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Tyler Pitre, Saad Abbasi, Johnny Su, Jasmine Mah, Dena Zeraatkar

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Home high flow nasal cannula for chronic hypercapnic respiratory failure in COPD: a systematic review and meta-analysis

Authors:

Tyler Pitre, MD, MA*[1]

Saad Abbasi*

Johnny Su, MD[2]

Jasmine Mah, MD MSc[3]

Dena Zeraatkar, PhD[4,5]

Affiliations

[1]Division of Respirology, Department of Medicine, University of Toronto, Toronto, ON

[2]Department of Medicine, McMaster University, Hamilton, ON

[3]Department of Medicine, Dalhousie University, Halifax, ON

[4]Health Research Methods Evidence and Impact, McMaster University Hamilton, ON

[5]Department of Anesthesia, McMaster University, Hamilton, ON

Correspondence:

Dena Zeraatkar, PhD

Email: dena.zera@gmail.com

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Background:

Chronic Obstructive Pulmonary Disease (COPD) with chronic hypercapnia is usually treated with non-invasive ventilation (NIV). High flow nasal cannula (HFNC) may be an appropriate alternative. However, the efficacy of HFNC in COPD patients with chronic hypercapnia is yet to be optimally summarized.

Methods:

We conducted a systematic review and meta-analysis using random effects with inverse variance methods. Randomized controlled trials involving adult COPD patients initiated on HFNC for at least one month were included. Outcomes of interest were all-cause mortality, acute exacerbations, hospitalizations, and change in St. George Respiratory Questionnaire (SGRQ). We assessed the risk of bias using ROB 2.0 and assessed the quality of the evidence using GRADE.

Results:

We included four randomized trials involving 440 patients. HFNC probably reduces acute exacerbations compared to standard care (RR 0.77 [95% CI 0.66 to 0.89]; moderate certainty), suggesting 69 fewer acute exacerbations per 1,000 patients. HFNC may reduce hospital admissions (RR 0.87 [95% CI 0.69 to 1.09]; low certainty) and may lower the SGRQ score (MD 8.12 units lower [95% CI 13.30 to 2.95 lower]; low certainty). However, HFNC may have no effect on mortality (RR 1.22 [95% CI 0.64 to 2.35]; low certainty).

Conclusion:

HFNC probably reduces acute exacerbations and might reduce hospital admissions in COPD patients with chronic hypercapnia. However, its effect on mortality is uncertain. Future larger RCTs with longer follow-up periods are recommended to provide more robust evidence on the efficacy of HFNC in patients with COPD.

Keywords: COPD, HFNC, meta-analysis, systematic review

Background

Chronic Obstructive Pulmonary Disease (COPD) is a highly prevalent and morbid condition. The use of non-invasive ventilation (NIV), with bilevel ventilation, is well established for acute hypercapnic respiratory failure in the hospital setting. There is evidence for NIV in patients with COPD for home use in several randomized trials, as well as a previously published meta-analysis of available trials (1). Current international guidelines recommend for NIV in COPD patients with chronic hypercapnia, but no societal guidelines have addressed the use of high flow nasal canula (HFNC) in the same population (2).

HFNC therapy has emerged as a pivotal respiratory support modality, particularly in the critical care setting. HFNC operates by delivering humidified and heated oxygen at high flow rates, typically ranging from 30 to 60 liters per minute. The high flow rates generate a positive end-expiratory pressure (PEEP), which aids in keeping the alveoli open, thereby improving oxygenation. Additionally, the consistent flow rate helps in washing out the nasopharyngeal dead space, leading to a reduction in the re-breathing of carbon dioxide and enhancing the efficiency of gas exchange (3, 4). This has led to interest in its efficacy in patients with both acute and chronic hypercapnic respiratory failure. Previous studies have shown physiologic benefit of HFNC in patients with COPD with chronic hypercapnia. These studies have largely focused on physiologic response and not on patient-important outcomes such as acute exacerbations and hospitalizations (5, 6). There has in addition been studies reviewing the efficacy of HFNC In patients with acute hypercapnic respiratory failure, demonstrating possible benefit compared to conventional oxygen (5, 7) More recently, there has been some evidence to suggest that HFNC may reduce exacerbations in stable patients with COPD and chronic hypercapnia in randomized trials (8, 9). However, the relative efficacy of HFNC in this population is still unclear and the evidence has not yet been optimally summarized.

