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REVIEW

Effect of high-flow nasal cannula oxygen therapy in patients with chronic obstructive pulmonary disease: A meta-analysis

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Background: High-flow nasal cannula oxygen therapy reduces the arterial partial pressure of carbon dioxide and acute exacerbation but does not increase exercise capacity or decrease hospitalisation or mortality. The study aimed to test the hypothesis that in chronic obstructive pulmonary disease patients, the use of high-flow nasal cannula decreases arterial partial pressure of carbon dioxide and increases the partial pressure of oxygen and 6-min walking distance.

Methods: PubMed, Embase and the Cochrane library were searched for eligible studies published from database inception to November 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist). The primary outcomes were partial pressure of carbon dioxide and partial pressure of oxygen, and the secondary outcomes were transcutaneous partial pressure of carbon dioxide and 6-min walking distance.

Results: Nine studies (680 patients) were included. high-flow nasal cannula did not decrease partial pressure of carbon dioxide compared with the control interventions (mean difference = −0.81, 95% confidence interval: −2.68 to 1.06, $p = .395$; $I^2 = 42.9\%$, $p_{heterogeneity} = .105$). high-flow nasal cannula decreased partial pressure of carbon dioxide compared with long-term oxygen therapy (mean difference = −3.25, 95% confidence interval: −5.65 to −0.85, $p = .008$; $I^2 = 0\%$, $p_{heterogeneity} = .375$); no difference was observed for the control modalities. high-flow nasal cannula resulted in better partial pressure of carbon dioxide compared with control interventions in hypoxemic patients (mean difference = −2.59, 95% confidence interval: −4.82 to −0.35, $p = .023$; $I^2 = 32.5\%$, $p_{heterogeneity} = .224$), but not in other types of patients. high-flow nasal cannula did not increase partial pressure of oxygen compared with the control interventions (mean difference = 1.17, 95% confidence interval: −1.50 to 3.83, $p = .390$; $I^2 = 0\%$, $p_{heterogeneity} = .660$). high-flow nasal cannula decreased transcutaneous carbon dioxide tension (transcutaneous partial pressure of carbon dioxide) compared with the control interventions (mean difference = 2.37, 95% confidence interval: 0.07–4.68, $p = .044$; $I^2 = 8.7\%$, $p_{heterogeneity} = .295$). high-flow nasal cannula increased 6-min walking distance compared with the control interventions (mean difference = 18.22, 95% confidence interval: 0.86–,35.57, $p = .040$; $I^2 = 0\%$, $p_{heterogeneity} = .918$). The sensitivity analyses showed that the results were robust.

Conclusions: High-flow nasal cannula did not significantly decrease partial pressure of carbon dioxide or increase partial pressure of oxygen in chronic obstructive pulmonary disease patients, which is different from the previous meta-analysis, but it

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decreases transcutaneous partial pressure of carbon dioxide and increased 6-min walking distance.

Relevance to clinical practice: This meta-analysis shows that in patients with chronic obstructive pulmonary disease, high-flow nasal cannula improves both transcutaneous partial pressure of carbon dioxide and 6-min walking distance, suggesting the high-flow nasal cannula has benefits in the management of chronic obstructive pulmonary disease. Considering that the literature suggests no impact of high-flow nasal cannula on hospitalisation and mortality, the benefits of high-flow nasal cannula might be limited to the patients who survive the chronic obstructive pulmonary disease events. Still, the global impact of high-flow nasal cannula on the quality of life of patients with chronic obstructive pulmonary disease should be examined.

KEYWORDS
chronic obstructive pulmonary disease, high-flow nasal cannula oxygen therapy, meta-analysis, partial pressure of carbon dioxide, partial pressure oxygen

1 | INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterised by significant airflow limitation associated with a chronic inflammatory response in the airways and lungs, resulting in the destruction of lung tissue (Global Initiative for Chronic Obstructive Lung Disease [GOLD], 2020; Qaseem et al., 2011). It commonly affects adults >40 years old who smoke (Global Initiative for Chronic Obstructive Lung Disease [GOLD], 2020; Qaseem et al., 2011), with an estimated worldwide prevalence of 4%–10% (Buist et al., 2007; Centers for Disease & Prevention, 2012; Halbert et al., 2003). The disease course is usually progressive, with a long-term decline in lung function, and is the third leading cause of mortality worldwide (Global Initiative for Chronic Obstructive Lung Disease [GOLD], 2020; Hogg et al., 2004; McDonough et al., 2011; Qaseem et al., 2011). It is a preventable and treatable disease commonly associated with comorbidities (such as cardiovascular disease) and significant systemic consequences (such as skeletal muscle dysfunction) (Global Initiative for Chronic Obstructive Lung Disease [GOLD], 2020; Qaseem et al., 2011). Smoking is the most common risk factor for COPD worldwide; other risk factors include occupational exposures (example.g., organic and inorganic dusts, chemical agents and fumes), α-1 antitrypsin deficiency and indoor air pollution (particularly from biomass smoke caused from burning biomass fuels in confined spaces) (Global Initiative for Chronic Obstructive Lung Disease [GOLD], 2020; Qaseem et al., 2011). COPD has several complications, including acute exacerbation, respiratory failure and pulmonary hypertension (Global Initiative for Chronic Obstructive Lung Disease [GOLD], 2020; Macnee, 2010; Qaseem et al., 2011). COPD is the fourth leading cause of death around the world (Rabe et al., 2007).

