

Review article

Effectiveness, Adherence and Safety of Home High Flow Nasal Cannula in Chronic Respiratory Disease and Respiratory Insufficiency: A Systematic Review



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ARTICLE INFO

Article history:

Received 16 February 2024

Accepted 1 May 2024

Available online 4 May 2024

Keywords:

Chronic obstructive pulmonary disease

High-flow cannula

High-flow nasal cannula oxygen therapy

Hypercapnic

Nasal high-flow

Pulmonary disease

ABSTRACT

Introduction: The effectiveness of home high flow nasal cannula (HFNC) for the treatment of chronic respiratory failure in patients with chronic respiratory diseases (CRDs) has not been summarized. We aimed to conduct a systematic review of the effectiveness, adherence, and safety of HFNC in the long-term treatment of patients with chronic respiratory diseases and respiratory failure.

Methods: A systematic review was conducted. PubMed, Web of science, and SCOPUS were searched up to August 2023. Long-term HFNC studies (≥ 4 weeks) reporting dyspnea; exacerbations, hospitalizations; peripheral oxygen saturation (SpO_2), comfort; patient experience, health-related quality of life or partial pressure of carbon dioxide ($paCO_2$) were included.

Results: Thirteen articles (701 patients) based on 10 studies were selected: randomized control trials ($n=3$), randomized crossover trials ($n=2$), crossover ($n=3$) and retrospective ($n=2$) studies. COPD ($n=6$), bronchiectasis ($n=2$), COPD/bronchiectasis ($n=1$) and ILD ($n=1$) were the underlined CRDs. HFNC reduced exacerbations when compared to usual care/home respiratory therapies ($n=6$). Quality of life outcomes were also in favor of HFNC in patients with COPD and bronchiectasis ($n=6$). HFNC had significant effects on hospitalizations, $paCO_2$, and lung function. Adherence ranged from 5.2 to 8.6 h/day ($n=5$). Three studies reported no events, 3 non-serious events and 2 no differences compared with other home respiratory therapies.

Conclusions: HFNC seems more effective than usual care or other home respiratory therapies in reducing exacerbations and improving quality of life in patients with COPD and bronchiectasis, while presenting good adherence and being safe. Its apparently superior effectiveness needs to be better studied in future real-world pragmatic trials.

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Introduction

In 2019, respiratory diseases accounted for three of the top 10 causes of death, resulting in more than 8 million deaths annually, with chronic obstructive pulmonary disease (COPD) being the third leading cause of death.¹ However, other chronic respiratory diseases also contribute to this high burden. The global incidence of non-cystic fibrosis bronchiectasis ranges from 67 to 566 per 100,000 inhabitants in Europe and North America.² Between 1990 and 2013, Interstitial Lung Disease (ILD) was among the top 50 causes of global years of life lost worldwide.³ In addition, regardless of the underlying chronic respiratory disease, patients experience frequent exacerbations, respiratory failure and a decrease in their quality of life.⁴ Various forms of treatment are available to improve physiological parameters, symptoms and patient-centered outcomes, including non-invasive ventilation and oxygen therapy. In recent years, high flow nasal cannula therapy has been introduced as another innovative approach to treat some groups of respiratory patients.

High flow nasal cannula (HFNC) has emerged as a home treatment for patients with chronic respiratory diseases to increase the carbon dioxide (CO₂) washout, while improving the mucociliary clearance.⁵ HFNC provides heated and humidified gas admixture at a high flow rate (up to 60 L/min) via a wide-bore nasal cannula. This therapy was widely studied in acute respiratory failure, including COVID-19 and has been shown to reduce intubation and mortality in comparison with conventional oxygen therapy.^{6–10} In addition, HFNC seems probably better than non-invasive ventilation in terms of dyspnea, comfort, and decreasing of respiratory rate in patients either post-extubation or during acute respiratory failure.¹¹

In the home setting, evidence has been pooled in patients with COPD, with HFNC shown to improve health-related quality of life¹² and reduce the rate of exacerbations.¹³ Other systematic reviews or meta-analysis of HFNC have shown inconsistent and conflicting results.^{14–16} These may be due to the fact that these syntheses included heterogeneous studies, mixing acute and chronic patients, short-term and long-term treatment. To our knowledge, there is only one systematic review focusing exclusively on stable patients with COPD, but unfortunately it was based on randomized control trials only.¹³ Adding information from real-world observational studies and other chronic respiratory diseases, such as bronchiectasis and ILD, may help in clinical reasoning.¹⁷ Furthermore, the adherence and safety of long-term HFNC treatment in patients with chronic respiratory diseases remains unclear.

Therefore, we aimed to conduct a systematic review of the effectiveness, adherence, and safety of HFNC in the long-term treatment of patients with chronic respiratory diseases and respiratory failure.

Material and methods

Study design

A systematic review was conducted and reported according to PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines.¹⁸ The protocol was registered at PROSPERO (CRD42023461837).

Search strategy

A comprehensive search of PubMed, Web of science, and SCOPUS databases was performed until August 8, 2023. The search strategy included 2 concept sets: (“chronic obstructive lung disease” OR COPD OR “chronic obstructive airway disease” OR “chronic obstructive lung disease” OR “interstitial lung disease” OR “ILD” OR “bronchiectasis” OR “hypercapnic” OR “normocapnic” OR

“pulmonary disease” OR “chronic respiratory insufficiency”) AND (“high-flow oxygen” OR “high flow nasal cannula” OR “high flow nasal oxygen” OR “high flow oxygen therapy” OR “nasal high flow” OR “HFNC” OR “HFNO” OR “HFOT” OR “NHF” OR “NHFT” OR “short-term nasal high-flow” OR “domiciliary high-flow nasal cannula oxygen therapy” OR “domiciliary nasal high flow therapy”). Additional searches were performed using weekly automatic updates retrieved from these databases. We also searched for relevant references in the list of references of the included studies. In addition, we manually searched published meta-analyses and systematic reviews, and the references of the included studies to identify other potentially relevant studies. No language restrictions were applied.

Eligibility criteria

Inclusion criteria were studies that included patients with chronic respiratory diseases such as COPD, bronchiectasis, ILD, and others and chronic respiratory failure (Population) and provided long-term HFNC, defined as at least 4 weeks with a flow of at least 20 L/min (Intervention), which could be or not compared with other forms of respiratory support (Comparators, not mandatory). To be included, primary articles had to report outcomes such as dyspnea; exacerbations, hospitalizations; peripheral oxygen saturation (SpO₂), comfort; patient experience, health-related quality of life or partial pressure of carbon dioxide (paCO₂). Randomized controlled trials (RCTs), randomized crossover studies, quasi-experimental studies, case-control studies and retrospective studies were included. Study protocols, book chapters, reviews, editorials/commentaries to articles, case reports and abstracts were excluded.

