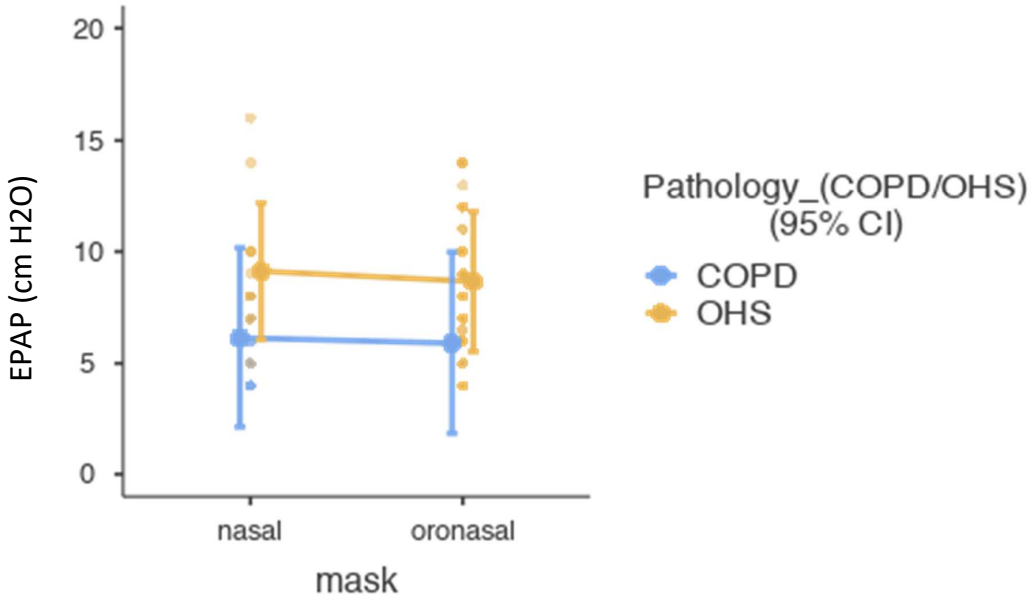
e-figure 4. Interaction between mask-type and underlying pathology for PaCO2 using marginal means



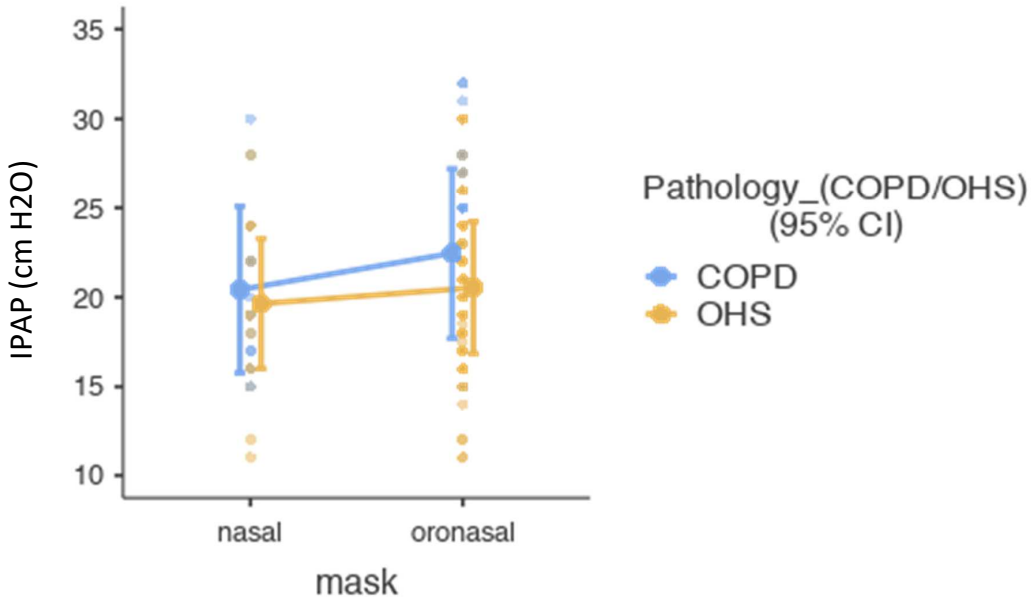
e-figure 5. Interaction between mask-type and underlying pathology for PaO2 using marginal means



e-figure 6. Interaction between mask-type and underlying pathology for NIV adherence using marginal means



e-figure 7. Interaction between mask-type and underlying pathology for EPAP using marginal means



e-figure 8. Interaction between mask-type and underlying pathology for IPAP using marginal mean

Non-inferiority analysis

Methods

We defined non-inferiority margins for nasal versus oronasal masks for each outcome based on the studies included as well as discussion with the research team and reviewers (ΔY = Ynasal – Yfacial): 3 mmHg for PaCO2 [1], -4mmHg for PaO2[2–5], -1 hour per day for compliance [1] and 2cmH2O for EPAP [6] and IPAP [7]. Nasal masks were thus deemed non-inferior to oronasal masks if the lower boundary of the mean difference was inferior to these thresholds.