Ventilatory support can decrease mortality and morbidity and relieve symptoms in patients with COPD exacerbations (Evensen, 2010; Global Initiative for Chronic Obstructive Lung Disease [GOLD], 2020). Ventilatory support includes both invasive- and noninvasive mechanical ventilation (Evensen, 2010; Global Initiative for Chronic Obstructive Lung Disease [GOLD], 2020). Numerous studies suggested that the success rate of noninvasive ventilation (NIV) is about 80%–85% and that it can facilitate weaning from invasive mechanical ventilation, reduce the incidence of respiratory failure, and improve the clinical outcomes (Agarwal et al., 2007; Brochard et al., 1995; Burns et al., 2013; 'Clinical indications for noninvasive positive pressure ventilation in chronic respiratory failure due to restrictive lung disease, COPD, & nocturnal hypoventilation – a consensus conference report', 1999; Lightowler et al., 2003; Meyer & Hill, 1994). Nevertheless, NIV is accompanied by several complications, including nasal congestion, mask discomfort, nasal dryness and gastric insufflation. Moreover, NIV is highly dependent on the health practitioner's competency and experience (Agarwal et al., 2007; Brochard et al., 1995; Burns et al., 2013; Clinical indications for noninvasive positive pressure ventilation in chronic respiratory failure due to

What does this paper contribute to the wider global clinical community?

- The study aimed to test the hypothesis that in chronic obstructive pulmonary disease (COPD) patients, the use of high-flow nasal cannula (HFNC) decreases partial pressure of carbon dioxide and increases the partial pressure of oxygen and 6-min walking distance (6MWD).
- This meta-analysis shows that in patients with COPD, HFNC improves both transcutaneous partial pressure of carbon dioxide and 6MWD, suggesting the HFNC has benefits in the management of COPD.

restrictive lung disease, COPD, & nocturnal hypoventilation – a consensus conference report', 1999; Evensen, 2010; Global Initiative for Chronic Obstructive Lung Disease [GOLD], 2020; Lightowler et al., 2003; Meyer & Hill, 1994).

High-flow nasal cannula (HFNC) oxygen therapy has been introduced as an alternative to NIV (Cortegiani et al., 2020). HFNC was found to be superior to standard nasal prongs and NIV in patients with severe hypoxemic respiratory failure concerning intubation rate and mortality (Frat et al., 2015). HFNC reduces upper airway resistance, improves alveolar recruitment, increases tidal volume, and causes a flow-dependent increase in airway pressure (Dysart et al., 2009; Lee et al., 2013; Nishimura, 2015). HFNC is well tolerated and reduces the arterial partial pressure of carbon dioxide (PaCO2) in people with stable or exacerbated COPD (Bräunlich et al., 2013, 2016; McKinstry et al., 2018; Pisani et al., 2019). Nevertheless, a subgroup analysis by Yoo et al., (2016) suggested that the reintubation rate and intensive care unit (ICU) mortality did not differ significantly from NIV in patients with PaCO2 > 45 mmHg.

In a meta-analysis carried out in 2019 (Bonnevie et al., 2019), the analysis of four quantitative studies showed that HFNC reduced PaCO2 and acute exacerbation but did not significantly increase exercise capacity or decrease hospitalisation or mortality. Some studies did not meet the eligibility criteria for the meta-analysis by Bonnevie et al., (2019), and since then, numerous randomised controlled trials (RCTs) and randomised cross-over studies were published (Bräunlich et al., 2019; Ferrer et al., 2009; Jing et al., 2019; Li et al., 2020; Longhini et al., 2019; Nagata et al., 2018; Pilcher et al., 2017; Pisani et al., 2020; Prieur et al., 2019; Ricard et al., 2018; Tan et al., 2020; Tung et al., 2020; Vaschetto et al., 2019; Vitacca et al., 2020).

1.1 | Aims

Therefore, this meta-analysis was conducted to test the hypothesis that in COPD patients, HFNC can decrease PaCO2 and transcutaneous partial pressure of carbon dioxide (PtCO2) and increase the partial pressure of oxygen (PaO2) and 6-min walking distance (6MWD).

2 | METHODS

2.1 | Literature search

This study is a systematic review and meta-analysis that was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Selcuk, 2019) (Supplementary Material). PubMed, Embase and the Cochrane library were searched for potentially eligible studies published from database inception to November 2020. The search was performed according to the PICO principles (Aslam & Emmanuel, 2010) and using the MeSH terms 'Chronic obstructive pulmonary disease', 'high-flow nasal cannula' and 'randomised controlled trial', as well as the relevant key words. The eligibility criteria were (i) population: COPD patients; (ii) intervention: HFNC oxygen therapy; (iii) outcome: PaCO2, PtCO2, PaO2 and 6MWD; (iv) study design: RCT and randomised cross-over studies; and (v) language: limited to English.

2.2 | Data extraction

The study characteristics (authors, year of publication, country, sample size, mean age, sex and type of COPD patients), treatment parameters (intervention group, control and time of assessment), the primary outcomes (PaCO2 and PaO2) and secondary outcomes (PtCO2 and 6MWD) were extracted by two authors independently. Discrepancies were solved by discussion to reach a consensus.

2.3 | Quality of the evidence

Finally, five RCTs and four randomised cross-over studies were included. The levels of evidence of all articles were assessed independently by two authors according to the Cochrane Handbook (Higgins et al., 2011, 2019). The Cochrane tool assesses six domains of possible bias: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and study staff), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting) and other bias. The risk of bias for each item for each study is determined as low, unclear or high. Discrepancies in the assessment were resolved through discussion until a consensus was reached.