Screening, selection process and data extraction

After removal of duplicate studies, the articles were screened independently by 2 reviewers (CJ and MJ) to identify relevant articles by the title and abstract using the Rayyan software.¹⁹ In case of disagreement, a third researcher (CC) was consulted. The 2 reviewers (MJ and CJ) used a standardized form to independently extract data from each article, including the author's surname and year of publication, study design, sample size, participants and condition, HTF protocol, outcomes, and results. The third author (CC) was consulted in case of discrepancies.

Assessment of methodological quality and risk of bias

Risk of bias and methodological quality of the included studies were independently assessed by 2 authors (MJ and CJ). The risk of bias for randomized studies was assessed using the Cochrane Collaboration's tool.²⁰ Risk of bias for observational studies was assessed using the Newcastle–Ottawa Scale (NOS).²¹ Disagreements were resolved by discussion or by a third reviewer (CC).

Data synthesis and analysis

As the included studies were clinically heterogeneous, narrative synthesis was used to report the findings. This was considered the most appropriate approach given the heterogeneity of data between the included studies. Findings were initially drafted by one researcher (CJ), then reviewed by a second researcher (MJ).

Results

Study selection

The database search yielded 938 studies. After removing duplicate results, 526 articles were screened for relevant content. During

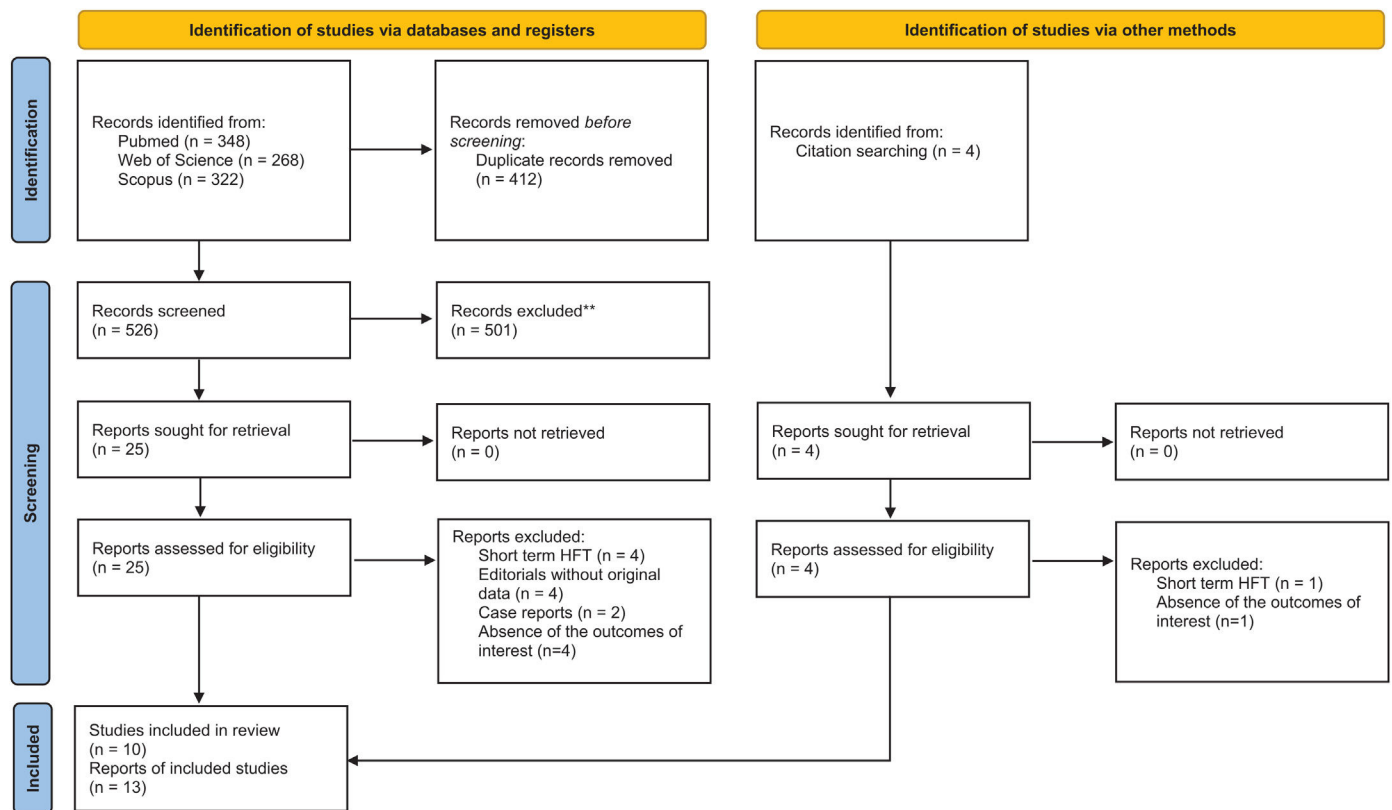


Fig. 1. PRISMA flowchart.

title and abstract screening, 501 articles were excluded. Finally, 24 articles were selected for full-text screening. Two additional papers were included through manual search and screening of the reference lists of full-text articles. After excluding 8 articles, 13 articles from 10 studies were selected for qualitative analysis (Fig. 1).

Methodological quality and risk of bias

Details of the included articles are shown in Table 1. The 13 articles were published between 2010 and 2023, mainly in European countries (n = 7).^{22–28} The articles had different designs, namely RCTs (n = 3),^{23,29,30} randomized crossover trials (n = 2),^{24,31} non-randomized crossover studies (n = 3)^{22,26,27} and retrospective studies (n = 2).^{25,28} Three articles were secondary analysis of RCTs.^{32–34} Risk of bias in RCTs was mainly related to blinding of participants/staff, blinding of outcome assessor and incomplete data (Supplementary Fig. 1), whereas in non-randomized studies it was related to the outcome assessment and groups comparability (Supplementary Table 2).

Study characteristics

Most studies were conducted in patients with COPD (n = 6), 2 studies in patients with bronchiectasis, one in both COPD and bronchiectasis, and one in patients with ILD. Inclusion criteria varied among studies, but prescription of long-term oxygen therapy (LTOT) (n = 5),^{23,27–29,31} chronic respiratory failure/hypercapnia (n = 4),^{22,24,29,31} history of exacerbations/hospitalizations (n = 4),^{25,26,29,30} stable hypercapnia (n = 4)^{22,24,29,31}, sputum production (n = 2)^{25,30} and body mass index < 30 kg/m² (n = 2)^{22,24} were some of the most commonly used. The studies included a total of 701 stable patients (sample sizes from 9 to 200). The average age of the patients was 65–76 years old. The average

FEV₁% predicted at baseline was 25–69%, with the lowest values found in studies with patients with COPD.