The objective of this systematic review and meta-analysis is to provide updated evidence profile for home HFNC versus standard care in patients with COPD and chronic hypercapnic respiratory failure

Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (10). We published our protocol on Open Science Framework on July 10 2023: https://osf.io/fwuaz.

Search strategy and study criteria

We worked with an experienced research librarian to develop a search strategy. We searched MEDLINE, EMBASE, Cochrane CENTRAL, SCOPUS, and Clinicaltrials.gov for randomized trials of patients from inception to July 16, 2023. eTable 1 presents our search strategy.

We included randomized controlled trials that randomize adult patients with COPD, who have been initiated on HFNC for at least one month. We included trials with stable patients, defined as absence of exacerbations for at least one month.

Our outcomes of interest are all-cause mortality, acute exacerbations, hospitalizations, and change in SGRQ, all reported at the longest possible follow-up.

Screening

Following training and calibration to ensure sufficient agreement, reviewers worked independently and in duplicate to screen the titles and abstracts of search records and subsequently the full texts of records deemed potentially eligible at the title and abstract screening stage. Reviewers resolved conflicts through discussion and if necessary, by adjudication with a third party.

Data extraction

Following training and calibration to ensure sufficient agreement, reviewers worked independently and in duplicate to extract data from eligible studies. Reviewers resolved discrepancies by discussion and if necessary, by adjudication with a third party.

Risk of bias assessments

Following training and calibration to ensure sufficient agreement, reviewers worked independently and in duplicate to assess risk of bias using the Cochrane RoB 2.0 tool. Reviewers resolved discrepancies by discussion and if necessary, by adjudication with a third party.

Data synthesis and analysis

For all outcomes, we performed a random effect pairwise meta-meta-analysis, using the restricted maximal likelihood (REML) estimator to calculate between study heterogeneity. We used the REMAL estimator based on evidence from simulation studies that show that it outperforms other heterogeneity estimators in a variety of scenarios (11). We used the inverse variance method to pool estimates to improve reliability of the overall estimate

We report dichotomous outcomes as relative risks (RR) and continuous outcomes as mean differences (MD) with associated 95% confidence intervals (95% CI). For dichotomous outcomes, we calculated absolute effects expressed as events per 1,000 patients, using the median risk in the standard care and placebo arms. For trials that reported only relative risk and 95% CI, we performed the meta-analysis using pre-determined effect sizes and calculated standard errors from the 95% CI (12).

We summarized heterogeneity using the I^2 statistic and interpret an I^2 value of 0% to 40% as not important, 30% to 60% as moderate heterogeneity, and 50% to 90% as substantial heterogeneity, and 75%to 100% may represent considerable heterogeneity (13). We planned to use egger's test and funnel plots if estimates have at least 10 studies included.

We have pre-defined subgroups using the following moderators: PaCO2, FEV1, and risk of bias. For PaCO2 and FEV1, we performed meta-regressions. For the subgroups, we determined that a patient's PaCO2 may be an important effect modifier, where patients randomized with high PaCO2 may have les benefit than those with lower levels due to reduced efficacy of HFNC to clear higher levels CO2. We used baseline FEV1 to determine whether disease severity would result in any heterogeneity in the effectiveness of the intervention. We planned to use the ICEMAN tool to assess the credibility of statistically significant subgroup effects. We hypothesized no significant difference in these subgroups (14).

We perform all analyses using Stata version 18 (15).

Assessment of the certainty (quality) of evidence

We evaluated the certainty of evidence using the GRADE approach for meta-analysis (16, 17). For each outcome, we rated certainty of each comparison as either high, moderate, low, or very low based on: risk of bias, inconsistency, indirectness, publication bias, and imprecision. We made judgements of imprecision using the minimally contextualized approach (18).

Results

Our search identified 1758 citations and included four randomized trials for this review (8, 9, 19, 20). The number of randomized patients in each trial varied, ranging from 32 to 200 patients (9, 20).

The age of randomized patients ranged from an average of 67.45 to 75.18 years old. The participants were predominantly male.