2.4 | Data synthesis

The continuous outcomes were expressed as mean differences (MDs) with a 95% confidence interval (95% CI). The effect size was obtained according to (measurement at the last assessment in the intervention group – measurement at baseline in the intervention group) – (measurement at the last assessment in the control group – measurement at baseline in the control group). All values were collected as mmHg (PaO2, PaCO2 and PtCO2) and meters (6MWD). Standard deviations (SDs) of the MDs were estimated according to SD = square root $[(\text{SD baseline})^2 + (\text{SD final})^2 - (2R * \text{SD baseline} * \text{SD final})]$, assuming a correlation coefficient of 0.5. Mean, and SD values were estimated when the outcome measures were reported as the median and interquartile range (or 95% CI) (Hozo et al., 2005).

2.5 | Statistical analysis

All analyses were performed using STATA SE 14.0 (StataCorp.). Effects (MDs) and corresponding 95% CIs were used to compare

the outcomes. Statistical heterogeneity among studies was calculated using Cochran's *Q*-test and the I^2 index. An I^2 > 50% and *Q*-test p < .1 indicated high heterogeneity. The meta-analysis was performed using a random-effects model. A p-value < .05 was considered statistically significant. Potential publication bias was not assessed using funnel plots and Egger's test because the number of studies included in each quantitative analysis was <10, in which case the funnel plots and Egger's test could yield misleading results (Higgins et al., 2011). Sensitivity analyses were performed by performing each meta-analysis and sequentially excluding each study, in turn. A sensitivity suggested the robustness of the analysis when each analysis with one excluded study yielded a 95% CI that included the MD of the original analysis.

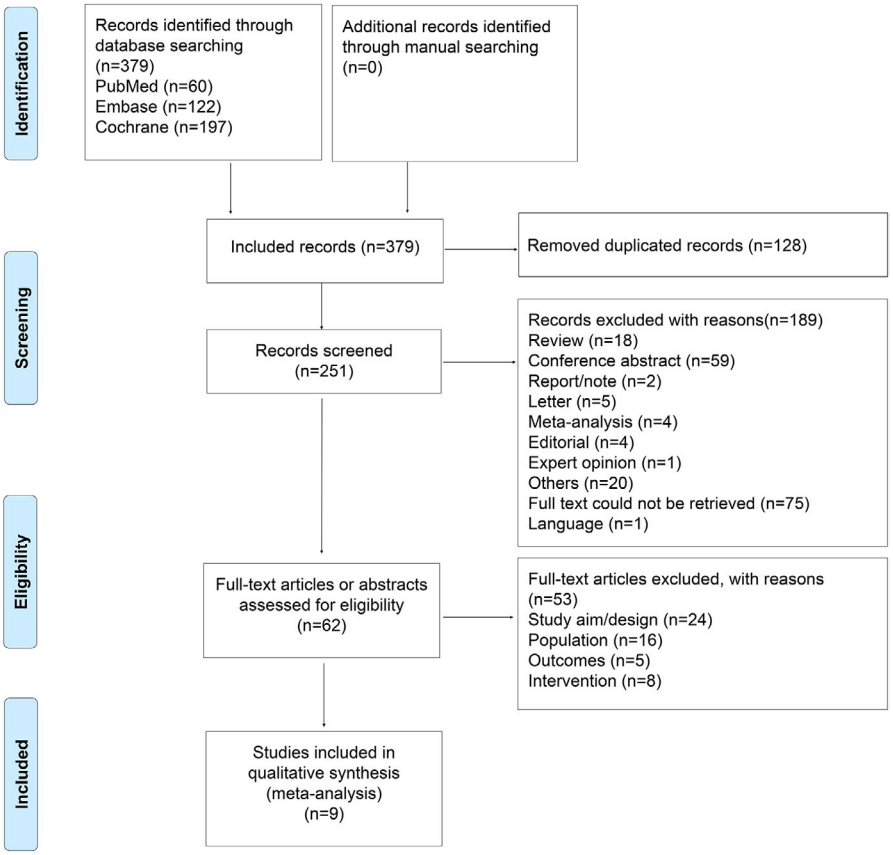


FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 flow diagram [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Characteristics of the included studies

Study	Design	Country	COPD patients
Jing, 2019 (Jing et al., 2019)	RCT	China	Hypercapnic
Storgaard, 2018 (Storgaard et al., 2018)	RCT	Denmark	Hypoxemia
Tan, 2020 (Tan et al., 2020)	RCT	China	Hypercapnic
Tung, 2020 (Tung et al., 2020)	RCT	Taiwan	AE
Vitacca, 2020 (Vitacca et al., 2020)	RCT	Italy	Hypoxemia
Bräunlich, 2019 (Bräunlich et al., 2019)	Randomized cross-over study	Germany	Hypercapnic
Mckinstry, 2019 (McKinstry et al., 2019)	Randomized cross-over study	New Zealand	Hypercapnic
Nagata, 2017 (Nagata et al., 2018)	Randomized cross-over study	Japan	Hypercapnic
Pilcher, 2017 (Pilcher et al., 2017)	Randomized cross-over study	New Zealand	AE

Abbreviations: AE, acute exacerbation; COPD, chronic obstructive pulmonary disease; HFNC, high-flow nasal cannula; LTOT, long-term oxygen therapy; NIV, noninvasive ventilation; PR, pulmonary rehabilitation; RCT, randomized controlled trial; SpO2, oxygen saturation.

3 | RESULTS

3.1 | Study selection

Figure 1 presents the study selection process. The initial search yielded 379 records. After removing the 128 duplicates, 251 records were screened, and 189 were excluded. Sixty-two full-text articles or abstracts were assessed for eligibility, and 53 were excluded (study aim/design, *n* = 24; population, *n* = 16; outcomes, *n* = 5; intervention, *n* = 8).