HFNC was mainly compared with standard care (n = 3)^{25,27,30}; LTOT (n = 3),^{23,29,31} and VNI+LTOT (n = 2) and NIV (n = 3).^{22,24,28} HFNC was prescribed at flow rates between 20–60 L/min, with or without O₂ supplementation. Patients were recommended to use HFNC between 2 and 8 hours/day, preferably during sleep. The effects of the intervention were evaluated both in the short-term (6 weeks, n = 4)^{22,24,27,31} and in the long-term (1^{23,25,28,30} and 2 years²⁶).

Summary of findings

Exacerbations

Most articles used exacerbations (n = 9) as an outcome measure, with 6 showing the ability of HFNC to reduce these events when compared with usual care^{25,26,30,33} or LTOT.^{23,29} The other three articles (2 post hoc analyses of²³) also showed significant improvements in exacerbations, particularly in hypercapnic patients and those with 2 or more exacerbations per year.^{31,32,34}

Hospitalizations

HFNC was also able to reduce the rate of hospitalizations in patients with COPD and bronchiectasis (n = 7)^{23,25,26,28,30,32,34}, although not superior to LTOT,²³ or even usual care.³⁰ Based on non-randomized studies and considering only patients with bronchiectasis, HFNC seemed to be more beneficial than usual care.^{25,26}

PaCO₂

PaCO₂ was a selected outcome in 6 articles. HFNC improved PaCO₂ in patients with COPD and was shown to be superior

Table 1
Details of the included articles.

First author, year	Country	Design	Eligibility criteria	Participants	Intervention	Comparator	Follow-up period	Outcomes	Main results
Rea et al., 2010 ³⁰	New Zealand	RCT	<p><u>Inclusion</u></p> <ul style="list-style-type: none"> - COPD diagnosis confirmed by spirometry - Bronchiectasis confirmed by high-resolution computed tomography - ≥ 2 exacerbations in the previous 12 months - >5 ml daily sputum - Stable for ≥ 4 weeks <p><u>Exclusion</u></p> <ul style="list-style-type: none"> - Bronchiectasis associated with cystic fibrosis or hypogammaglobulinaemia 	<p>HFNC</p> <p>34 patients with stable COPD/26 patients with stable bronchiectasis</p> <p>66.2 (9.5) years</p> <p>52% male</p> <p>FEV₁ 44.7 (20.7)% pred</p> <p>Control</p> <p>29 patients with stable COPD/19 patients with stable bronchiectasis</p> <p>69.0 (11) years</p> <p>56% male</p> <p>FEV₁ 45.3 (14.7)% pred</p>	<p>HFNC</p> <ul style="list-style-type: none"> - Flow 20–25 L/min, 37° - O₂ for patients on LTOT - ≥ 2 h/day 	Usual care	12 months	<p>Primary</p> <p>Rate of exacerbations (worsening of ≥ 2 respiratory symptoms for ≥ 2 days that required antibiotics or oral prednisone)</p> <p>Secondary</p> <p>Time to 1st exacerbation</p> <p>Exacerbation days</p> <p>Hospital admissions</p> <p>SGRQ total</p> <p>Lung function</p> <p>6MWT</p> <p>Sputum cell counts</p> <p>mMRC</p> <p>Adherence</p> <p>Willingness to use</p> <p>Adverse events</p>	<p>Exacerbations/patient/year</p> <p>HFNC 2.97 vs Control 3.63, $p = 0.067$</p> <p>Annual exacerbation days</p> <p>HFNC 18.2 vs Control 33.5, $p = 0.045$</p> <p>Days to 1st exacerbation</p> <p>HFNC 52 vs Control 27, $p = 0.049$</p> <p>Patients free of exacerbations</p> <p>HFNC 20% vs Control 8.3%, $p = 0.043$</p> <p>SGRQ total</p> <p>Sig. differences (>5.9 units) favor HFNC at 3&12 months</p> <p>FEV₁ & FVC</p> <p>Sig. differences favor HFNC at 3&12 months</p> <p>Other outcomes</p> <p>No sig. differences between groups</p> <p>Adherence</p> <p>1.6 (0.67) h/day; 32% ≥ 2 h/day</p> <p>Willingness to use</p> <p>77% wished to continue HFNC</p> <p>Adverse events</p> <p>None reported</p>
Bräunlich et al., 2015 ²²	Germany	Non-randomized, crossover study	<p><u>Inclusion</u></p> <ul style="list-style-type: none"> - COPD - Body mass index < 30 kg/m² - Stable hypercapnia (≥ 50 mmHg) - Stable disease (exacerbation-free time of 6 weeks) <p><u>Exclusion</u></p> <ul style="list-style-type: none"> - Heart decompensation - Acute illness - Acute respiratory insufficiency 	<p>11 patients with COPD</p> <p>66.7 years</p> <p>64% male</p> <p>FEV₁ 29.7% pred</p>	<p>HFNC (First)</p> <ul style="list-style-type: none"> - 20 L/min with O₂ - ≥ 5 h/day 	<p>NIV (Second)</p> <ul style="list-style-type: none"> with O₂ ≥ 5 h/day 	12 weeks (6 weeks each arm, no washout)	<p>Primary</p> <p>PaCO₂</p>	<p>PaCO₂ mmHg</p> <p>HFNC 45.5 vs NIV 46.4, $p > 0.05$</p> <p>Spontaneous breathing 53.7 vs HFNC 45.5, $p < 0.05$</p> <p>Spontaneous breathing 53.7 vs NIV 46.4, $p < 0.05$</p>

Table 1 (Continued)