The baseline FEV1) % predicted ranged from 26.34% to 45%. The lowest average baseline CO2 was 48.3 mmHg and the highest was 51.9 mmHg.

The follow-up across trials was predominantly 12 months, except for one which had a follow-up period of 1.3 months (9).

All trials randomized stable patients. The flow rates used ranges from as low as 20 L/min to 40 L/min. The intervention across all trials was HFNC, with varying settings. The comparison in all trials was standard care/long-term oxygen therapy.

Risk of bias

All trials were probably or at high risk of bias for acute exacerbations. No trials were at risk of bias due to issues with the randomization process. All four trials were at risk of bias due to deviations from the intended interventions, mostly due to issues with blinding of participants and investigators. Two trials were at risk of bias due to missing outcome data. No trials were at risk of bias due to issues with selection of the reported results or measurements of the outcome. One trial was assessed for period and carry-over effects and was rated at low risk of bias.

Figure 2 presents our risk of bias assessments.

Mortality

Three trials reported on mortality, including 397 patients and 31 deaths, with a median follow-up of 12 months.

We found that HFNC may have no effect mortality compared to standard care (RR 1.22 [95% CI 0.64 to 2.35]; low certainty). There was unimportant heterogeneity (I^2=0%).

Table 2 and Figure 3 presents more details on the summary of findings.

Acute exacerbations

Four trials reported on acute exacerbations, involving 440 patients, with a median follow-up of 12 months.

We found that HFNC probably reduces acute exacerbations compared to standard care (RR 0.77 [95% CI 0.66 to 0.89]; moderate certainty). This suggests that for every 1,000 patients, there are 69 fewer acute exacerbations with HFNC (ranging from 102 fewer to 33 fewer). There was unimportant heterogeneity (I^2=17.23%).

Table 2 and Figure 4 presents more details on the summary of findings.

Hospital Admissions

Two trials reported on hospital admissions, involving 100 patients, with a median follow-up of 12 months.

We found that HFNC may reduce hospital admissions compared to standard care (RR 0.87 [95% CI 0.69 to 1.09]; low certainty). This suggests that for every 1,000 patients, there may be 20 fewer hospital admissions with HFNC (ranging from 47 fewer to 14 more). There was unimportant heterogeneity (I^2=0%).

Table 2 and Figure 5 presents more details on the summary of findings.

St. George Respiratory Questionnaire

Four trials reported on SGRQ, involving 430 patients, with a median follow-up of 12 months.

We found that HFNC may lower the SGRQ score compared to standard care (MD 8.12 units lower [95% CI 13.30 to 2.95 lower]; low certainty). This suggests that the quality of life, as measured by SGRQ, might improve with HFNC. There was substantial heterogeneity detected (I^2=70.8%).

Table 2 and Figure 6 presents more details on the summary of findings.

Subgroups and meta-regressions

We found no credible subgroup effect based on risk of bias, baseline PaCO2 or FEV1 (%). eFigures 1-3 present the analysis.

Discussion

We evaluated the efficacy of HFNC compared to standard care in patients with COPD with chronic hypercapnia. We found that HFNC probably reduces acute exacerbations and might reduce hospital admissions compared to standard care, with the evidence certainty being moderate and low, respectively.

Our analysis showed uncertain effect on mortality, with significant imprecision from the few participants and few deaths included in the individual trials. Future studies will be needed to demonstrate whether there is a mortality benefit similar to those shown in patients received bilevel ventilation (1).

We also found that HFNC may lower the SGRQ score compared to standard care, indicating a potential improvement in the quality of life. This is keeping with previous analysis suggesting high comfort scores in patients with HFNC as compared to NIV in the hospital and outpatient setting (5, 21).

In Relation to Previous Findings

NIV for chronic hypercapnia is well-established and recommended by international guidelines (1, 2). However, HFNC has not been considered for this population in terms of making recommendations in the past, as there were no RCTs until recently.

Previous systematic reviews and meta-analysis have been performed on HFNC in this population however, of which have focused on physiologic effects of HFNC and not patient important outcomes, such as acute exacerbations and instead focused on outcomes such as change in PaCO2 (5). Interest in HFNC has included to acute hypercapnic respiratory failure and there have been evidence of efficacy in this population as well (7). Furthermore, previous analyses have not contextualized the results using the GRADE approach, making the analysis more difficult to interpret for evidence users, patients, and clinicians.