Finally, nine studies were included (Bräunlich et al., 2019; Jing et al., 2019; McKinstry et al., 2019; Nagata et al., 2018; Pilcher et al., 2017; Storgaard et al., 2018; Tan et al., 2020; Tung et al., 2020; Vitacca et al., 2020), including five RCTs (Jing et al., 2019; Storgaard et al., 2018; Tan et al., 2020; Tung et al., 2020; Vitacca et al., 2020) and four randomised cross-sectional studies (Bräunlich et al., 2019; McKinstry et al., 2019; Nagata et al., 2018; Pilcher et al., 2017) (Table 1). A total of 680 patients were included. The risk of bias was relatively elevated in all included studies (see Supplementary Table S1).

3.2 | Effect of HFNC on PaCO2

Seven studies (Bräunlich et al., 2019; Jing et al., 2019; Nagata et al., 2018; Storgaard et al., 2018; Tan et al., 2020; Tung et al., 2020; Vitacca et al., 2020) examined the effect of HFNC on PaCO2. The results showed that HFNC did not decrease PaCO2 compared with the control interventions (MD = −0.81, 95% CI: −2.68 to 1.06, p = .395; I^2 = 42.9%, $p_{heterogeneity}$ = .105) (Figure 2a; Table 2). When performing a subgroup analysis based on the type on control intervention, HFNC decreased PaCO2 compared with long-term oxygen therapy (LTOT) (MD = −3.25, 95% CI: −5.65 to −0.85, p = .008; I^2 = 0%, $p_{heterogeneity}$ = .375), while HFNC did not decrease PaCO2 compared with NIV (MD = 1.11, 95% CI: −0.79 to 3.01, p = .253; I^2 = 0%, $p_{heterogeneity}$ = .460) and other interventions (MD = −1.41, 95% CI: −3.91 to 1.08, p = .267; I^2 = 0%, $p_{heterogeneity}$ = .837) (Figure 2b; Table 2). When examining the types of patients, HFNC resulted in better PaCO2 compared with control interventions in hypoxemic patients (MD = −2.59, 95% CI: −4.82 to −0.35, p = .023; I^2 = 32.5%, $p_{heterogeneity}$ = .224), while no difference was observed in hypercapnic (MD = 0.91, 95% CI: −0.89 to 2.71, p = .323; I^2 = 0%, $p_{heterogeneity}$ = .577) and exacerbated patients (MD = −0.20, 95% CI: −12.04 to 11.64, p = .974) (Figure 2c; Table 2).

3.3 | Effect of HFNC on PaO2

Seven studies (Bräunlich et al., 2019; Jing et al., 2019; Nagata et al., 2018; Tan et al., 2020; Tung et al., 2020; Vitacca et al., 2020) examined the effect of HFNC on PaO2. The results showed that HFNC did not increase PaO2 compared with the control interventions (MD = 1.17, 95% CI: −1.50 to 3.83, p = .390; I^2 = 0%, $p_{heterogeneity}$ = .660) (Figure 3a; Table 2). When performing a subgroup analysis based on the type on control intervention, HFNC did not increase PaO2 compared with NIV (MD = −1.61, 95% CI: −10.01 to 6.78, p = .706; I^2 = 12.8%, $p_{heterogeneity}$ = .318), LTOT (MD = 1.65, 95% CI: −1.35 to 4.65, p = .992), and other interventions (MD = 1.65, 95% CI: −1.35 to 4.65, p = .282; I^2 = 0%, $p_{heterogeneity}$ = .479) (Figure 3b; Table 2). When examining the types of patients, HFNC did not increase PaO2 compared with control interventions in hypercapnic (MD = −0.61, 95% CI: −6.40 to 5.17, p = .835; I^2 = 0%, $p_{heterogeneity}$ = .513), hypoxemic (MD = 2.00, 95% CI: −1.15 to 5.15, p = .7322) and exacerbated (MD = −1.70, 95% CI: −11.44 to 8.04, p = .214) patients (Figure 3c; Table 2).

Intervention group	Control group	Sample size	Time of assessment	Age (year, mean or median)		Male, *n* (%)	
				HFNC	Control	HFNC	Control
SpO2 at 88%–92%; air temperature: 37°C	NIV	42	Day 2	77.4 ± 6.8	73.9 ± 6.9	—	—
Air flow rate: 20 L/min; SpO2 > 88% 6–7 h/day. Mean oxygen flow rate of LTOT: 1.6 L/min	LTOT	200	12 months	71 ± 8.2	70.4 ± 9.0	44 (44)	37 (37)
Airflow rate: 50 L/min	NIV	86	Day 2	68.4 ± 9.3	71.4 ± 7.8	27 (64.3)	23 (55.6)
Usual care + PR program + air flow 50 L/min	Other	44	12 weeks	72.3 ± 7.7	73.1 ± 6.4	17 (77.3)	15 (77.3)
FiO2: 36.5% ± 8.8%. airflow: 45 ± 12 L/min	Other	137	4 weeks	71.1 ± 7.8	71.8 ± 8.4	52(73.8)	45(68.9)
Airflow rate: 19.8 ± 0.6 L/min	NIV	94	6 weeks	65.3 ± 9.3		37 (39.4)	
Air temperature: 37°C. Flow rate: 45 L/min	NIV	24	60 min	68.0 ± 9		13 (54.2)	
Flow rates 30–40 L/min; SpO2 > 80%.	LTOT	29	6 weeks	73.8 ± 6.9	76.2 ±9 .3	12 (92.3)	14 (88)
Air temperature: 37°C. Flow rate: 35 L/min	Other	24	30 min	70 ± 9		—	—