First author, year	Country	Design	Eligibility criteria	Participants	Intervention	Comparator	Follow-up period	Outcomes	Main results
Nagata et al., 2018 ³¹	Japan	Randomized crossover trial	<u>Inclusion</u> - ≥ 20 years - Hypercapnia - GOLD stages 2–4 - LTOT ≥ 16 h/day for ≥ 1 month <u>Exclusion</u> - Exacerbation within 6 weeks of enrolment - Used nocturnal NIV within 6 weeks of enrolment - Active malignancy	Group A (HFNC/LTOT then LTOT) 13 patients with COPD 73.8 (6.9) years 92.3% males FEV ₁ 29.44 (16.82)% pred Group B (LTOT then HFNC/LTOT) 16 patients with COPD 76.2 (9.3) years 88% males FEV ₁ 29.43 (11.21)% pred	HFNC+LTOT Flow rate 30–40 L/min with O ₂ Flow to maintain SpO ₂ > 88% If discomfort, minimum flow of 20 L/min ≥ 4 h/night	LTOT O ₂ 0.25–4 L/min	12 weeks (6 weeks each arm, no washout)	Primary SGRQ-C <u>Secondary</u> PaCO ₂ Nocturnal PtcCO ₂ Exacerbations (worsening of baseline respiratory symptoms that required treatment with oral corticosteroids and/or antibiotics) PaO ₂ SpO ₂ EQ-5D-5L mMRC Lung function Physical activity 6MWT Adherence Adverse events	SGRQ-C Total -7.8 ($-11.9, -3.7$), $p < 0.01$ Symptom -10.8 ($-15.3, -6.3$), $p < 0.01$ Activity -4.7 ($-8.7, -0.6$), $p = 0.03$ Impact -8.7 ($-15, -2.5$), $p = 0.01$ PaCO ₂ -4.1 ($-6.5, -1.7$) mmHg, $p < 0.01$ Nocturnal PtcCO ₂ -5.1 ($-8.4, -1.8$) mmHg, $p < 0.01$ <u>Exacerbations</u> HFNC + LTOT 0% vs LTOT 19% EQ-5D-5L Score 0.05 ($-0.01, 0.11$), $p = 0.08$ VAS 7.9 (2.9, 12.9), $p = 0.01$ Steps/day -233 ($-483, 16$), $p = 0.07$ <u>Other outcomes</u> No sig. differences observed for mMRC, PaO ₂ , SpO ₂ , Lung function, 6MWT <u>Adherence HFNC + LTOT</u> Group A 7.1 (1.5) h/day (flow 29.2 (1.9) L/min) Group B 8.6 (2.9) h/day (flow 30.3 (4.6) L/min) <u>Adverse events HFNC+LTOT</u> Night sweat ($n = 4$) Nasal discharge ($n = 1$) Insomnia ($n = 1$) Skin rash ($n = 1$)

Table 1 (Continued)

First author, year	Country	Design	Eligibility criteria	Participants	Intervention	Comparator	Follow-up period	Outcomes	Main results
Storgaard et al., 2018 ²³	Denmark	RCT	<u>Inclusion</u> - COPD with chronic hypoxemic respiratory failure - ≥ 3 months LTOT <u>Exclusion</u> - Malignant disease - Terminal nonmalignant disease - Unstable psychiatric disease - Home NIV	HFNC + LTOT 100 patients with COPD with chronic hypoxemic respiratory failure 71.0 (8.2) years 44% males FEV1 29.8 (12.6) % pred LTOT 100 patients with COPD with chronic hypoxemic respiratory failure 70.4 (9.0) years 37% males FEV1 31.8 (12.9) % pred	HFNC + LTOT Flow rate 20 L/min O ₂ to maintain SpO ₂ > 88% 8 h/day, during sleep	LTOT	12 months	<u>Primary</u> Exacerbations (worsening of dyspnea, cough and sputum production for >2 consecutive days leading to treatment with systemic glucocorticoids or antibiotics) <u>Secondary</u> PaCO ₂ PaO ₂ SaO ₂ Lung function mMRC SGRQ 6MWT Borg scale Hospitalization Mortality Adherence Adverse events	Exacerbations/patient/year HFNC + LTOT 3.12 vs LTOT 4.95, $p < 0.001$ Hospitalizations/patient/year HFNC + LTOT 1.08 vs LTOT 1.22, $p = 0.373$ mMRC HFNC+LTOT lower mean score (vs LTOT) at 3, 6, 9, 12 months ($p < 0.001$). SGRQ total HFNC + LTOT lower mean score (vs LTOT) at 6 ($p = 0.002$) & 12 months ($p = 0.033$) PaCO ₂ HFNC + LTOT lower mean value (vs LTOT) at 12 months ($p = 0.005$) 6MWT HFNC + LTOT higher mean value at 12 months ($p = 0.005$) <u>Other outcomes</u> No differences in hospitalizations, mortality, Borg, lung function, PaO ₂ , SaO ₂ <u>Adherence HFNC+LTOT</u> 86% used 286 days, mean 7 h/day <u>Adverse events</u> None reported
Bräunlich et al., 2019 ²⁴	Germany	Randomized crossover trial	<u>Inclusion</u> - COPD patients with chronic respiratory insufficiency - Stable daytime hypercapnia (PaCO ₂ ≥ 50 mmHg) - ≥ 18 y <u>Exclusion</u> - Exacerbation in the 4 weeks prior - NIV in the 14 days prior - Body mass index > 30 kg/m ²	94 patients with COPD 65.3 (9.3) years 39% males FEV1 28.5 (10.2) % pred	HFNC + LTOT Flow 20L/min O ₂ not changed from baseline 6 h/day, during sleep	NIV + LTOT	6 weeks	<u>Primary</u> PaCO ₂ <u>Secondary</u> pO ₂ SaO ₂ Respiratory rate Lung function 6MWT Borg scale SRI SGRQ VAS state of health Adherence Adverse events	HFNC + LTOT vs NIV + LTOT PaCO ₂ MD -1.4 (-3.1, 0.4), $p = 0.12$ <u>Other outcomes</u> No significant differences. HFNC + LTOT (pre vs post) PaCO ₂ MD -2.8 (95%CI -4.6, -1.1), $p = 0.002$ <u>Respiratory rate</u> MD -1.4 (95%CI -2.9, -0.0), $p = 0.046$ SRI MD 3.5 (95%CI 1.1, 5.8), $p = 0.004$ (and in 3 sub-scales Respiratory Complaints, Physical Functioning, Attendant Symptoms and Sleep) SGRQ total MD -6.2 (95%CI -8.9, -3.5), $p < 0.001$ (and all sub-scales) <u>VAS state of health</u> MD 1 (95%CI 0.2, 1.8), $p = 0.015$ <u>Other outcomes</u> No significant differences. <u>Adherence</u> HFNC + LTOT 5.2 (3.3) h/day NIV + LTOT 3.9 (2.5) h/day Difference 1.6 h/day (95%CI 0.9, 2.4), $p < 0.001$ <u>Adverse events</u> Death ($n = 2$ HFNC+LTOT; $n = 2$ NIV+LTOT) Number of severe adverse events ($n = 17$ HFNC+LTOT, $n = 21$ NIV+LTOT) Number of adverse events ($n = 33$ HFNC+LTOT, $n = 55$ NIV+LTOT)

Table 1 (Continued)