Strengths and Limitations

Our review has several strengths, including a comprehensive search strategy that we developed with an experienced research librarian, the inclusion of RCTs, and the use of the GRADE approach for assessing the certainty of evidence. We also followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

However, we also acknowledge several limitations. We based most outcomes on low to moderate certainty evidence, suggesting that the true effect might be substantially different from the effect estimate. The number of included trials and participants was relatively small, and the follow-up period varied across trials. Furthermore, the HFNC settings varied across trials, which could influence the results.

Patients included in existing trials had mild hypercapnia, therefore, we cannot be certain of the effects on patients with more severe disease and further trials will need to be done to confirm equal or comparable effectiveness. However, most RCTs that investigated bilevel ventilation in patients with chronic hypercapnic respiratory failure randomized patients with similar levels of PaCO2. Therefore, it is unclear what the efficacy of either of these interventions is in patients with higher PaCO2 burden (1).

Furthermore, there are few head-to-head trials investigating the efficacy of HFNC versus other types of non-invasive ventilation in this patient population. Therefore, the comparative efficacy remains unclear and future studies should aim to perform high quality studies to address this.

Future Directions

We recommend conducting larger RCTs with longer follow-up periods in future research to provide more robust evidence on the efficacy of HFNC in patients with COPD. Standardizing the HFNC settings across trials could reduce variability in the intervention and would be beneficial. Future research could also explore the impact of HFNC on other outcomes relevant to patients with COPD, such as exercise capacity, dyspnea, and health-related quality of life.

Near future guideline panels will need to address whether HFNC is appropriate given the existing body of evidence, which patients could be selected, and the types of monitoring required to ensure safe practice.

Conclusion

We found that HFNC probably reduces acute exacerbations in patients with COPD and chronic hypercapnia. Future studies will need to be done to confirm the effectiveness across other patient important outcomes.

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Figure 1. PRISMA flow diagram of included studies

Figure 2. Risk of bias assessments for all outcomes.

Figure 3. Forest plot for mortality with relative risk (RR) and 95% confidence intervals (CI)

Figure 4. Forest plot for acute exacerbations with relative risk (RR) and 95% confidence intervals (CI)

Figure 5. Forest plot for hospitalizations with relative risk (RR) and 95% confidence intervals (CI)

Figure 6. Forest plot for change in SGRQ with relative risk (RR) and 95% confidence intervals (CI)