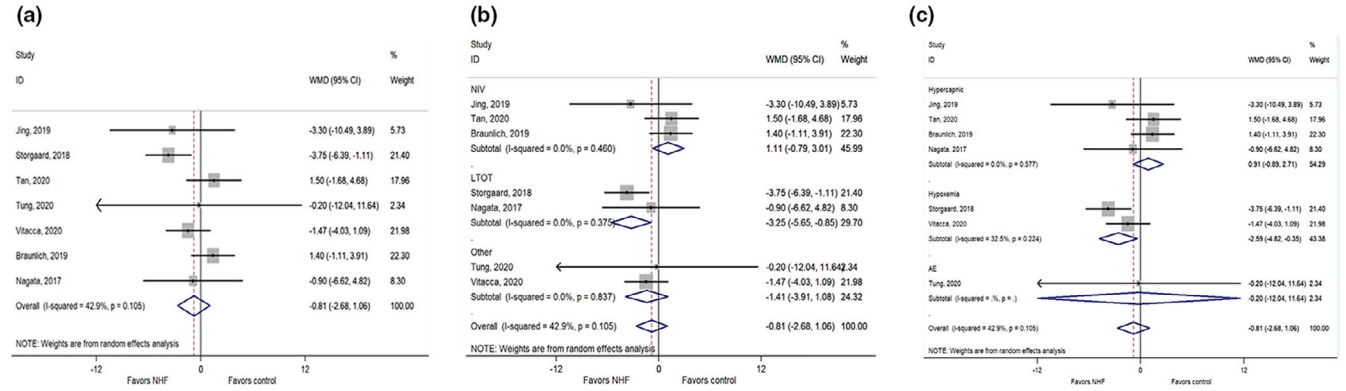


FIGURE 2 (a) Forest plot of partial pressure of carbon dioxide (PaCO2). (b) Forest plot of PaCO2 by the control group. (c) Forest plot of PaCO2 by patients [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Summary of the meta-analyses

	N	MD (95% CI)	*p*	I^2 (%)	$p_{heterogeneity}$
PaCO2	7	−0.812 (−2.683 to 1.058)	.395	42.9	.105
Patients					
Hypercapnic	4	0.909 (−0.894 to 2.711)	.323	0	.577
Hypoxemia	2	−2.585 (−4.819 to −0.352)	.023	32.5	.224
AECOPD	1	−0.200 (−12.044 to 11.644)	.974		
Control					
NIV	3	1.108 (−0.791 to 3.007)	.253	0	.460
LTOT	2	−3.251 (−5.647 to −0.855)	.008	0	.375
Other	2	−1.414 (−3.911 to 1.084)	.267	0	.837
PaO2	6	1.169 (−1.495 to 3.832)	.390	0	.660
Patients					
Hypercapnic	4	−0.615 (−6.397 to 5.168)	.835	0	.513
Hypoxemia	1	−1.700 (−11.444 to 8.044)	.732		
AECOPD	1	2.000 (−1.155 to 5.155)	.214		
Control					
NIV	4	−1.614 (−10.009 to 6.780)	.706	12.8	.318
LTOT	1	−0.100 (−20.757 to 20.557)	.992		
Other	2	1.649 (−1.352 to 6.650)	.282	0	.479
PtCO2	2	2.375 (0.067 to 4.683)	.044	8.7	.295
6MWD	3	18.215 (0.863 to 35.568)	.040	0	.918

6MWD, 6-min walking distance; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; CI, confidence interval; LTOT, long-term oxygen therapy; MD, mean difference; PaCO2, arterial partial pressure of carbon dioxide; PaO2, arterial partial pressure of oxygen; NIV, noninvasive ventilation.

3.4 | Effect of HFNC on PtCO2

Two studies (McKinstry et al., 2019; Pilcher et al., 2017) examined the effect of HFNC on PtCO2. The results showed that HFNC decreased PtCO2 compared with the control interventions (MD = 2.37, 95% CI: 0.07–4.68, p = .044; I^2 = 8.7%, $p_{heterogeneity}$ = .295) (Figure 4; Table 2).

3.5 | Effect of HFNC on 6MWD

Three studies (Storgaard et al., 2018; Tung et al., 2020; Vitacca et al., 2020) examined the effect of HFNC on 6MWD. The results showed that HFNC increased 6MWD compared with the control interventions (MD = 18.22, 95% CI: 0.86–35.57, p = .040; I^2 = 0%, $p_{heterogeneity}$ = .918) (Figure 5; Table 2).