First author, year	Country	Design	Eligibility criteria	Participants	Intervention	Comparator	Follow-up period	Outcomes	Main results
Weinreich, 2019 ³²	Denmark	Post hoc analysis of a RCT (Storgaard et al., 2018)	<p>Inclusion</p> <ul style="list-style-type: none"> - COPD with chronic hypoxemic respiratory failure - ≥ 3 months LTOT <p>Exclusion</p> <ul style="list-style-type: none"> - Malignant disease - Terminal nonmalignant disease - Unstable psychiatric disease - Home NIV 	<p>HFNC+LTOT</p> <p>100 patients with COPD with chronic hypoxemic respiratory failure</p> <p>71.0 (8.2) years</p> <p>44% males</p> <p>FEV₁ 29.8 (12.6) % pred</p> <p>Divided in two groups:</p> <p>Group 0–1</p> <p>exacerbation in 1year prior</p> <p>32 patients</p> <p>74 (9) years</p> <p>50% males</p> <p>FEV₁ 31.1% pred</p> <p>Group ≥ 2</p> <p>exacerbations in 1year prior</p> <p>68 patients</p> <p>70 (7.6) years</p> <p>41% males</p> <p>FEV₁ 29.0 (12.2) % pred</p>	<p>HFNC+LTOT</p> <p>Flow rate 20 L/min</p> <p>O₂ to maintain SpO₂ > 88%</p> <p>8 h/day, during sleep</p>	<p>LTOT</p> <p>1–2 L/min</p>	12 months	<p>Exacerbations</p> <p>Hospitalizations</p>	<p>Exacerbations</p> <p>Group 0–1 –increase in number ($p=0.01$)</p> <p>Group ≥ 2 – reduction in number ($p=0.03$)</p> <p>Group differences ($p=0.05$)</p> <p>Hospitalizations</p> <p>Group 0–1 –increase in number ($p=0.01$)</p> <p>Group ≥ 2 – reduction in number ($p=0.002$)</p> <p>Group differences pre ($p=0.004$) and during study ($p<0.001$)</p> <p>Hospitalization days</p> <p>Group 0–1 –increase in days ($p=0.08$)</p> <p>Group ≥ 2 – reduction in days ($p=0.025$)</p> <p>Group differences pre ($p=0.003$) and during study ($p=0.01$)</p>
Storgaard et al., 2020 ³⁴	Denmark	Post hoc analysis of a RCT (Storgaard et al., 2018)	<p>Inclusion</p> <ul style="list-style-type: none"> - COPD with chronic hypoxemic respiratory failure - ≥ 3 months LTOT - Persistent hypercapnic failure (PaCO₂ > 6 kPa) <p>Exclusion</p> <ul style="list-style-type: none"> - Malignant disease - Terminal nonmalignant disease - Unstable psychiatric disease - Home NIV 	<p>HFNC+LTOT</p> <p>31 patients with COPD</p> <p>67 years</p> <p>32% males</p> <p>FEV₁ 24.5 (8.8) % pred</p> <p>LTOT</p> <p>43 patients with COPD</p> <p>68 years</p> <p>30% males</p> <p>FEV₁ 26.1 (6.2)% pred</p>	<p>HFNC+LTOT</p> <p>Flow rate 20 L/min</p> <p>O₂ to maintain SpO₂ > 88%</p> <p>8 h/day, during sleep</p>	<p>LTOT</p> <p>1–2 L/min</p>	12 months	<p>PaCO₂</p> <p>PaO₂</p> <p>Exacerbations</p> <p>Hospitalizations</p>	<p>PaCO₂</p> <p>HFNC+LTOT 1.3% decrease ($p=0.624$)</p> <p>PaO₂</p> <p>LTOT 7% increase ($p=0.003$)</p> <p>Exacerbations rate/year</p> <p>HFNC+LTOT decreased 0.15 ($p=0.661$)</p> <p>LTOT increased 2.2 ($p<0.001$)</p> <p>Hospitalizations/year</p> <p>HFNC+LTOT decreased 0.67 ($p=0.013$)</p> <p>LTOT increased +0.3 ($p=0.180$)</p> <p>Other outcomes</p> <p>No sig. differences in PaO₂ between groups</p>
Good et al., 2021 ³³	New Zealand	Post hoc analysis of a RCT (Rea et al., 2010)	<p>Inclusion</p> <ul style="list-style-type: none"> - Bronchiectasis confirmed by high-resolution computed tomography - ≥ 2 exacerbations in the previous year - >5 ml daily sputum - Stable for ≥ 4 weeks <p>Exclusion</p> <ul style="list-style-type: none"> - bronchiectasis associated with cystic fibrosis or hypogammaglobulinaemia 	<p>HFNC</p> <p>26 patients with stable bronchiectasis</p> <p>63 (11.4) years</p> <p>42% male</p> <p>FEV₁ 56.5 (20.2)% pred</p> <p>Control</p> <p>19 patients with stable bronchiectasis</p> <p>65 (13.9) years</p> <p>37% male</p> <p>FEV₁ 42.42 (15.2)% pred</p>	<p>HFNC</p> <p>- Flow 20–25 L/min, 37°</p> <p>- O₂ for patients on LTOT</p> <p>- ≥ 2 h/day</p>	<p>Usual care</p>	12 months	<p>Primary</p> <p>Rate of exacerbations (worsening of ≥ 2 respiratory symptoms for ≥ 2 days that required antibiotics or oral prednisone)</p> <p>Secondary</p> <p>Time to 1 st exacerbation</p> <p>N of exacerbated days</p> <p>SGRQ</p> <p>Lung function</p> <p>6MWT</p>	<p>Exacerbations/patient/year</p> <p>HFNC 2.39 vs Control 3.48, $p=0.034$</p> <p>Annual exacerbation days</p> <p>HFNC 10.3 vs Control 29.9, $p=0.056$</p> <p>Days to 1st exacerbation</p> <p>HFNC 84 vs Control 54, $p=0.316$</p> <p>Patients free of exacerbations</p> <p>HFNC 20% vs Control 8.3%, $p=0.043$</p> <p>SGRQ changes</p> <p>Total HFCN –12.3 vs Control –1.2, $p=0.028$</p> <p>Impact HFCN –14.7 vs Control –1.6, $p=0.018$</p> <p>Other outcomes</p> <p>No differences between groups for FEV₁, FVC, 6MWT, SGRQ symptoms/activity</p>

Table 1 (Continued)

First author, year	Country	Design	Eligibility criteria	Participants	Intervention	Comparator	Follow-up period	Outcomes	Main results
Crimi et al., 2022 ²⁵	Italy	Retrospective case-control study	<p>Inclusion</p> <ul style="list-style-type: none"> - A diagnosis of radiologically and clinically significant bronchiectasis - Chronic cough, sputum production most days of the week and/or frequent respiratory infections - ≥ 1 severe exacerbation 1 year prior - Optimized treatment <p>Exclusion</p> <ul style="list-style-type: none"> - Cystic fibrosis - Tracheobronchiectasis 	<p>HFNC</p> <p>20 patients with bronchiectasis</p> <p>70.7 (9.4) years</p> <p>30% males</p> <p>FEV1 58.8 (18)% pred</p> <p>Control</p> <p>20 patients with bronchiectasis</p> <p>68.6 (8.9) years</p> <p>30% males</p> <p>FEV1 63.2 (17.7)% pred</p>	<p>HFNC</p> <p>Flow 25–40 L/min</p> <p>34 °C or 37 °C (according to tolerance)</p> <p>O₂ adjusted to maintain SpO₂ \geq 92%</p> <p>6 h/day, during sleep</p>	Usual care	12 months	<p>Primary</p> <p>Rate of exacerbations (physician determining a change in treatment in the presence of deterioration in ≥ 3 Symptoms for ≥ 48 h)</p> <p>Secondary</p> <p>Hospitalizations</p> <p>mMRC</p> <p>Sputum color</p> <p>Difficulty of mucus expectoration (VAS 1–10)</p> <p>SGRQ</p> <p>Lung function</p> <p>SpO₂</p> <p>Adherence</p> <p>Adverse events</p>	<p>Exacerbations</p> <p>MD (HFNC- Control) -1.9 (95%CI $-2.8, -0.9$), $p = 0.001$</p> <p>Hospitalizations</p> <p>MD -0.7 (95%CI $-1.1, -0.3$), $p = 0.001$</p> <p>Difficulty of mucus expectoration</p> <p>MD -2.2 (95%CI $-3.9, -0.5$), $p = 0.012$</p> <p>SGRQ total</p> <p>MD -10.4 (95%CI $-20.2, -0.6$), $p = 0.039$</p> <p>FEV₁, %pred</p> <p>MD 6.1 (95%CI 1,11.3), $p = 0.022$</p> <p>FVC, %pred</p> <p>MD 4.6 (95%CI 0.8,8.3), $p = 0.019$</p> <p>Other outcomes</p> <p>No significant differences in mMRC and SpO₂</p> <p>Adherence</p> <p>6.3 (1.8) h/day</p> <p>Adverse events</p> <p>No serious events</p> <p>Poor tolerance ($n = 1$)</p> <p>Personal reasons ($n = 1$)</p>
Nagata et al., 2022 ²⁹	Japan	RCT	<p>Inclusion</p> <ul style="list-style-type: none"> - ≥ 40 years - Daytime hypercapnia (PaCO₂ > 45 mmHg and pH > 7.35) - GOLD stages 2–4 - LTOT for ≥ 16 h/day for ≥ 1 month - ≥ 1 moderate/severe exacerbation 1 year prior - Stable and free from a exacerbation 4 weeks prior <p>Exclusion</p> <ul style="list-style-type: none"> - NIV 4 weeks prior - HFNC 1 year prior - History/suspicion of obstructive sleep apnea 	<p>HFNC+LTOT</p> <p>49 patients with COPD</p> <p>72.9 (7.4) years</p> <p>90% males</p> <p>FEV₁ 25.6 (8.4)% pred</p> <p>LTOT</p> <p>50 patients with COPD</p> <p>75.2 (6.7) years</p> <p>88% males</p> <p>FEV₁ 27.1 (8.9)% pred</p>	<p>HFNC+LTOT</p> <p>Flow 30–40 L/min</p> <p>If discomfort, minimum flow of 20 L/min</p> <p>37 °C (if discomfort 34 °C or 31 °C)</p> <p>O₂ adjusted to maintain SpO₂ > 88%</p> <p>>4 h/day during sleep</p>	LTOT	52 weeks	<p>Primary</p> <p>Rate of moderate/severe exacerbations</p> <p>Secondary</p> <p>Time to the 1st exacerbation</p> <p>Death</p> <p>mMRC</p> <p>SGRQ</p> <p>Pittsburgh Sleep Quality Index</p> <p>6MWT</p> <p>Lung function</p> <p>SpO₂</p> <p>Physiological parameters</p> <p>Adherence</p> <p>Adverse events</p>	<p>Rate of moderate/severe exacerbations</p> <p>LTOT (ref HFNC+LTOT) Adjusted mean count 2.85 (95%CI 1.48–5.47), $p = 0.002$</p> <p>Time to 1st moderate/severe exacerbation</p> <p>LTOT vs HFNC+LTOT, $p = 0.032$</p> <p>SpO₂</p> <p>HFNC+LTOT 1.01 (0.33)% vs LTOT -0.20 (0.32)%, $p = 0.010$</p> <p>Other outcomes</p> <p>No significant differences.</p> <p>Adherence HFNC/LTOT</p> <p>7.3 (3) h/day (flow 28.5 (4.6) L/min)</p> <p>Adverse events</p> <p>Infections and infestations: HFNC/LTOT 26.5% vs LTOT 32%</p> <p>Respiratory, thoracic, and mediastinal disorders: HFNC/LTOT 38.8% vs LTOT 42%</p>

Table 1 (Continued)

First author, year	Country	Design	Eligibility criteria	Participants	Intervention	Comparator	Follow-up period	Outcomes	Main results
Weinreich et al., 2022 ²⁷	Denmark	Crossover study	<u>Inclusion criteria</u> - ILD diagnosis - prescribed ambulatory oxygen treatment or LTOT < 12 months prior - Age > 18 years <u>Exclusion criteria</u> - Life expectancy < 3 months - Pneumonia/exacerbation of ILD < 3 months prior	9 patients with ILD 69 (5) years 56% males FEV ₁ 69.9 (20)% pred	HFNC Flow ≥ 30 L/min 37 °C O ₂ as prescribed for LTOT/ambulatory oxygen treatment 8 h/day, preferably during sleep	No HFNC	6 weeks	6MWT (distance and time to SpO ₂ recovery) Lung function PaO ₂ PaCO ₂ mMRC SGRQ Richards-Campbell sleep questionnaire Adherence Adverse events	<u>6MWT distance</u> 393 (42) m vs after HFNC 441 (22) m, <i>p</i> = 0.049 <u>Time to SpO₂ recovery</u> 3.4 (3.0) min vs after HFNC 2.2 (1.1) min, <i>p</i> = 0.001 <u>Other outcomes</u> No significant differences. Adjusting for hours of HFNC use, mMRC (<i>p</i> = 0.04) and minimum oxygen saturation during 6MWT (<i>p</i> = 0.01) improved. <u>Adherence</u> 6.5 (1) h/day <u>Adverse events</u> Mild rhinorrhea (<i>n</i> = 5) Bothered by the device heat (<i>n</i> = 3) Exacerbation (=1)
Simioli et al., 2023 ²⁶	Italy	Non-randomized crossover study	<u>Inclusion criteria</u> - ≥ 18 years - Radiological evidence of bronchiectasis on HRCT - ≥ 2 exacerbations/hospitalizations - Smoke cessation > 3 months - Ability to use electronic devices <u>Exclusion criteria</u> - Exacerbation 7 days prior - pO ₂ < 60 mmHg - LTOT > 2 L/min - Chronic use of NIV (...)	78 patients with bronchiectasis M 70 (IQR 60–76) years 46.2% males FEV ₁ 2.39 (0.87)L	HFNC (Second) Flow 35–60 L/min 31–37 °C FiO ₂ 0.21 O ₂ not added 2 years	Usual care (First) 12 months	36 months	<u>Primary</u> Exacerbations (warrant additional treatment (e.g., antibiotic, systemic corticosteroid, bronchodilators)) <u>Secondary</u> Hospitalizations Lung function mMRC Adherence (≥ 2 h/day, ≥ 4 days/week) Adverse events	<u>Exacerbations/year</u> 2.81 (2.15) vs 2 months 2.36 (0.69), <i>p</i> = 0.98 2.81 (2.15) vs 2 years 0.45 (0.66), <i>p</i> < 0.001 <u>Hospitalizations/year</u> 1.65 (2.10) vs 2 years 0.56 (0.98), <i>p</i> < 0.001 <u>Lung function</u> FEV ₁ 2.39 (0.87)L vs 2 years 2.55 (0.82)L, <i>p</i> = 0.45 <u>FVC</u> 2.73 (0.88)L vs 2 years 2.84 (0.90)L, <i>p</i> = 0.66 <u>mMRC</u> 2.4 (0.81) vs 2 months 0.97 (0.97), <i>p</i> < 0.001 2.4 (0.81) vs 2 years 0.60 (0.78), <i>p</i> < 0.001 <u>Adherence</u> 100%, 2 months 100%, 2 years 95% <u>Adverse events</u> Minor epistaxis (<i>n</i> = 1) Interface discomfort (<i>n</i> = 1), Dysphagia (<i>n</i> = 2)

Table 1 (Continued)

First author, year	Country	Design	Eligibility criteria	Participants	Intervention	Comparator	Follow-up period	Outcomes	Main results
Weinreich et al., 2023 ²⁸	Denmark	Retrospective study	Inclusion criteria - Patients with COPD - Treated with LTOT plus either long-term HFNC or NIV, in whom a 2nd add-on (NIV or HFNC) was initiated	HFNC+LTOT baseline 17 patients with COPD 66.8 (7.3) years 35% males FEV ₁ 27.1 (8.2)% pred NIV+LTOT baseline 16 patients with COPD 68.3 (7.5) years 43.8% males FEV ₁ 30.5 (8.8)% pred	HFNC+LTOT baseline Prescribed according to the Danish Respiratory Society guidelines (or physician discretion before 2019) 12 patient started also NIV (night)	NIV+LTOT baseline Prescribed according to the Danish Respiratory Society guidelines 13 patients started also HFNC (day)	~29 months (908/586 days)	Hospitalizations	Hospitalizations HFNC+LTOT 2.5 (0.4) vs 12 months 1.5 (0.4), p=0.022 NIV+LTOT 2.9 (0.5) vs 12 months 1.6 (0.4), p=0.014

Abbreviations: 6MWT, 6 min walking test; FEV₁, forced expiratory volume in the first second; FiO₂, fraction of inspired oxygen; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HFNC, high-flow nasal cannula; IQR, interquartile range; LTOT, long-term oxygen treatment; MD, mean difference; M, median; mMRC, modified Medical Research Council scale; NIV, non-invasive ventilation; PaCO₂, partial pressure of carbon dioxide; PO₂, partial pressure of oxygen; pred predicted; PtcCO₂, transcutaneous carbon dioxide pressure; SGRQ, St George Respiratory Questionnaire; SRI, Severe Respiratory Insufficiency.

to LTOT^{23,31,34} or non-invasive ventilation (NIV).²⁴ This was not observed in patients with ILD.²⁷

Health-related quality of life

Quality of life was used as an outcome measure in 8 articles, 6 of which showed results in favor of HFNC in patients with COPD,^{23,24,31} bronchiectasis,^{25,33} or both.³⁰ Different patient-reported outcome measures were used to assess this health domain: SGRQ general or the COPD specific version,^{23–25,30,31,33} EQ-5D-5L,³¹ health state visual analog scale,²⁴ Severe Respiratory Insufficiency Questionnaire.²

Lung function

Lung function, specifically FEV₁ and FVC, were one of the most common used outcome measures (n=9 articles). However, only two studies with long-term follow up of patients with COPD and bronchiectasis were able to demonstrate the superiority of HFNC over usual care for lung function.^{25,30}

Other outcomes

The 6MWT (n=7) and mMRC (n=6) were other commonly used outcomes, with the 6MWT demonstrating the superior effect of HFNC compared to LTOT and usual care in patients with COPD and ILD^{23,27}; and the mMRC compared to usual care patients with bronchiectasis.²⁶

Adherence

Adherence to HFNC has been reported in 8 studies, with most reporting adherences between 5.2 and 8.6 h/day,^{24,25,27,29,31} or a percentage of users above a certain threshold (32%³⁰ and 100%²⁶ ≥2 h, 86% 7 h/day²³). In four studies HFNC was compared to NIV/LTOT, but only Bräunlich et al. showed that adherence of HFNC was superior to NIV.²⁴

Safety

With regard to safety, 8 articles presented data on adverse events associated with HFNC, of which 3 reported no events,^{23,25,30} and the remaining presented common non-serious events^{26,27,31} or showed no differences between events observed under LTOT/NIV.^{24,29}

Discussion

In this systematic review, we comprehensively evaluated the effectiveness, adherence and safety of HFNC therapy in stable patients with COPD, bronchiectasis and ILD with chronic respiratory failure. We found that HFNC seems more effective as a long-term strategy for reducing exacerbations and improving quality of life than usual care or other home respiratory therapies, although more robust evidence is still needed. HFNC appears to have also beneficial effects on hospitalizations, paCO₂, and lung function, while being safe and having good adherence.

This review shows that HFNC is associated with a reduction in exacerbations in patients with COPD and bronchiectasis that is not inferior to NIV and greater than LTOT or usual care.^{23,25,26,29,30,33} This is an important benefit, demonstrating that HFNC contributes to the key long-term goal of reducing the frequency and severity of exacerbations in patients with chronic respiratory diseases. In addition, the reduction appears to be more significant in both hypoxic and hypercapnic patients and in those with 2 or more exacerbations in the last year.^{31,32,34} HFNC can therefore be considered as an alternative to consider in a selective group: patients with COPD and frequent acute exacerbations. As exacerbations are a major determinant of health status, this effect is probably related to the observed improvement in quality of life. It is noteworthy

that most of the studies showing effects on quality of life used the SGRO and exceeded its minimal clinically important difference (MICD) of 4 units. The improvement in quality of life highlighted in this narrative synthesis is in line with meta-analytic findings from previous systematic reviews on the effects of HFNC in COPD.^{12,13} The effectiveness of HFNC in these two health domains has also been assessed using cost-effectiveness analyses, which have shown that HFNC has the potential to provide substantial cost savings.^{35,36}