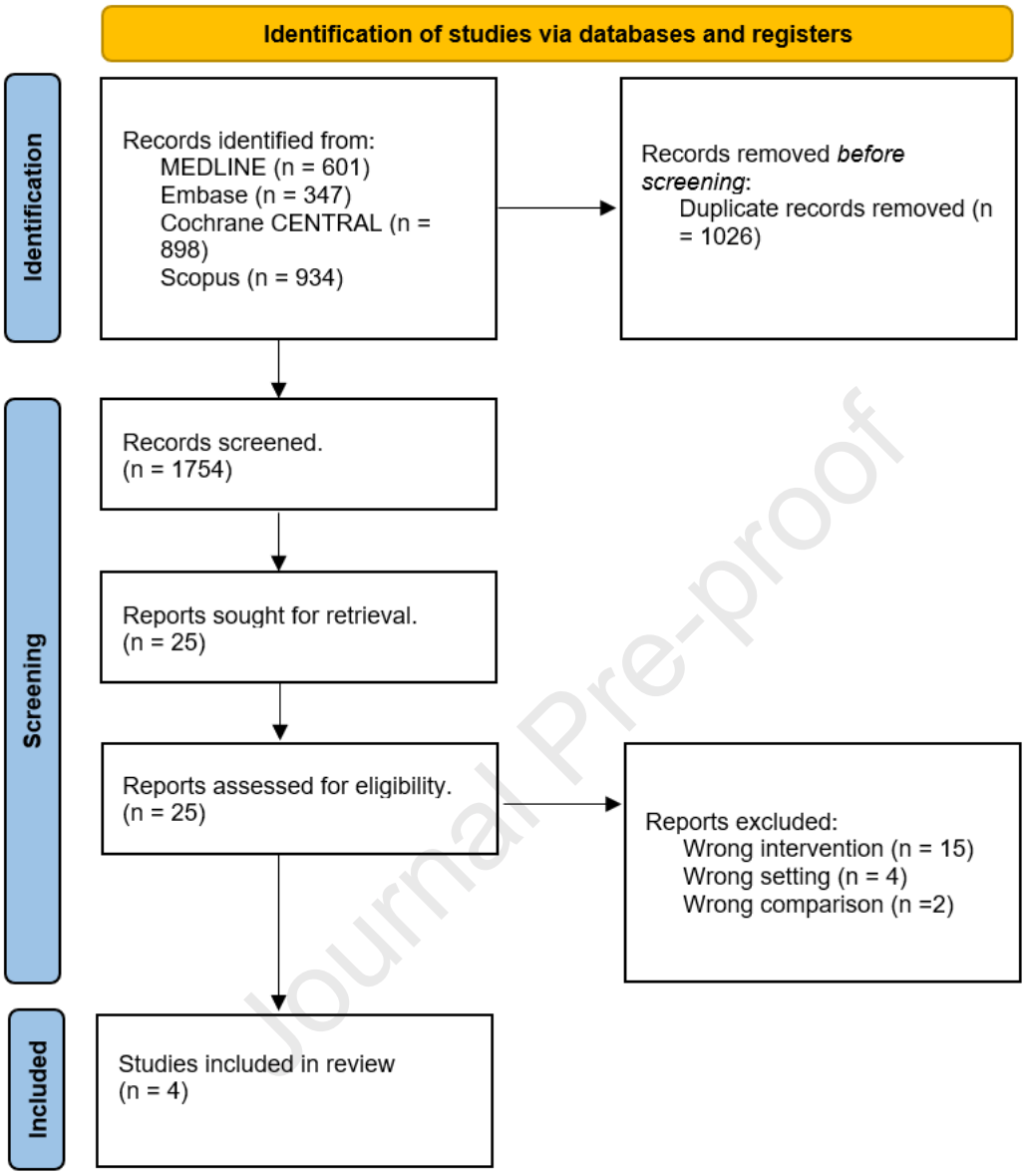
Table 2. Summary of findings table using the GRADE approach.

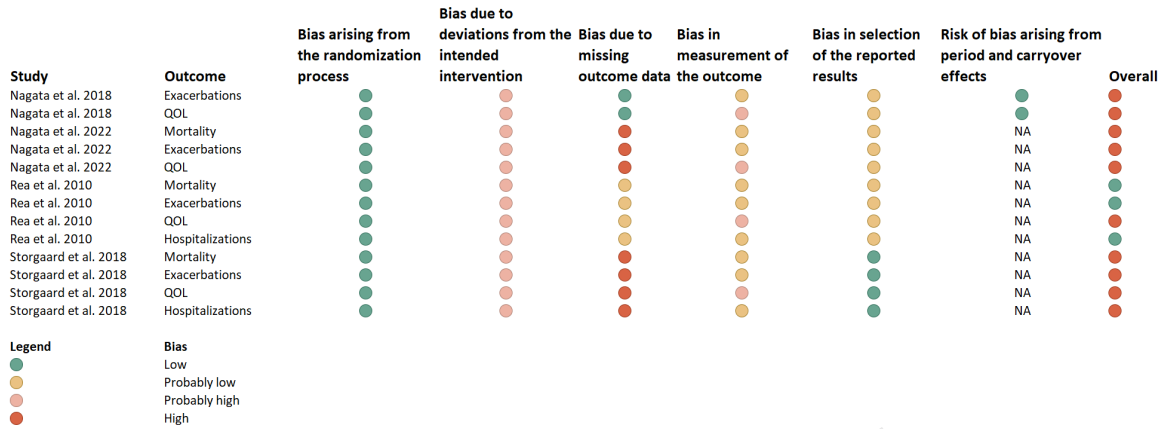
Outcomes	Number of participants (studies)	Certainty of the evidence (GRADE)	Relative risk (95% CI)	Anticipated absolute effects	
				Risk with Standard care	Risk difference with HFNC
Mortality	397 (3 RCTs)	⊕⊕◯◯ Low	**RR 1.22** (0.64 to 2.35)	73 per 1,000	**16 more per 1,000** (26 fewer to 98 more)
Acute exacerbations	440 (4 RCTs)	⊕⊕⊕◯ Moderate	**RR 0.77** (0.66 to 0.89)	300 per 1,000	**69 fewer per 1,000** (102 fewer to 33 fewer)
Hospital Admissions	100 (2 RCTs)	⊕⊕◯◯ Low	**RR 0.87** (0.69 to 1.09)	150 per 1,000	**20 fewer per 1,000** (47 fewer to 14 more)
SGRQ	430 (4 RCTs)	⊕⊕◯◯ Low	-		MD **8.14 units lower** (13.49 lower to 2.8 lower)