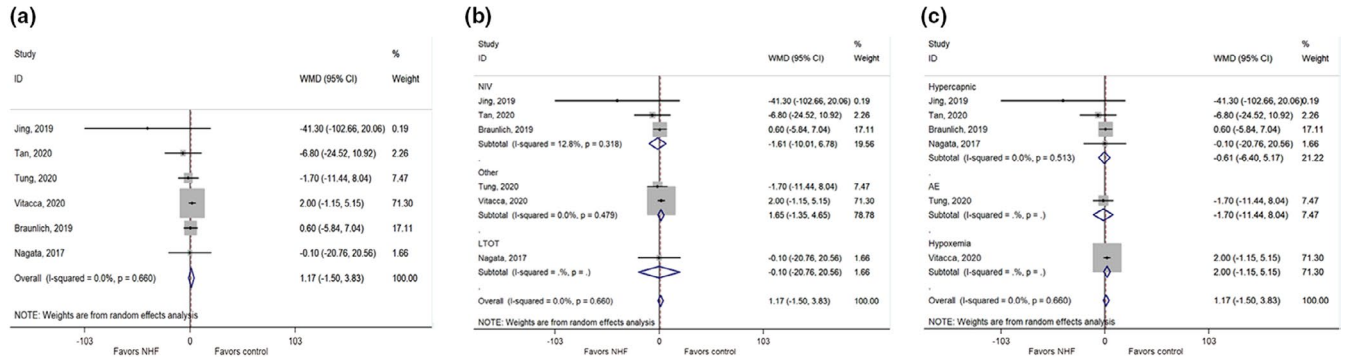
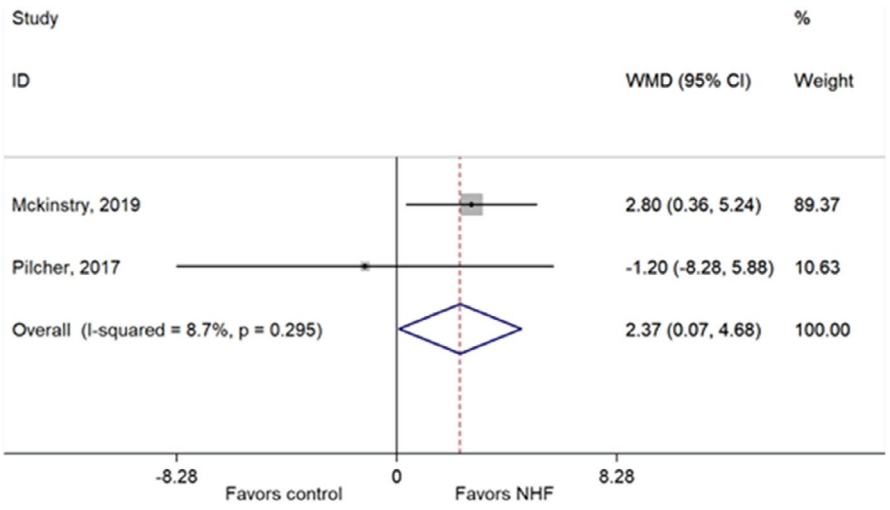


FIGURE 3 (a) Forest plot of partial pressure of oxygen (PaO2). (b) Forest plot of PaO2 by the control group. (c) Forest plot of PaO2 by patients [Colour figure can be viewed at wileyonlinelibrary.com]

FIGURE 4 Forest plot of the effect of high-flow nasal cannula on transcutaneous partial pressure of carbon dioxide (PtCO2) [Colour figure can be viewed at wileyonlinelibrary.com]



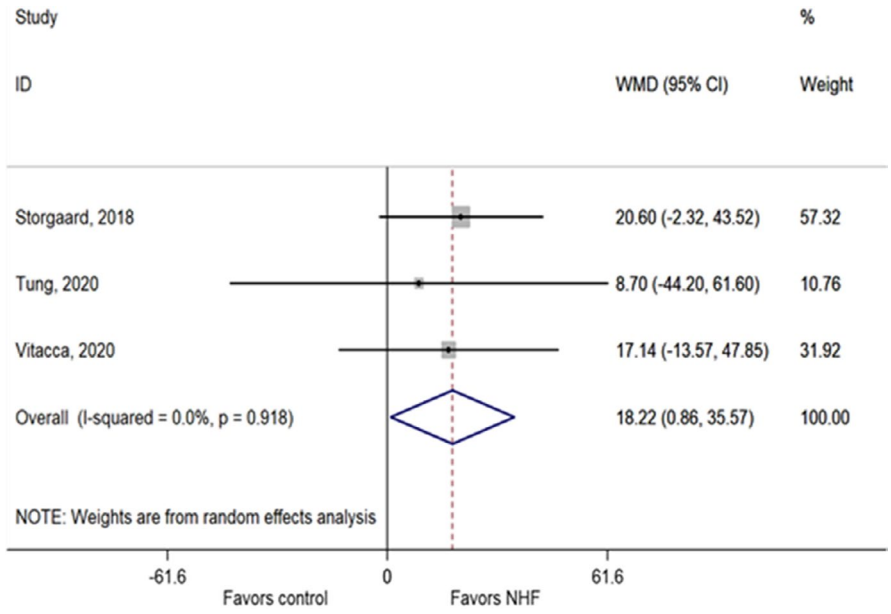


FIGURE 5 Forest plot of 6-min walking distance (6MWD) [Colour figure can be viewed at wileyonlinelibrary.com]

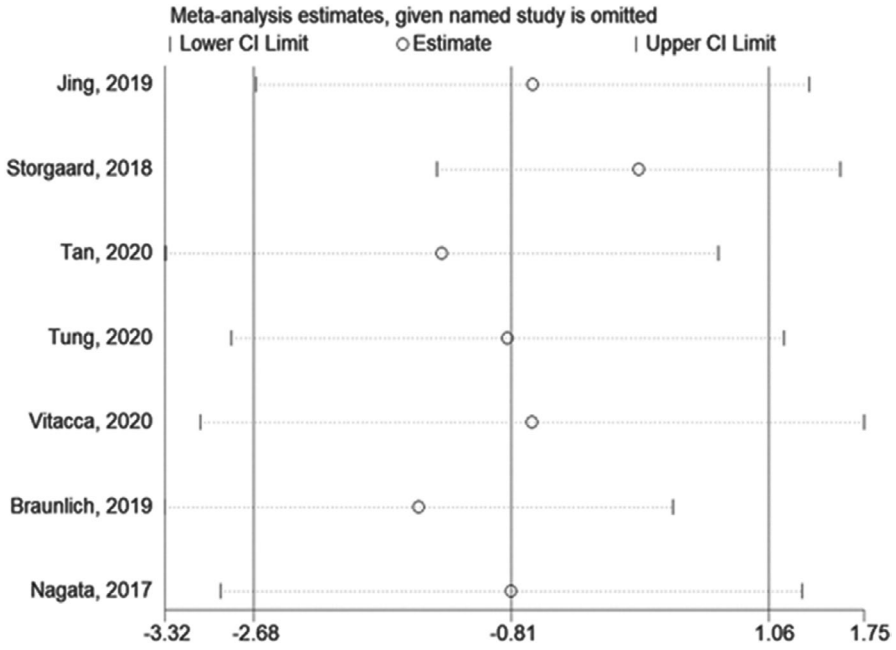


FIGURE 6 Sensitivity analysis of partial pressure of carbon dioxide (PaCO2)