HFNC improved paCO_2 in patients with COPD and has shown to be superior to LTOT or NIV.^{23,24,31,34} This finding is consistent with a previous review in patients with COPD.¹⁴ Nevertheless, this improvement in paCO_2 needs to be considered with caution as it may be a result of the selection process and not translate the improvement expected in real-world patients with COPD. Indeed, in 4 of the 6 studies recruiting solely patients with COPD, stable hypercapnia (defined as $\text{paCO}_2 > 45$ mmHg or > 50 mmHg) was one of inclusion criteria. Benefits of HFNC on hospitalizations and lung function were also found,^{25,26,30} but this evidence comes mainly from non-randomized studies. The potential of HFNC in comparison with usual care or other home respiratory therapies in changing these outcomes needs to be further explored in future studies with larger samples and long-term follow-up. Two trials are underway that will shed light on the effect of HFNC on these outcomes.^{37,38}

The effects of HFNC on exercise tolerance and dyspnea are fragile,^{23,26,27} which may be related to the short follow-up of most studies, but also to the responsiveness of the selected outcome measures to HFNC. The MICD of the 6MWT has been estimated to be 30 m in chronic respiratory diseases,³⁹ and unless HFNC is combined with specific interventions to improve exercise tolerance, it is unlikely that its benefit will be demonstrated with such a specific measure of fitness. It has already been shown that the mMRC scale is a good tool to discriminate patients in terms of their dyspnea, but is not sensitive enough to change to be useful as an outcome in clinical trials.⁴⁰ Future studies should therefore consider including other measures that replicate activities of daily living and associated dyspnea, such as 1-min sit to stand⁴¹ and London Chest Activity of Daily Living scale.⁴²

The effectiveness of HFNC will be more clearly demonstrated if the patients' perspective is considered in the design and evaluation of interventions. Unfortunately, none of the studies in this review mentioned that the design of the interventions included input from patients or carers, or assessed patient comfort or experience. Twelve participants in one of the trials included in this review and 8 relatives participated in a qualitative study addressing the experience with HFNC.²³ Patients reported improved sleep and more energy for daily activities and found the ease of use of the device to be a strong motivator for adherence.⁴³ Future trials evaluating the effectiveness of home-based care should consider including patient-reported outcome and experience measures.⁴⁴ A combination of both is essential to fully understand the performance of home respiratory therapies and to allow patient-centered comparisons. Currently, there is no specific patient-reported experience measure for this health context, and this should be a research priority.⁴⁵ In the meantime, a COPD-specific⁴⁶ and other generic^{47,48} measures can be used. This, together with the design of pragmatic trials that take into account patient preference and experience, will provide robust real-world evidence on the role of HFNC.

Patients adhered well to HFNC, with most studies showing adherence between 5 and 8 h/day.^{24,25,27,29,31} Unfortunately at this stage we cannot know if adherence to HFNC is better than other home respiratory therapies (LTOT/NIV) as only one study made this comparison and showed results favoring HFNC.²⁴ Nevertheless the adherence reported for HFNC seems in line with the real-world adherence to NIV⁴⁹ and the common cut-offs of 4–5 h/day to define good adherence.^{50,51} The study with lower adherence (mean

1.6 h/day) was also the one in which patients were advised to use the therapy for a shorter period (2 h), which is understandable as it was one of the pioneers in testing the feasibility and safety of implementing long-term HFNC.³⁰ In addition, HFNC has been shown to be an overall safe therapy that can be deliverable at home, with adverse events similar to those known for LTOT or NIV.⁵² The concern in reporting adverse events is a stronger point of the included studies (8 out of 10 original studies). However, the method of collecting adverse events was poorly reported, with some studies appearing to use standard collection methods, while others may have relied on spontaneous patient reporting. Future trials should improve the consistency of reporting important adverse events.⁵³

Different HFNC protocols were used, differing mainly in the flow provided, the use of O_2 and the prescribed hours per day. Most studies used flows of 20–40 L/min and recommended sessions of 6–8 h per day, preferably at night. In patients on LTOT, the supplemental oxygen flow was maintained unchanged during HFNC unless a $\text{SpO}_2 < 88\%$ was detected. Differences may be related to the characteristics of the devices, but mainly to the lack of specific guidelines at the time the studies were conducted. The Danish guidelines published this year are pioneering,⁵ although based mostly on narrative review of findings and expert opinion. Other clinical practice guidelines are likely to follow, ideally using the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach.⁵⁴ This is crucial because HFNC is already being used in routine practice, as evidenced by the two retrospective studies included in this review,^{25,28} the number of editorials published,^{11,55–58} and the European Respiratory Society survey on HFNC practice (although with results not yet available). Recently, three strategies or ventilatory modalities have been described related to HFNC settings.⁵⁵ Future studies are necessary to enhance our understanding of this technique and the impact of different HFNC settings on clinical outcomes.

This systematic review has some limitations that need to be considered. Our search strategy did not include the effectiveness of HFNC in stable patients during exercise or pulmonary rehabilitation programs, for which there is also a growing body of evidence.^{59–61} This can be considered as a limitation of our work and should be addressed in future reviews. This review is the first attempt to gather evidence on the long-term use of HFNC in patients with different chronic respiratory diseases. As it was expected, the number of studies is still limited and most of the evidence comes from patients with COPD and bronchiectasis, with only one study including patients with ILD. This limits the ability to generalize the results to patients with chronic respiratory diseases. Different study designs were included that used different outcome measures. This prevented us from doing a meta-analysis. In addition, the included reports were generally of moderate to low quality. Future studies can use these previous works to better select the most responsive outcome measures, to substantiate their sample size estimates and to design feasible HFNC protocols. This will improve the overall quality of the evidence being produced, which will allow stronger research synthesis of the evidence with the addition of meta-analysis.

Conclusions

HFNC seems more effective than usual care or other home respiratory therapies as a long-term strategy for reducing exacerbations and improving quality of life in patients with COPD and bronchiectasis. This review also showed that HFNC has good adherence levels and is safe in the home setting. Real-world pragmatic trials are nevertheless needed to better clarify the effectiveness of HFNC in patients with stable chronic respiratory diseases with chronic respiratory failure.

Funding

No funding was received for this work.

Conflict of interests

Cristina Jácome, Marta Jácome, Mónica Duarte, João Carlos Winck, Savador Díaz Lobato, Manel Luján and Cátia Caneiras have no competing interests to declare. Sara Correia, Inês Flores and Patrícia Farinha are employees of ResMed. Javier Sayas Catalan received lecture honoraria from ResMed and Philips.

Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version available at <https://doi.org/10.1016/j.arbres.2024.05.001>.

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