Results

For PaCO2, the overall result and the results of 2 individual studies showed that nasal masks were non-inferior to oronasal masks. The remaining studies were underpowered and the results were inconclusive (e-Figure 9A). The results for PaO2 were more heterogeneous: 2 individual studies showed non-inferiority of nasal masks whilst another showed clear inferiority, and the results of the remaining 4 studies and the overall result were inconclusive (e-Figure 9B). With regards to compliance, no studies provided conclusive results (e-Figure 9C). For EPAP and IPAP (e-Figures 10A and 10B), the overall result and the results of 2 studies showed non-inferiority, and the remaining studies were inconclusive.

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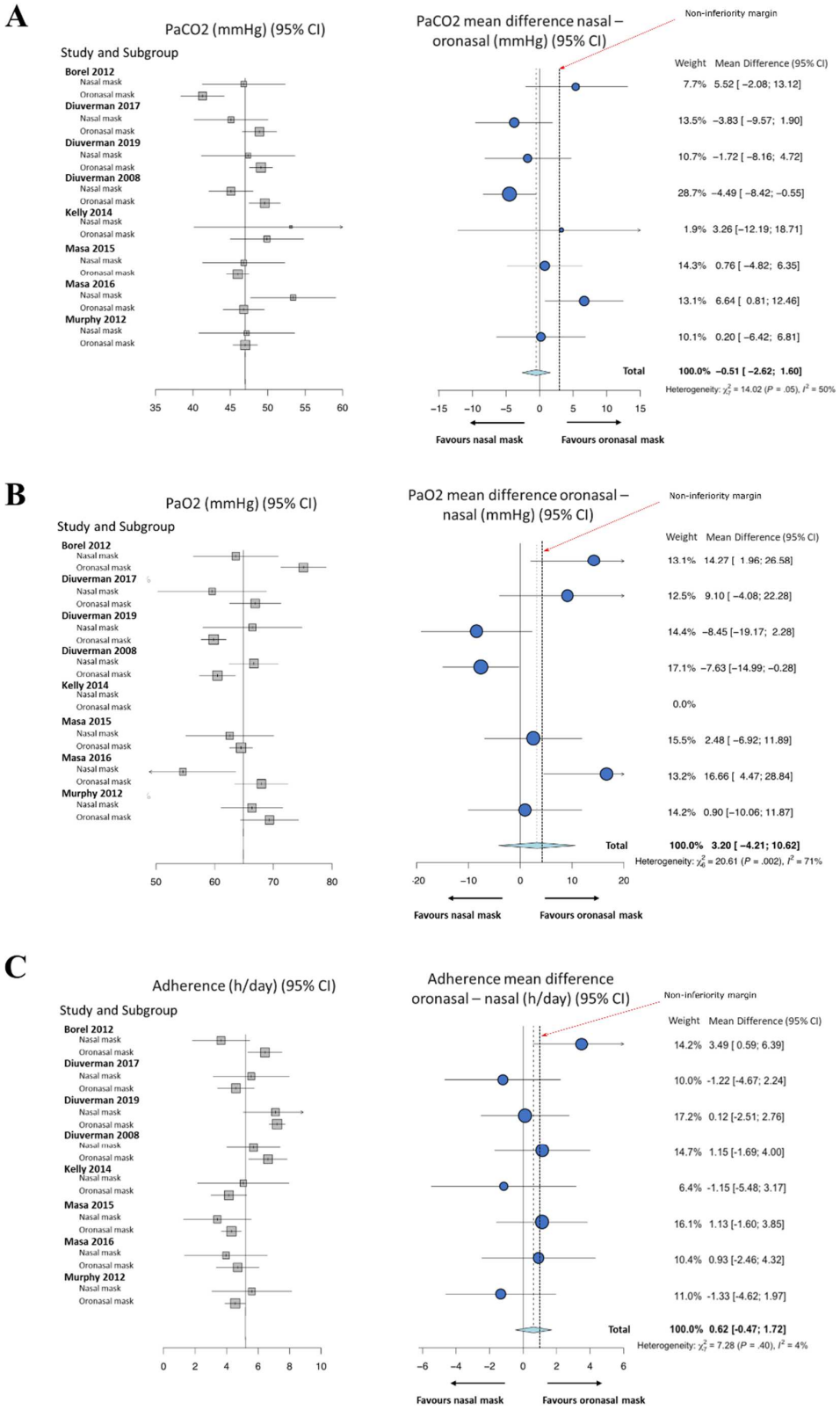
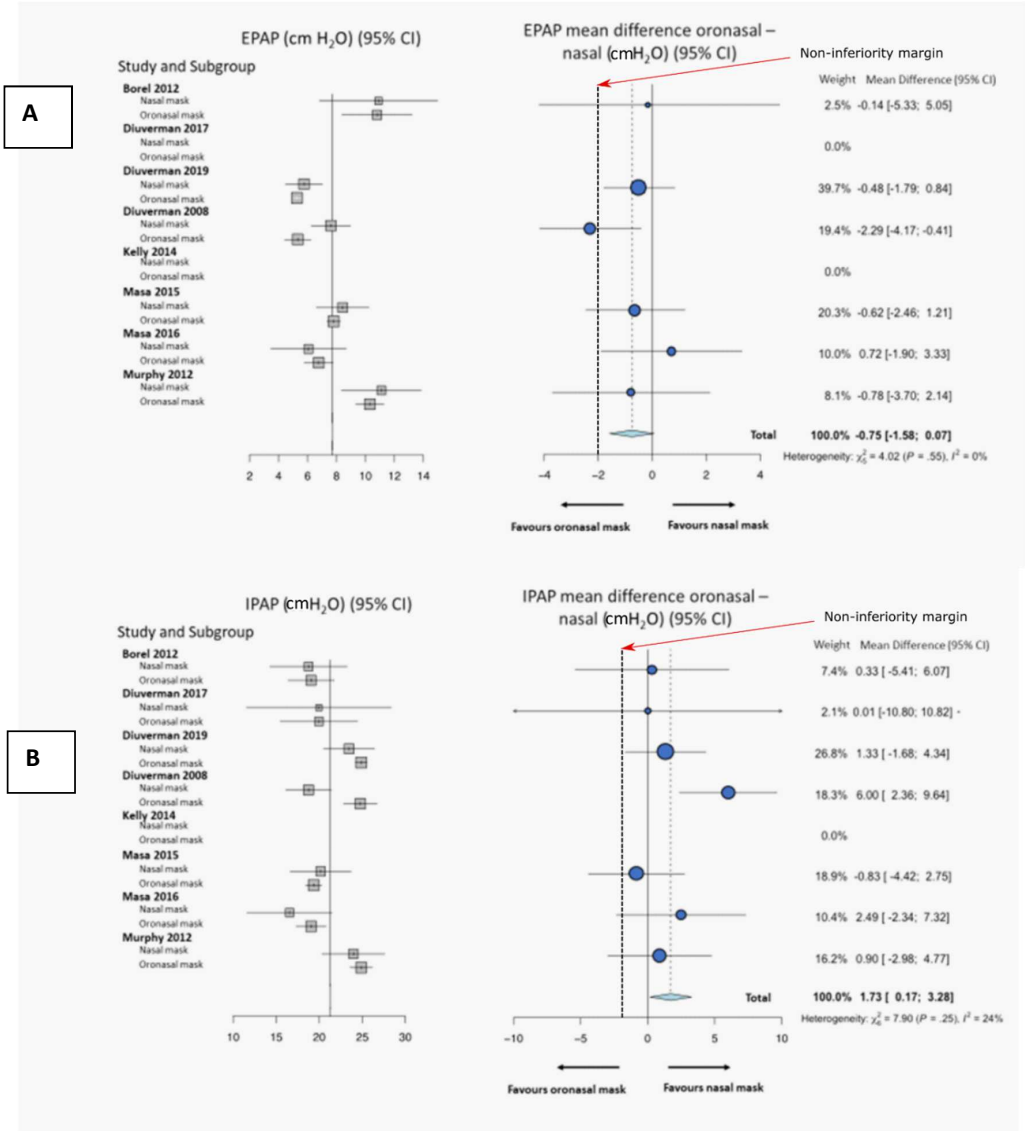