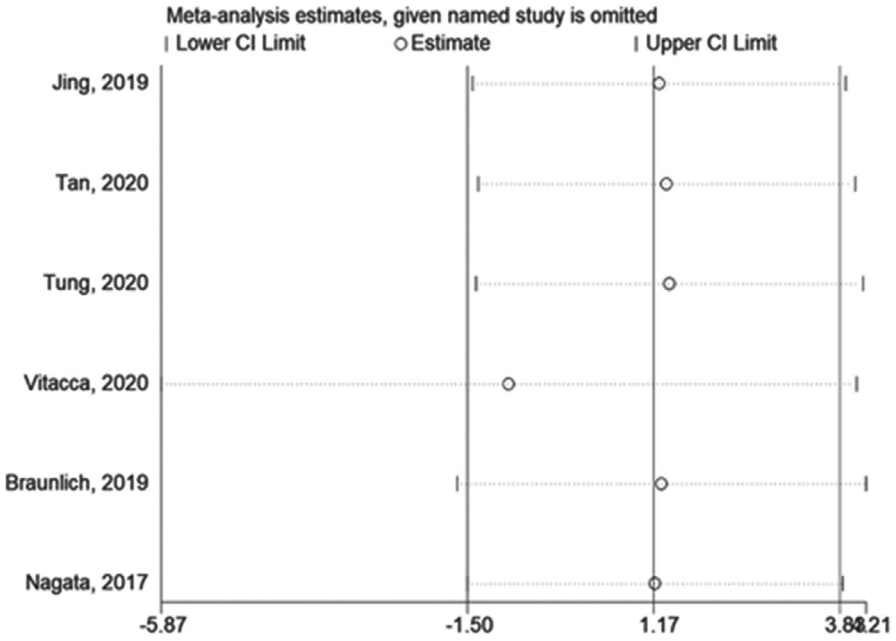


FIGURE 7 Sensitivity analysis of partial pressure of oxygen (PaO2)

3.6 | Sensitivity analyses

The sensitivity analyses showed that the results were robust regarding PaCO2 (Figure 6), PaO2 (Figure 7), PtCO2 (Figure 8) and 6MWD (Figure 9) since all 95% CI of the subanalyses included the MD of the entire analysis.

4 | DISCUSSION

A meta-analysis carried out in 2019 (Bonnevie et al., 2019) showed that HFNC oxygen therapy reduced PaCO2 and acute exacerbation but did not significantly increase exercise capacity or decrease hospitalisation rate or mortality. Since then, new studies were published. Therefore, this meta-analysis aimed to test the hypothesis that in COPD patients, the use of HFNC can decrease PaCO2 and PtCO2 and increase PaO2 and 6MWD. The results showed that HFNC did not significantly decrease PaCO2 or increase PaO2 in COPD patients, which is different from the previous meta-analysis, but it decreases PtCO2 and increased 6MWD.

In the meta-analysis by Bonnevie et al. (2019), the analysis of four studies showed that HFNC reduced PaCO2 and acute exacerbations but did not significantly increase exercise capacity or decrease hospitalisation rate or mortality. In the present meta-analysis of nine

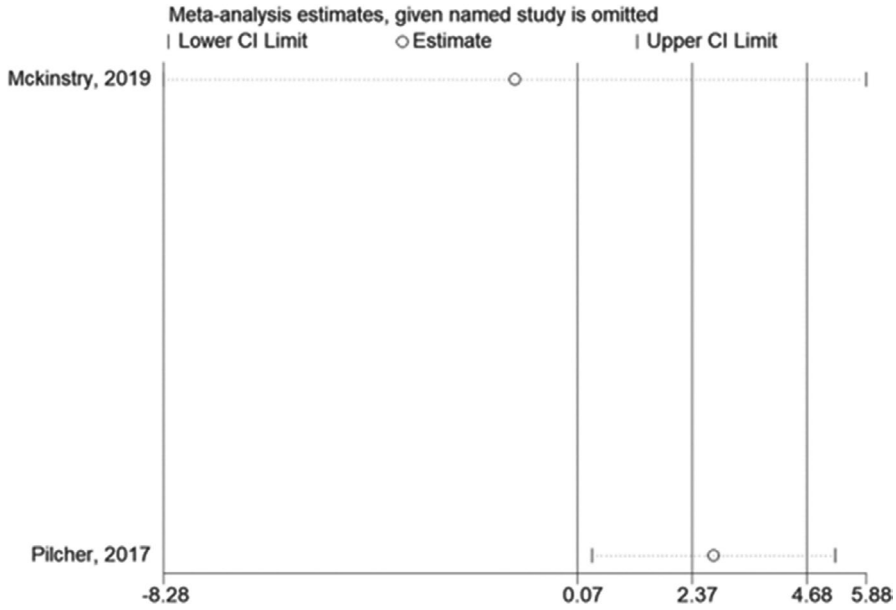


FIGURE 8 Sensitivity analysis of transcutaneous partial pressure of carbon dioxide (PtCO2)

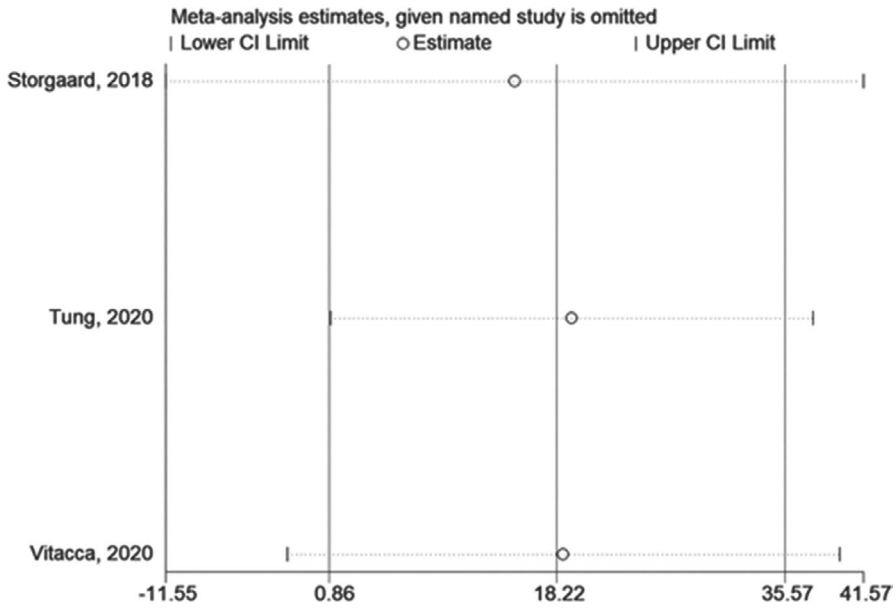


FIGURE 9 Sensitivity analysis of 6-min walking distance (6MWD)

studies, HFNC did not decrease PaCO2 and increase PaO2 but did increase 6MWD. Other outcomes like acute exacerbations, hospitalisation rate and mortality could not be analysed because of insufficient reporting by the included studies. Nevertheless, for the two outcomes in common between the two meta-analyses (i.e., PaCO2 and exercise capacity), the results were the opposite. This could be due to the differences in selection criteria that lead to different studies being included and the higher number of studies included in the present meta-analysis. Nevertheless, the two meta-analyses agree that HFNC does not increase PaO2, which might be an issue concerning the indicated necessity to titrate oxygen during HFNC to avoid flushing (Pisani et al., 2017). Furthermore, HFNC is reported to be better tolerated than control interventions (Lee et al., 2016; Monro-Somerville et al., 2017; Ni et al., 2017), which could be in itself a reason for higher use of HFNC, but this could not be examined here.

In this meta-analysis, HFNC had benefits on PaCO2 only in hypoxemic patients and when compared with LTOT as the control group. Indeed, hypoxemic patients have decreased blood oxygen levels, while hypercapnic patients have elevated blood carbon dioxide levels. Therefore, HFNC could be more appropriate to help the patients increase their oxygen levels than displace the accumulated carbon dioxide. Previous studies reported improvements in some outcomes when using HFNC in hypoxemic non-hypercapnic patients (Frat et al., 2015; Rochwerg et al., 2019), supporting the present study. Previous studies also support the advantages of HFNC over LTOT (Elshof & Duiverman, 2020; Nishimura, 2016; Storgaard et al., 2018).

Besides, various particularities of the included studies could lead to bias and heterogeneity. Indeed, Nagata et al. (2018) performed a randomised cross-over study but without a washout period, and we only extracted the data by the end of the first period. In addition,

since most of the included studies have different follow-up durations, the follow-up duration was categorised as long- and short-term. The short-term follow-up studies included two studies (Jing et al., 2019; Tan et al., 2020) with a 48-h follow-up period and two studies with 30 (Pilcher et al., 2017) and 60 (McKinstry et al., 2019) min follow-ups, respectively. Long-term was defined as follow-up longer than 4 weeks; five studies were included in this group (Bräunlich et al., 2019; Nagata et al., 2018; Storgaard et al., 2018; Tung et al., 2020; Vitacca et al., 2020).

This meta-analysis has limitations that must be considered when weighing the results. First, for the studies that did not report the *r*-value, a correlation coefficient of .5 was used to calculate the MD and SD. The estimated mean and SD could potentially bias the results, but the sensitivity analyses suggested a robust outcome even when single studies were left out of the analysis. Second, due to the small sample size in the included studies in this meta-analysis, outcomes such as extubation failure, reintubation rate and ICU mortality could not be investigated in this study.

4.1 | Conclusions

In conclusion, the results showed that HFNC did not significantly decrease PaCO2 or increase PaO2 in COPD patients, which is different from the previous meta-analysis, but it decreases PtCO2 and increases 6MWD. Considering the differences between this meta-analysis and the previous one (Bonnevie et al., 2019), studies should still be carried out to examine the impact of HFNC in patients with COPD.

CONFLICT OF INTEREST

The authors declare that they have no competing interests in this section.

AUTHORS CONTRIBUTIONS

Conception and design: DL; collection and assembly of data: XCD; data analysis and interpretation: ZN; manuscript writing: all authors; final approval of manuscript: all authors.

DATA AVAILABILITY STATEMENT

Since it is a meta-analysis, all data were extracted from public database, then all data were available.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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