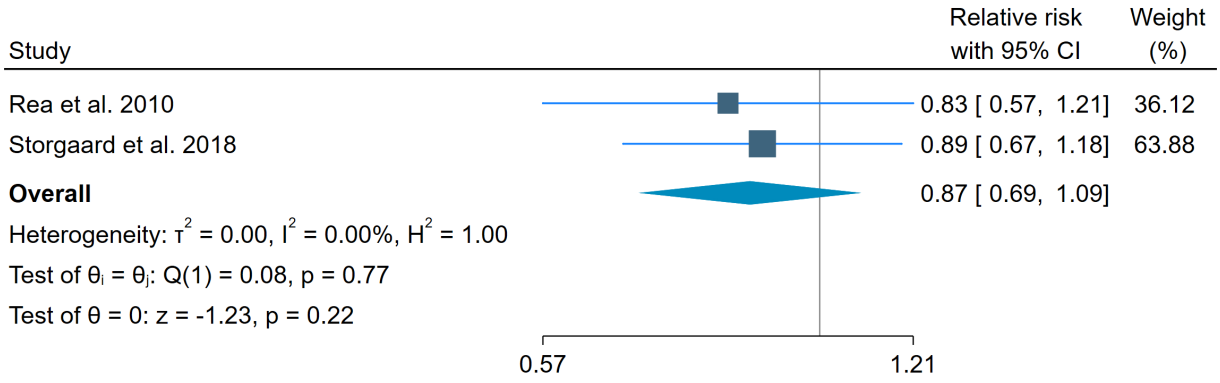
*****The risk in the intervention group **(and its 95% confidence interval) is based on the assumed risk in the comparison group and the** relative effect **of the intervention (and its 95% CI).**

CI: **confidence interval;** MD: **mean difference;** RR: **risk ratio**

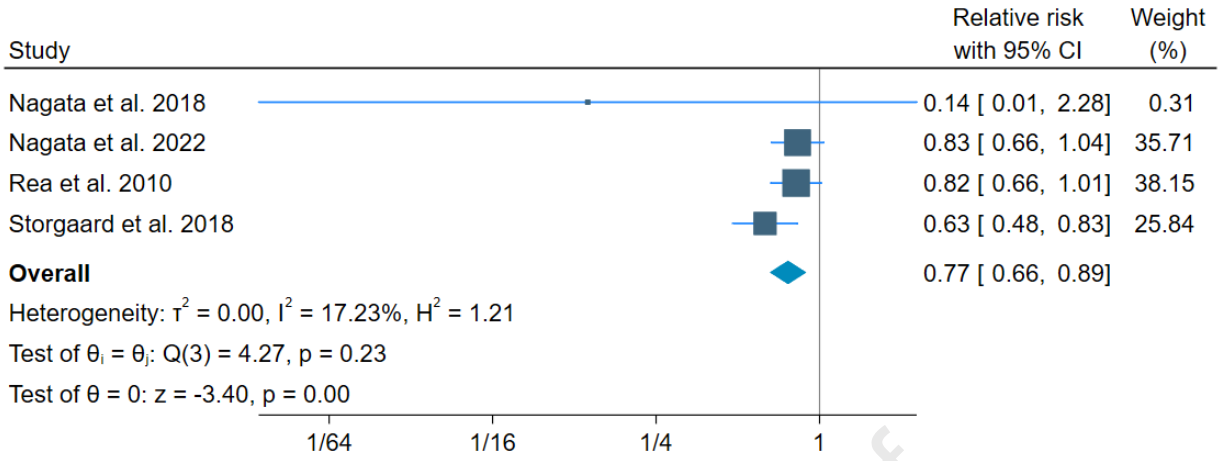
GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.