A
PaCO2 (mmHg) (95% CI)
Study and Subgroup
Borel 2012
Nasal mask
Oronasal mask
Diuverman 2017
Diuverman 2019
Diuverman 2008
Kelly 2014
Masa 2015
Masa 2016
Murphy 2012
35 40 45 50 55 60
PaCO2 mean difference nasal – oronasal (mmHg) (95% CI)
Non-inferiority margin
Weight Mean Difference (95% CI)
7.7% 5.52 [−2.08; 13.12]
13.5% −3.83 [−9.57; 1.90]
10.7% −1.72 [−8.16; 4.72]
28.7% −4.49 [−8.42; −0.55]
1.9% 3.26 [−12.19; 18.71]
14.3% 0.76 [−4.82; 6.35]
13.1% 6.64 [0.81; 12.46]
10.1% 0.20 [−6.42; 6.81]
Total 100.0% −0.51 [−2.62; 1.60]
Heterogeneity: χ^2_7 = 14.02 (P = .05), I^2 = 50%
−15 −10 −5 0 5 10 15
Favours nasal mask
Favours oronasal mask
B
PaO2 (mmHg) (95% CI)
Study and Subgroup
Borel 2012
Diuverman 2017
Diuverman 2019
Diuverman 2008
Kelly 2014
Masa 2015
Masa 2016
Murphy 2012
50 60 70 80
PaO2 mean difference oronasal – nasal (mmHg) (95% CI)
Non-inferiority margin
Weight Mean Difference (95% CI)
13.1% 14.27 [1.96; 26.58]
12.5% 9.10 [−4.08; 22.28]
14.4% −8.45 [−19.17; 2.28]
17.1% −7.63 [−14.99; −0.28]
0.0%
15.5% 2.48 [−6.92; 11.89]
13.2% 16.66 [4.47; 28.84]
14.2% 0.90 [−10.06; 11.87]
Total 100.0% 3.20 [−4.21; 10.62]
Heterogeneity: χ^2_6 = 20.61 (P = .002), I^2 = 71%
−20 −10 0 10 20
Favours nasal mask
Favours oronasal mask
C
Adherence (h/day) (95% CI)
Study and Subgroup
Borel 2012
Diuverman 2017
Diuverman 2019
Diuverman 2008
Kelly 2014
Masa 2015
Masa 2016
Murphy 2012
0 2 4 6 8 10
Adherence mean difference oronasal – nasal (h/day) (95% CI)
Non-inferiority margin
Weight Mean Difference (95% CI)
14.2% 3.49 [0.59; 6.39]
10.0% -1.22 [-4.67; 2.24]
17.2% 0.12 [-2.51; 2.76]
14.7% 1.15 [-1.69; 4.00]
6.4% -1.15 [-5.48; 3.17]
16.1% 1.13 [-1.60; 3.85]
10.4% 0.93 [-2.46; 4.32]
11.0% -1.33 [-4.62; 1.97]
Total 100.0% 0.62 [-0.47; 1.72]
Heterogeneity: χ^2_7 = 7.28 (P = .40), I^2 = 4%
−6 −4 −2 0 2 4 6
Favours nasal mask
Favours oronasal mask

e-figure 9 A; B and C: Summary results of the two step meta-analysis for PaCO2 (A), PaO2 (B) and NIV adherence (C) with the non-inferiority margins. The results for each type of mask in each study are displayed on the left forest plot and the interaction between mask-type and the effect on the outcomes at the end of the studies are displayed on the right forest plot. Results are presented using mean differences and 95% CI. Squares are used to depict effects and circles to depict the interaction effects, with sizing in proportion to the inverse of the variance of the estimates.



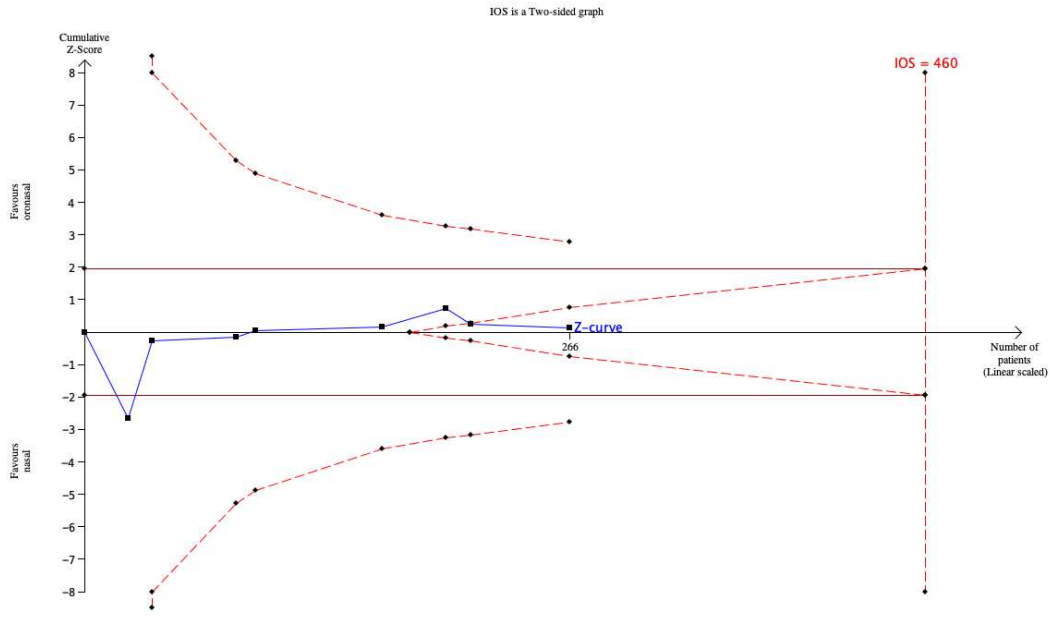
e-figure 10 A and B: Summary results of the two step meta-analysis for EPAP (A) and IPAP (B) with the non-inferiority margins. The results for each type of mask in each study are displayed on the left forest plot and the interaction between mask-type and the effect on the outcomes at the end of the studies are displayed on the right forest plot. Results are presented using mean differences and 95% CI. Squares are used to depict effects and circles to depict the interaction effects, with sizing in proportion to the inverse of the variance of the estimates

Trial sequential analysis

As highlighted by a reviewer, the small number of patients with nasal masks compared to oronasal masks may have reduced the power of the analysis. However, both the CIs and the point estimates were centered on the null value, thus we believe that a greater power would have given similar results. Moreover, we calculated the optimal information size of our meta-analysis for the primary outcome (PaCO2). The optimal information size (OIS) is equivalent to a sample size calculation for a clinical trial but adjusted on the variance introduced by the heterogeneity across included trials (populations, interventions, methods etc.) [8]. This OIS was also used to grade the imprecision of the estimates according to GRADE guideline 6 [9]. We thus calculated the OIS with an alpha type 1 error of 5%, a power of 80%, and the variance and the heterogeneity estimated from the meta-analysis in order to determine the minimally clinical difference that was then used to define non-inferiority margins. When the OIS was not reached we calculated O'brian and Flemming adjusted boundaries for statistical significance and futility.

Results

The optimal sample size to highlight a mean difference in PaCO2 of 3mmHg between the two mask types was 460. With the 266 patients included, the actual power of the analysis was 58%. However, the meta-analysis estimates crossed the adjusted futility boundaries suggesting that oronasal masks are unlikely to be superior to nasal masks based on a minimally clinical important difference of 3mmHg."



e-figure 11: Trial sequential analysis for PaCO2

References

1. Duiverman, M. L. *et al.* Home initiation of chronic non-invasive ventilation in COPD patients with chronic hypercapnic respiratory failure: a randomised controlled trial. *Thorax* **75**, 244–252 (2020).
2. Borel, J.-C. *et al.* Noninvasive ventilation in mild obesity hypoventilation syndrome: a randomized controlled trial. *Chest* **141**, 692–702 (2012).
3. Murphy, P. B. *et al.* Volume targeted versus pressure support non-invasive ventilation in patients with super obesity and chronic respiratory failure: a randomised controlled trial. *Thorax* **67**, 727–734 (2012).
4. Duiverman, M. L. *et al.* Nocturnal non-invasive ventilation in addition to rehabilitation in hypercapnic patients with COPD. *Thorax* **63**, 1052–1057 (2008).
5. Masa, J. F. *et al.* Efficacy of Different Treatment Alternatives for Obesity Hypoventilation Syndrome. Pickwick Study. *Am. J. Respir. Crit. Care Med.* **192**, 86–95 (2015).
6. Patout, M. *et al.* Polysomnography versus limited respiratory monitoring and nurse-led titration to optimise non-invasive ventilation set-up: a pilot randomised clinical trial. *Thorax* **74**, 83–86 (2019).
7. Fernandez, R. *et al.* Nasal versus oronasal mask in home mechanical ventilation: the preference of patients as a strategy for choosing the interface. *Respir. Care* **57**, 1413–1417 (2012).
8. Wetterslev, J., Jakobsen, J. C. & Gluud, C. Trial Sequential Analysis in systematic reviews with meta-analysis. *BMC Med. Res. Methodol.* **17**, 39 (2017).
9. Guyatt, G. H. *et al.* GRADE guidelines 6. Rating the quality of evidence--imprecision. *J. Clin. Epidemiol.* **64**, 1283–1293 (2011).