Random-effects REML model



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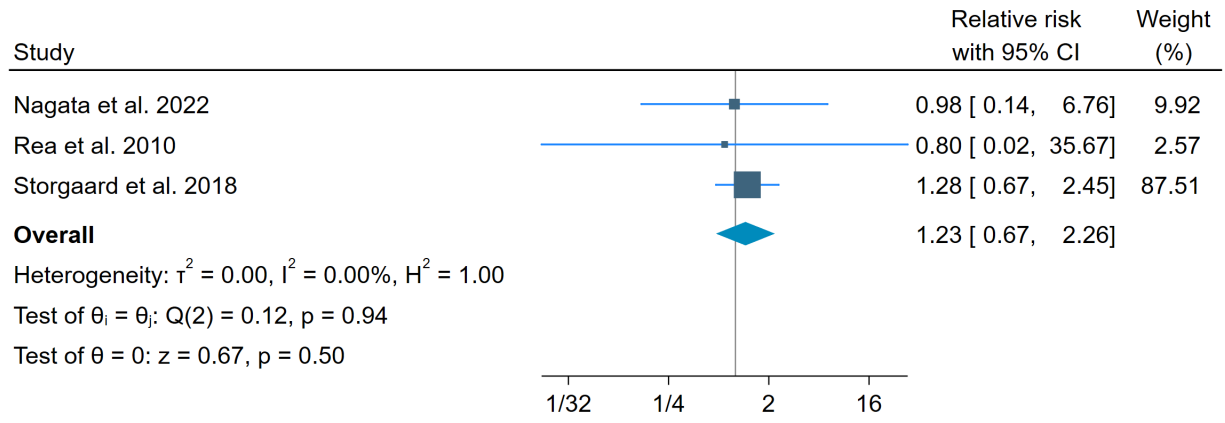

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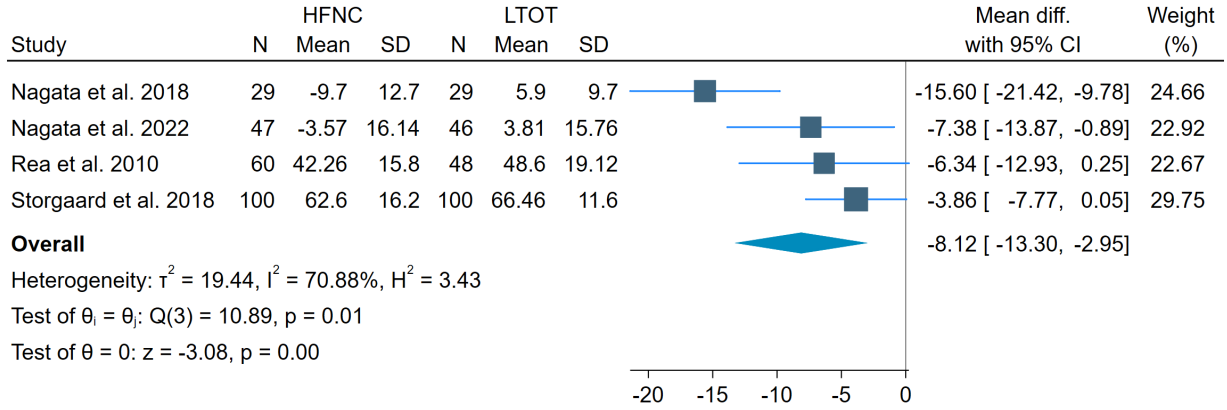

Random-effects REML model

Highlights

- Recent evidence suggests that home HFNC may be effective for COPD patients with chronic hypercapnic respiratory failure.
- Our review found that HFNC probably reduces acute exacerbations and may reduce hospitalizations as well as improve quality of life.
- Further studies are needed to determine the comparative efficacy of HFNC versus NIV

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: