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Chronic non-invasive ventilation for chronic obstructive pulmonary disease

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Chronic non-invasive ventilation for chronic obstructive pulmonary disease (Review)

Raveling T, Vonk J, Struik FM, Goldstein R, Kerstjens HAM, Wijkstra PJ, Duiverman ML

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[Intervention Review]

Chronic non-invasive ventilation for chronic obstructive pulmonary disease

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ABSTRACT

Background

Chronic non-invasive ventilation (NIV) is increasingly being used to treat people with COPD who have respiratory failure, but the evidence supporting this treatment has been conflicting.

Objectives

To assess the effects of chronic non-invasive ventilation at home via a facial mask in people with COPD, using a pooled analysis of IPD and meta-analysis.

Search methods

We searched the Cochrane Airways Register of Trials, MEDLINE, Embase, PsycINFO, CINAHL, AMED, proceedings of respiratory conferences, clinical trial registries and bibliographies of relevant studies. We conducted the latest search on 21 December 2020.

Selection criteria

We included randomised controlled trials (RCTs) comparing chronic NIV for at least five hours per night for three consecutive weeks or more (in addition to standard care) versus standard care alone, in people with COPD. Studies investigating people initiated on NIV in a stable phase and studies investigating NIV commenced after a severe COPD exacerbation were eligible, but we reported and analysed them separately. The primary outcomes were arterial blood gases, health-related quality of life (HRQL), exercise capacity (stable COPD) and admission-free survival (post-exacerbation COPD). Secondary outcomes for both populations were: lung function, COPD exacerbations and admissions, and all-cause mortality. For stable COPD, we also reported respiratory muscle strength, dyspnoea and sleep efficiency.

Data collection and analysis

We used standard methodological procedures expected by Cochrane. After inclusion of a study, we requested the IPD. We analysed continuous and time-to-event data using linear- and cox-regression mixed-effect models with a random effect on study level. We analysed dichotomous IPD using generalised estimating equations. We adjusted all models for age and sex. We assessed changes in outcomes after three and 12 months. We also conducted a meta-analysis on aggregated trial data.

Main results

We included 14 new RCTs in this review update, in addition to the seven previously included. Seventeen studies investigated chronic NIV in stable COPD and four studies investigated chronic NIV commenced after a severe COPD exacerbation. Three studies compared NIV to sham continuous positive airway pressure (2 to 4 cmH₂O). Seven studies used a nasal mask, one study used an oronasal mask and eight studies used both interfaces. Five studies did not report the interface. The majority of trials (20/21) were at high risk of performance bias due to an unblinded design. We considered 11 studies to have a low risk of selection bias and 13 to have a low risk of attrition bias. We collected and analysed the IPD from 13 stable COPD studies (n = 778, 68% of the participants included) and from three post-exacerbation studies (n = 364, 96% of the participants included).

In the stable COPD group, NIV probably results in a minor benefit on the arterial partial pressure of oxygen (PaO₂) after three months (adjusted mean difference (AMD) 0.27 kPa, 95% CI 0.04 to 0.49; 9 studies, 271 participants; moderate-certainty evidence), but there was little to no benefit at 12 months (AMD 0.09 kPa, 95% CI -0.23 to 0.42; 3 studies, 171 participants; low-certainty evidence). The arterial partial pressure of carbon dioxide (PaCO₂) was reduced in participants allocated to NIV after three months (AMD -0.61 kPa, 95% CI -0.77 to -0.45; 11 studies, 475 participants; high-certainty evidence) and persisted up to 12 months (AMD -0.42 kPa, 95% CI -0.68 to -0.16; 4 studies, 232 participants; high-certainty evidence).

Exercise capacity was measured with the 6-minute walking distance (minimal clinical important difference: 26 m). There was no clinically relevant effect of NIV on exercise capacity (**3 months**: AMD 15.5 m, 95% CI -0.8 to 31.7; 8 studies, 330 participants; low-certainty evidence; **12 months**: AMD 26.4 m, 95% CI -7.6 to 60.5; 3 studies, 134 participants; very low-certainty evidence). HRQL was measured with the Severe Respiratory Insufficiency and the St. Georges's Respiratory Questionnaire and may be improved by NIV, but only after three months (**3 months**: standardised mean difference (SMD) 0.39, 95% CI 0.15 to 0.62; 5 studies, 259 participants; very low-certainty evidence; **12 months**: SMD 0.15, 95% CI -0.13 to 0.43; 4 studies, 200 participants; very low-certainty evidence). Lastly, the risk for all-cause mortality is likely reduced by NIV (adjusted hazard ratio (AHR) 0.75, 95% CI 0.58 to 0.97; 3 studies, 405 participants; moderate-certainty evidence).

In the post-exacerbation COPD group, there was little to no benefit on the PaO₂ after three months, but there may be a slight decrease after 12 months (**3 months**: AMD -0.10 kPa, 95% CI -0.65 to 0.45; 3 studies, 234 participants; low-certainty evidence; **12 months**: -0.27 kPa, 95% CI -0.86 to 0.32, 3 studies; 170 participants; low-certainty evidence). The PaCO₂ was reduced by NIV at both three months (AMD -0.40 kPa, 95% CI -0.70 to -0.09; 3 studies, 241 participants; moderate-certainty evidence) and 12 months (AMD -0.52 kPa, 95% CI -0.87 to -0.18; 3 studies, 175 participants; high-certainty evidence). NIV may have little to no benefit on HRQL (**3 months**: SMD 0.25, 95% CI -0.01 to 0.51; 2 studies, 219 participants; very low-certainty evidence; **12 months**: SMD 0.25, 95% CI -0.06 to 0.55; 2 studies, 164 participants; very low-certainty evidence). Admission-free survival seems improved with NIV (AHR 0.71, 95% CI 0.54 to 0.94; 2 studies, 317 participants; low-certainty evidence), but the risk for all-cause mortality does not seem to improve (AHR 0.97, 95% CI 0.74 to 1.28; 2 studies, 317 participants; low-certainty evidence).

Authors' conclusions

Regardless of the timing of initiation, chronic NIV improves daytime hypercapnia. In addition, in stable COPD, survival seems to be improved and there might be a short term HRQL benefit. In people with persistent hypercapnia after a COPD exacerbation, chronic NIV might prolong admission-free survival without a beneficial effect on HRQL.

In stable COPD, future RCTs comparing NIV to a control group receiving standard care might no longer be warranted, but research should focus on identifying participant characteristics that would define treatment success. Furthermore, the optimal timing for initiation of NIV after a severe COPD exacerbation is still unknown.

PLAIN LANGUAGE SUMMARY

Non-invasive ventilation (ventilators) used at night by people with chronic obstructive pulmonary disease (COPD)

Background: Non-invasive ventilation (NIV) is a method to assist or replace spontaneous breathing (or normal breathing) with the aid of a machine called a ventilator, using a mask fitted over the nose or both the nose and mouth. NIV can be used chronically (long-term) at the person's home if they have levels of carbon dioxide in their blood that are persistently too high. We wanted to discover if using chronic NIV at home during the night alongside standard therapy was better or worse than standard therapy alone in people with chronic obstructive pulmonary disease (COPD) who have raised carbon dioxide levels. In 2002 and 2013, we published our original Cochrane Reviews investigating this. It is important to check if new studies have been done that could be added to the existing studies of the original review and would change the findings.

What is individual participant data: In this review we used individual participant data (IPD). This means that we attempted to collect original research data for each person who had participated in the original studies by requesting these individuals' data from the researcher who performed the study. We used IPD as this offers a greater chance to detect changes between groups of participants and enable the investigation of additional hypotheses. We used the IPD to perform our calculations.

Review question: What is the effect of chronic NIV in people with COPD on blood gases (oxygen and carbon dioxide), exercise capacity, quality of life, lung function, respiratory muscle function, COPD exacerbations and admissions, and survival?

Study characteristics: The evidence is current to 21 December 2020. This review update identified 14 new studies in addition to those already in the review, so in total we included 21 studies. Ten of the studies looked at people in a stable phase (stable COPD) and four studies looked at people shortly after a COPD hospital admission (post-exacerbation COPD). All studies included men and women. For our analyses, we used data from 778 people with stable COPD and 364 people with post-exacerbation COPD.

Results: In all people with COPD who had raised levels of carbon dioxide, chronic NIV for three and 12 months improved blood gases. In stable COPD, chronic NIV also might have improved quality of life, and survival seemed to be better compared to people who were treated with standard care only. There was no relevant benefit of NIV on exercise capacity. People using chronic NIV after a COPD admission experienced less benefit; carbon dioxide levels decreased, the time to the next hospital admission might have been longer when treated with NIV but quality of life and survival were not affected by chronic NIV.

Certainty of the results: Our confidence in the certainty (according to GRADE criteria) is good when looking at the blood gases. For the other outcomes, the certainty of the evidence is moderate to very low because the participants and the researcher were aware of the treatment the people received, and due to a wide range in the observed effect. This means that further research might change the results.

SUMMARY OF FINDINGS

Summary of findings 1. Summary of Findings Table - Chronic non-invasive ventilation compared to standard treatment for people with stable COPD

Chronic non-invasive ventilation compared to standard treatment for people with stable COPD

Patient or population: stable COPD **Setting:** home treatment **Intervention:** NIV **Comparison:** Standard care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Standard care	Risk with NIV				
Change in arterial partial pressure of oxygen follow up: 3 months	The mean change in arterial partial pressure of oxygen was -0.07 kPa ^a	MD 0.27 kPa higher (0.04 higher to 0.49 higher) ^b	-	271 (9 RCTs)	⊕⊕⊕⊖ MODERATE ^{c, d}	Chronic NIV probably results in a slightly greater increase in arterial partial pressure of oxygen after 3 months.
Change in arterial partial pressure of oxygen follow up: 12 months	The mean change in arterial partial pressure of oxygen was -0.06 kPa	MD 0.09 kPa higher (0.23 lower to 0.42 higher) ^b	-	171 (3 RCTs)	⊕⊕⊖⊖ LOW ^{c, e}	Chronic NIV may result in little to no difference in arterial partial pressure of oxygen after 12 months.
Change in arterial partial pressure of carbon dioxide follow up: 3 months	The mean change in arterial partial pressure of carbon dioxide was -0.17 kPa	MD 0.61 kPa lower (0.77 lower to 0.45 lower) ^b	-	475 (11 RCTs)	⊕⊕⊕⊕ HIGH ^{c, f}	Chronic NIV results in a reduction in the arterial partial pressure of carbon dioxide after 3 months.
Change in arterial partial pressure of carbon dioxide follow up: 12 months	The mean change in arterial partial pressure of carbon dioxide was -0.05 kPa	MD 0.42 kPa lower (0.68 lower to 0.16 lower) ^b	-	232 (4 RCTs)	⊕⊕⊕⊕ HIGH ^c	Chronic NIV results in a reduction in arterial partial pressure of carbon dioxide after 12 months.
Change in 6-minute walking distance follow up: 3 months	The mean change in 6-minute walking distance was 16.0 metres	MD 15.5 metres higher (0.8 lower to 31.7 higher) ^b	-	330 (8 RCTs)	⊕⊕⊖⊖ LOW ^{d, g}	The evidence suggests that chronic NIV results in little to no difference on the 6-minute walking distance test. Sensitivity analysis limited to high-quality studies suggest a significant benefit; however, this treatment estimate does not reach the minimal important difference of 26m.

Change in 6-minute walking distance follow up: 12 months	The mean change in 6-minute walking distance was -10.7 metres	MD 26.4 metres higher (7.6 lower to 60.5 higher) ^b	-	134 (3 RCTs)	⊕⊕⊕⊕ VERY LOW ^{g, h}	Chronic NIV may increase the 6-minute walking distance but the evidence is very uncertain. This treatment estimate reaches the clinical relevance of 26m in this specific population.
Change in the health-related quality of life assessed with: SRI and SGRQ follow up: 3 months ⁱ	-	SMD 0.39 SD higher (0.15 higher to 0.62 higher) ^b	-	259 (5 RCTs)	⊕⊕⊕⊕ VERY LOW ^{d, j}	Chronic NIV may increase health-related quality of life after 3 months but the evidence is very uncertain. Considering the standard deviation of 12 units on the SRI, the observed SMD does seem to reach the minimal important difference of approximately 5 points in this specific population.
Change in the health-related quality of life assessed with: SRI and SGRQ follow up: 12 months ⁱ	-	SMD 0.15 SD higher (0.13 lower to 0.43 higher) ^b	-	200 (4 RCTs)	⊕⊕⊕⊕ VERY LOW ^{h, j}	The evidence is very uncertain about the effect of chronic NIV on health-related quality of life after 12 months. Considering a standard deviation of 12.2 units on the SRI, the observed SMD does not seem to reach the minimal important difference of approximately 5 points.
All-cause mortality follow up: median 30 months	Study population		HR 0.75 (0.58 to 0.97) [All-cause mortality] ^k	405 (3 RCTs)	⊕⊕⊕⊕ MODERATE ^{c, d}	Chronic NIV likely reduces all-cause mortality (number needed to treat for an additional beneficial outcome 14, 95% CI 8 to 120).
	655 per 1000	550 per 1000 (461 to 644)				

***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; **SMD:** Standardised mean difference; **HR:** Hazard 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

See interactive version of this table: https://gdt.gradeapro.org/presentations/#/isof/isof_question_revman_web_417569665332318026.

- For the risk with standard care, we calculated an absolute difference in the outcome between the baseline measurement and both follow-up measurements (3 and 12 months)
- The mean difference was obtained from the pooled individual participant data, and was adjusted for age and sex.
- Not downgraded; although the participants and investigators were not blinded in the majority of the trials, this is unlikely to affect blood gases and survival.
- Downgraded by one for serious imprecision; the CI includes the possibility of no (relevant) benefit and of a substantial benefit.
- Downgraded by one due to serious imprecision: the CI includes the possibility of harm and of a large substantial benefit.

- f. Inconsistency not downgraded; although substantial heterogeneity was observed ($P = 0.001$, $I^2 = 65\%$), this could be explained by the subgroup analysis.
- g. Downgraded by one due to high risk of bias; the majority of the trials did not blind participants and investigators/personnel to the treatment allocation.
- h. Downgraded by two due to serious imprecision: the CI includes the possibility of harm and of a large substantial benefit.
- i. SRI: Severe Respiratory Insufficiency questionnaire; SGRQ: St. George's Respiratory Questionnaire
- j. Downgraded by one due to high risk of bias; no trials blinded participants and investigators/personnel to the treatment allocation.
- k. The hazard ratio was obtained from the pooled individual participant data, and was adjusted for age, sex and the baseline arterial pressure of carbon dioxide.

Summary of findings 2. Summary of Findings Table - Chronic non-invasive ventilation compared to standard treatment following a severe exacerbation for people with severe COPD

Chronic non-invasive ventilation compared to standard treatment following a severe exacerbation for people with severe COPD

Patient or population: post-exacerbation COPD **Setting:** home treatment **Intervention:** NIV **Comparison:** Standard care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Standard care	Risk with NIV				
Change in arterial partial pressure of oxygen follow up: 3 months	The mean change in arterial partial pressure of oxygen was 0.19 kPa ^a	MD 0.1 kPa lower (0.65 lower to 0.45 higher) ^b	-	234 (3 RCTs)	⊕⊕⊕⊖ LOW c, d	The evidence suggests that chronic NIV results in little to no difference in arterial partial pressure of oxygen after 3 months.
Change in arterial partial pressure of oxygen follow up: 12 months	The mean change in arterial partial pressure of oxygen was 0.48 kPa	MD 0.27 kPa lower (0.86 lower to 0.32 higher) ^b	-	170 (3 RCTs)	⊕⊕⊕⊖ LOW c, d	Chronic NIV may result in a slight reduction in arterial partial pressure of oxygen after 12 months.
Change in arterial partial pressure of carbon dioxide follow up: 3 months	The mean change in arterial partial pressure of carbon dioxide was -0.59 kPa	MD 0.4 kPa lower (0.7 lower to 0.09 lower) ^b	-	241 (3 RCTs)	⊕⊕⊕⊖ MODERATE c, e	Chronic NIV likely reduces the arterial partial pressure of carbon dioxide after 3 months.
Change in arterial partial pressure of carbon dioxide follow up: 12 months	The mean change in arterial partial pressure of carbon dioxide was -0.61 kPa	MD 0.52 kPa lower (0.87 lower to 0.18 lower) ^b	-	175 (3 RCTs)	⊕⊕⊕⊕ HIGH c	Chronic NIV results in a reduction in the arterial partial pressure of carbon dioxide after 12 months.

Change in the health-related quality of life assessed with: SRI and SGRQ follow up: 3 months ^f	-	SMD 0.25 SD higher (0.01 lower to 0.51 higher) ^b	-	219 (2 RCTs)	⊕⊕⊕⊕ VERY LOW ^{e, g}	Chronic NIV may increase/have little to no effect on health-related quality of life after 3 months but the evidence is very uncertain. Considering a standard deviation of 11.2 on the SRI, the SMD does not seem to reach the minimal important difference.
Change in the health-related quality of life assessed with: SRI and SGRQ follow up: 12 months ^f	-	SMD 0.25 SD higher (0.06 lower to 0.55 higher) ^b	-	164 (2 RCTs)	⊕⊕⊕⊕ VERY LOW ^{e, g}	Chronic NIV may increase/have little to no effect on health-related quality of life after 12 months but the evidence is very uncertain. Considering a standard deviation of 11.9 on the SRI, the SMD does not seem to reach the minimal important difference.
Admission-free survival follow up: 1 year	Study population		HR 0.71 (0.54 to 0.94) [readmission or death] ^h	317 (2 RCTs)	⊕⊕⊕⊕ LOW ^{e, i, j}	The evidence suggests chronic NIV improves admission-free survival (number needed to treat for an additional beneficial outcome 12, 95% CI 7 to 61).
	333 per 1000	458 per 1000 (356 to 552)				
All-cause mortality follow up: median 21 months	Study population		HR 0.97 (0.74 to 1.28) [All-cause mortality] ^h	318 (2 RCTs)	⊕⊕⊕⊕ LOW ^{c, d}	The evidence suggests that chronic NIV does not improve all-cause mortality.
	642 per 1000	631 per 1000 (532 to 731)				

***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; **SMD:** Standardised mean difference; **HR:** Hazard 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

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- a.** For the risk with standard care, we calculated an absolute difference in the outcome between the baseline measurement and both follow-up measurements (3 and 12 months).
- b.** The mean difference was obtained from the pooled individual participant data, and was adjusted for age and sex.
- c.** Not downgraded; although the participants and investigators were not blinded in the majority of the trials, this is unlikely to affect blood gases and survival.
- d.** Downgraded by two due to serious imprecision: the CI includes the possibility of significant harm and of a substantial benefit.
- e.** Downgraded by one due to serious imprecision: the CI includes the possibility of no (relevant) benefit and of a substantial benefit.
- f.** SRI: Severe Respiratory Insufficiency questionnaire; SGRQ: St. George's Respiratory Questionnaire

- g.** Downgraded by two due to high risk of bias; no trials blinded participants and investigators/personnel to the treatment allocation.
- h.** The hazard ratio was obtained from the pooled individual participant data, and was adjusted for age sex, baseline arterial partial pressure of carbon dioxide and number of COPD hospitalisations.
- i.** Downgraded by one; the majority of the participants were unblinded which could affect the likelihood of attending the emergency department. Other domains low risk of bias
- j.** Inconsistency not downgraded; although substantial heterogeneity was observed ($P = 0.05$, $I^2 = 75\%$), this heterogeneity might be explained by differences in participant selection and the timing of NIV.

BACKGROUND

Description of the condition

Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable but incurable disease that is characterised by chronic airflow obstruction due to airway disease and lung parenchymal destruction (GOLD 2021). In 2016, COPD affected over 251 million people worldwide, and is currently the third leading cause of death, claiming approximately 3.2 million lives in 2015 (WHO 2020). In general, the treatment of COPD is directed at slowing down the progression of its natural history, symptom alleviation, improvement in daily functioning and health-related quality of life (HRQL). Many patients experience exacerbations of their COPD, defined as an acute worsening of symptoms and requiring additional treatment (GOLD 2021). Exacerbations are a major problem as patients who experience frequent exacerbations, especially those requiring hospitalisation, experience accelerated deterioration of their condition, a faster decline in lung function, a high risk of rehospitalisation and a higher mortality risk (Donaldson 2002; Hurst 2010). Therefore, treatment options that reduce the risk of exacerbations are particularly attractive. As the disease progresses to an advanced stage, people experience severe symptoms of dyspnoea and are usually severely disabled in activities of daily living. In some people with advanced disease, chronic hypercapnic respiratory failure (CHRF) may follow with related symptoms, such as morning headache, and fragmented and un-refreshing sleep resulting in chronic fatigue and daytime sleepiness (Windisch 2015). At this advanced stage, treatment options are urgently needed but unfortunately still limited (van Dijk 2020).

Description of the intervention

Non-invasive ventilation (NIV) is the application of ventilatory support through a non-invasive interface, usually a nasal or oronasal mask. NIV is currently applied as evidence-based therapy for COPD patients admitted to hospital with acute hypercapnic respiratory failure (AHRF) due to an exacerbation. In this situation, NIV reduces the likelihood of endotracheal intubation, complications associated with treatment, duration of hospital stay and in-hospital mortality (Osadnik 2017). During an exacerbation, NIV is often applied intermittently or continuously for a few days to overcome the acute life-threatening respiratory failure, after which the person is weaned from ventilation and NIV can be stopped. Chronic NIV, however, entails the long-term use of nocturnal NIV. There has been much discussion about the need for chronic NIV in stable COPD, mainly because the earlier trials published conflicting results (Rossi 2000). The previous version of this Cochrane Review, which investigated chronic NIV in people with stable COPD, did not find any significant benefits on gas exchange, exercise capacity, lung function or HRQL (Struik 2013). However, it did find that a subgroup of people with more severe hypercapnia was more likely to benefit, especially when treated with higher inspiratory pressures and when NIV was used for more than five hours per day (Struik 2014).

How the intervention might work

Several theories exist as to why chronic NIV may be beneficial in stable COPD. First, chronic nocturnal NIV ameliorates nocturnal hypoventilation. This effect is intended to persist during the daytime; improved lung mechanics, improved respiratory muscle

function and resetting of the chemoresponsiveness might all contribute to a more advantageous breathing pattern, enabling the person to maintain the improved gas exchange during the day (Elliott 1991). Several studies have indicated that NIV probably stabilises forced expiratory volume in one second (FEV₁) (Duiverman 2008; Köhnlein 2014); some observations indicate that NIV might also decrease residual volume (Diaz 1999). The observation regarding FEV₁ is interesting as this was also observed without changes in static lung volume (Duiverman 2008), so might be caused by a different mechanism, possibly through the reduction of airway inflammation and oedema. It has also been postulated that NIV might rest chronically fatigued respiratory muscles. Periods of rest may lead to recovery of the inspiratory muscle function, thereby leading to an increased muscle strength and endurance capacity of the respiratory muscles during the daytime (Ambrosino 1990). Finally, NIV has been shown to improve sleep time and efficiency (Meecham Jones 1995), an effect that might be especially important for improving daily functioning and HRQL.

Why it is important to do this review

Despite all these theoretical benefits, the added value of chronic NIV in people with stable COPD remains unclear and needs further investigation. This is the second update of a Cochrane Review on this topic, the first being published in 2002 and subsequently updated in 2013 (Struik 2013; Wijkstra 2002). Since the 2013 update, more studies have been reported, including the large 2014 randomised controlled trial (RCT) by Köhnlein 2014, which showed improved gas exchange and HRQL, and a survival benefit with NIV compared to standard care alone. Also, the role of chronic NIV in the treatment of people with severe stable COPD has become more established with the publication of the European Respiratory Society (ERS) and American Thoracic Society (ATS) guidelines on long-term NIV in COPD (Ergan 2019; Macrea 2020). Additionally, since the last review update, important RCTs with conflicting results have been published that investigated the initiation of chronic NIV shortly after a severe COPD exacerbation with AHRF (Murphy 2017; Struik 2014). It has been suggested that these conflicting results are due to differences in participant selection and timing of NIV initiation. Despite these conflicting results, it is common practice in many countries to initiate chronic NIV in this specific COPD population. These new trials justify the current update of the 2013 review, which in addition to stable COPD also includes trials which investigated chronic NIV following an exacerbation of COPD, as we realise this has become part of regular clinical care by many healthcare providers.

As in the earlier versions of this review, we conducted a systematic review and a pooled analysis of individual participant data (IPD). We aimed to collect the original data of each participant from the trial authors for data checking, validation and re-analysis. Compared to conventional meta-analysis based on aggregated trial data, pooled analyses of IPD yields greater power and enables the investigation of additional hypotheses related to individual characteristics, for example within subgroups or treatment across trials. Although IPD reviews are regarded as the highest standard in systematic reviews, these reviews rely on the willingness of trial authors to share the IPD, which poses a threat to the review process. Potential risks might arise if trial authors do not agree to share the IPD as this could reduce the body of evidence. This could also introduce bias as the trials that do agree to share the IPD could

differ from trials that did not agree, e.g. differ on the population or methodological approaches. To minimise this threat, we also conducted a meta-analysis of aggregate trial data in addition to the analysis of IPD.

OBJECTIVES

To assess the effects of chronic non-invasive ventilation at home via a facial mask in people with COPD, using a pooled analysis of IPD and meta-analysis.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs in participants with COPD comparing chronic NIV at home plus standard therapy with standard therapy alone.

We differentiated between studies investigating chronic NIV in the following COPD populations:

1. stable COPD: concerns studies of people with COPD initiated on chronic NIV in a stable clinical state;
2. post-exacerbation COPD: concerns studies of people with COPD initiated on chronic NIV following an exacerbation of COPD with acute respiratory failure.

Types of participants

We included people with COPD (a ratio of FEV₁ to forced vital capacity (FVC) < 0.70), according to the most recent guideline of the Global initiative for chronic Obstructive Lung Disease at the time of writing ([GOLD 2021](#)).

Types of interventions

The intervention of interest was NIV, applied through a facial mask, prescribed for at least five hours during the night and for at least three consecutive weeks. Participants also received their usual standard COPD therapy, which comprised supplementary oxygen, optimised medication or pulmonary rehabilitation or exercise programs.

The intervention in the control group was standard therapy alone. The control group did not receive chronic NIV; sham treatment in the form of continuous positive airway pressure (without pressure support) was permitted.

Types of outcome measures

We analysed the following outcome measures with a short-term follow-up (up to three months) and a long-term follow-up (12 months).

Primary outcomes

Stable COPD

1. Change in daytime arterial blood gas tensions (partial pressure of oxygen (PaO₂), partial pressure of carbon dioxide (PaCO₂))
2. Change in exercise capacity, measured with the six-minute walking distance (6MWD)

3. Change in HRQL, measured with the Severe Respiratory Insufficiency questionnaire (SRI) ([Windisch 2003](#)) or the St George's Respiratory Questionnaire (SGRQ) ([Jones 1991](#))

Post-exacerbation COPD

1. Change in daytime arterial blood gas tensions (PaO₂ and PaCO₂)
2. Change in HRQL, measured with the SRI or the SGRQ
3. Admission-free survival, time to readmission or death of any cause

Secondary outcomes

Stable COPD

1. Change in lung function (FEV₁, FVC and residual volume/total lung capacity (RV/%TLC))
2. Change in respiratory muscle function (maximal inspiratory pressure (P_Imax), maximal expiratory pressure (P_Emax))
3. Change in dyspnoea (measured with the Transitional Dyspnoea Index (TDI) ([Mahler 1984](#)), or the (modified) Medical Research Council (MRC) dyspnoea scale) ([Bestall 1999](#))
4. Change in sleep efficiency (percentage time asleep of total time in bed)
5. Number of COPD exacerbations and hospital admissions, either self-reported or documented
6. All-cause mortality, time to death of any cause

Post exacerbation COPD

1. Change in lung function (FEV₁ and FVC)
2. Number of COPD exacerbations and hospital admissions, either self-reported or documented
3. All-cause mortality, time to death of any cause

Search methods for identification of studies

Electronic searches

We identified trials from the Cochrane Airways Register of Trials, which is maintained by the Information Specialist at the Cochrane Airways editorial base. The Register contains trial reports identified through searches of the following bibliographic databases:

- monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL), through the Cochrane Register of Studies (CRS);
- weekly searches of MEDLINE Ovid SP; 1946 to December 2020;
- weekly searches of Embase Ovid SP; 1974 to December 2020;
- monthly searches of PsycINFO Ovid SP; 1967 to December 2020;
- monthly searches of CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature); 1937 to December 2020;
- monthly searches of AMED EBSCO (Allied and Complementary Medicine); all years to December 2020;
- handsearches of the proceedings of major respiratory conferences.

Full details of the search strategies used to maintain the Cochrane Airways Register of Trials are presented in [Appendix 1](#).

The full search details of the previous versions of this review are presented in [Appendix 2](#). The search terms used for this update

can be found in [Appendix 3](#). As some adjustments were made to the inclusion criteria, we conducted the search for this update with no date restrictions. We conducted this most recent search on 21 December 2020 without any language restrictions.

The current search additionally included the following trial registries; the World Health Organization International Clinical Trials portal (www.who.int/ictrp/en/) and ClinicalTrials.gov (www.clinicaltrials.gov) (see [Appendix 3](#)).

Searching other resources

We searched the bibliographies of each RCT for additional papers that may have contained RCTs, and searched the reference lists of relevant clinical guidelines and systematic reviews for additional papers. We contacted authors of identified RCTs for other published and unpublished studies.

Data collection and analysis

Selection of studies

Two review authors independently assessed all identified abstracts; PJW and RSG for the 2002 version, FMS and PJW for the 2013 update, and TR and MD for the current update. When the review authors selected an abstract, we attempted to retrieve the full papers. The same two review authors read these in detail, and resolved any disagreements by consensus.

Data extraction and management

After inclusion of the studies, one author (TR) extracted the study characteristics of all included studies. We then contacted all trial authors by email to request the IPD of the following variables: treatment allocation, age, sex, body mass index, number of exacerbations and hospitalisations, arterial blood gases (PaO₂, PaCO₂, rate of oxygen flow), lung function (FEV₁, FVC, FEV₁/FVC), lung volumes (RV%/TLC), maximum static expiratory (PE_{max}) and inspiratory (PI_{max}) mouth pressures, 6MWD, sleep studies, dyspnoea and HRQL measures (TDI, (modified) MRC dyspnoea scale, SRI, SGRQ), time-to-event and event status, NIV settings (inspiratory- and expiratory positive airway pressures (IPAP, EPAP)) and NIV compliance (mean hours of usage per night, as read from the ventilator counter). We requested missing data from the included primary studies from the authors. We checked supplied data against study publications, after which we copied raw data from all included studies to one main database.

For the aggregated data, we calculated the mean of the absolute change between the baseline measurement and the value at the follow-up visits (three and 12 months) of the identified outcome variables ($\pm$ standard deviations (SD)) from the IPD. If the IPD were not available, two review authors (TR and MD) independently extracted the aggregated data from the studies' primary references.

Assessment of risk of bias in included studies

Two review authors (TR and MD) assessed the risk of bias of each study independently, including the seven studies of the 2013 review. We resolved disagreements by consensus. We used criteria for assessment of risk of bias as provided in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We considered potential for bias using the following domains:

- random sequence generation (selection bias);

- allocation concealment (selection bias);
- blinding of participants and personnel (performance bias);
- blinding of outcome assessment (detection bias), separately for:
 - * participant-reported outcomes (HRQL, dyspnoea),
 - * lung function, respiratory muscle testing, exercise tests,
 - * arterial blood gases, hospitalisations, mortality;
- incomplete outcome data (attrition bias);
- selective outcome reporting (reporting bias);
- other sources of bias.

We judged each domain as 'high', 'low' or 'unclear' risk of bias. If a trial reported insufficient details, the judgment was 'unclear'.

Measures of treatment effect

For continuous data, we calculated and presented an absolute difference in the outcome between the baseline measurement and both follow-up measurements (three and 12 months). Of these differences, we obtained an overall treatment effect that is presented as the adjusted mean difference (AMD) or standardised mean difference (SMD) for the pooled IPD analysis and as mean difference (MD) or SMD with associated 95% CI for the aggregated data meta-analysis. We measured the number of COPD exacerbations and hospitalisations as continuous data. We dichotomised these data to participants who experienced none versus at least one exacerbation and obtained the odds ratio (OR). Lastly, we analysed survival data as time-to-event. The survival data obtained from the IPD are presented as adjusted hazard ratio (AHR) and as hazard ratio (HR) when obtained from the aggregated data meta-analysis.

All outcome measures were presented with associated 95% confidence interval (CI). If available, estimates of the treatment effect were related to the minimal clinical important difference (MCID) for this specific population. Different proportions of participants and studies contributed to the different outcomes.

Unit of analysis issues

We expressed study outcomes in the same natural units across the trials. We analysed arterial blood gases as kPa, and converted data provided as mmHg to kPa by dividing the mmHg value by 7.5. If we obtained data on capillary blood gases, we only used the data for the PaCO₂ analysis, as the PaO₂ cannot be obtained reliably from capillary blood gases ([Magnet 2017](#)). We analysed lung function parameters in absolute values (litres). If we could only collect the percentage of predicted values, we calculated the absolute values using the regression equations of the European Community for Steel and Coal reference values ([Quanjer 1993](#)). We standardised the IPD of the SRI and SGRQ. Since the direction of effect differs between the SGRQ and the SRI, we inverted the SGRQ scores after which the data were pooled the data with the SRI. If a study measured both questionnaires, we preferred the data of the SRI over the SGRQ as the SRI was designed and validated specifically for this population ([Windisch 2003](#); [Windisch 2008](#)). We could not pool the data on the dyspnoea measurements (TDI and the MRC dyspnoea scale), as the data of the MRC dyspnoea scale were not normally distributed.

In the case of cross-over studies, we considered only the first study period (prior to the cross-over). In case of multi-arm studies, we only considered the control arm (receiving only standard

treatment) and the arm receiving NIV in addition to standard treatment. We did not consider cluster-randomised trials to be relevant to this review.

Dealing with missing data

We contacted the trial authors to obtain the IPD for the included studies. We only used data on continuous variables if both baseline data and data from at least one follow-up visit were available. For the exacerbation and hospitalisation data, we did not use baseline data. For this outcome, we only used the data of the participants that completed the follow-up visit. For time-to-event data, we used all available data.

If the authors did not respond to our request, we only used the studies for the meta-analysis of the aggregated trial data and not for the pooled IPD analysis.

Assessment of heterogeneity

We assessed statistical heterogeneity between the studies in each meta-analysis using the χ^2 test and I^2 statistic. For the χ^2 test, we considered a P value of < 0.1 significant. The I^2 statistic ranges from 0 to 100%, with 0% representing no heterogeneity and 100% representing considerable heterogeneity. We categorised the I^2 statistics according to the recommendations in the *Cochrane Handbook* (Higgins 2011):

- 0% to 40%: heterogeneity might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: shows considerable heterogeneity.

Assessment of reporting biases

We created and inspected a funnel plot of the meta-analysis of the primary outcomes where we were able to meta-analyse 10 or more studies for an outcome, and if the results of the outcome were homogeneous between studies.

Data synthesis

For the analysis of the IPD, we used a one-stage approach. We conducted all our models with a random effect on study level to account for the clustering of participants within the studies. We analysed the continuous IPD using linear mixed-effect models to obtain the AMD. We analysed age, sex and treatment (NIV versus controls) as fixed factors. Normality of the outcome distributions was required, and we assessed this by visual inspection of normal probability plots and histograms. We used generalised estimating equations to obtain the OR from dichotomous IPD, with age, sex and treatment (NIV versus controls) as fixed factors. We ran separate models for both follow-up times (3 and 12 months).

We assessed time-to-event data using a mixed-effect Cox regression analysis to obtain the AHR. For the cohort of people with stable COPD, we entered age, sex, baseline PaCO_2 and treatment (NIV versus controls) as fixed factors. For the post-exacerbation cohort, we entered age, sex, number of hospital admissions (less than three versus three or more admissions) in the year prior to randomisation, baseline PaCO_2 and treatment (NIV versus controls). We conducted all analyses in RStudio 2020.

Additionally, conducted a meta-analysis on the (unadjusted) aggregated data of all included studies using Review Manager Web (RevMan Web 2020). In addition to the aggregated IPD, we included the extracted data from the studies that did not provide any IPD. We calculated the mean differences (MD) and associated 95% CI, and combined them in a random-effects model to obtain an overall effect estimate.

Subgroup analysis and investigation of heterogeneity

If we identified any substantial heterogeneity between the studies ($I^2 > 50\%$), we considered subgroup analyses if sufficient numbers of studies could be included in the analysis (≥ 10 studies). A priori, the following sources of heterogeneity were postulated.

- Participants with more severe hypercapnia ($\text{PaCO}_2 > 7.3$ kPa) might benefit more from NIV; the division of the subgroups was made based on guidelines from a consensus report (Chest 1999).
- Participants receiving higher ventilatory support (IPAP ≥ 18 cmH₂O) might have a greater benefit from NIV; the division of the subgroups was made based on the first trial that showed an effect of NIV on gas exchange (Meecham Jones 1995).
- The benefits of NIV might be greater among participants who actually adhere to the NIV for at least five hours per night; division of the subgroups was made based on the inclusion criteria for this review that the NIV should be prescribed for at least five hours per night.

Sensitivity analysis

We conducted sensitivity analyses based on methodological quality by repeating the IPD analysis among only those studies that we judged to be of 'high quality.' Studies defined as 'high-quality' studies were studies that we judged to be at low risk of bias for the following domains: random sequence generation, allocation concealment, incomplete outcome data. We limited the sensitivity analysis to the primary outcomes.

Summary of findings and assessment of the certainty of the evidence

We created the summary of findings tables using GRADEpro GDT software, and presented separate tables for participants with stable COPD and for post-exacerbation COPD. We included the primary outcomes and the (admission-free) survival outcomes of the pooled IPD analysis in the tables.

Two review authors (TR and MD) assessed the certainty of the evidence using the GRADE working group criteria (GRADE 2013), considering the following domains: risk of bias, inconsistency, indirectness, imprecision, publication bias. We described our decisions to downgrade the certainty of the evidence.

RESULTS

Description of studies

See: [Characteristics of included studies](#).

Results of the search

The search conducted on 21 December 2020 identified 2291 records. After deduplication 1709 records remained, of which we considered 1653 records ineligible after title and abstract screening. Of the 56 records that remained, we retrieved 22 full-text

papers. The remaining records were conference abstracts ($n = 27$) or records from trial registries ($n = 7$). Of the 56 records, we excluded nine records of the current search for the following reasons.

1) Ineligible study design:

- study not randomised ([Ali 2012](#); [Clini 1998](#); [Kamei 1999](#));
- duration of NIV was less than four hours per night prescribed use and prescribed at daytime ([Diaz 1999](#));
- use of NIV was less than three weeks ([Lin 1996](#));
- participants were randomised to either terminate or continue NIV after an exacerbation ([Funk 2011](#)).

2) Ineligible study population:

- mixed population of participants with obstructive lung diseases ([Chiang 2004](#), two records).

3) Ineligible intervention:

- intervention group received inspiratory positive pressure breathing during daytime ([Nicolini 2014](#)).

Three studies (one full text paper and two conference abstracts) are awaiting classification as the authors did not respond to clarify important issues ([Baturova 2013](#); [Guan 2018](#); [Xiang 2007](#)). We identified six studies (seven records) that were ongoing at the time of this review ([Ankjaergaard](#); [Beth Israel Deaconess Medical Center](#); [Gonzales](#); [Lamia](#); [Pepin](#); [Wijkstra](#)). Additionally, we identified five records of studies that were included in the previous version of this review.

This update identified 10 studies (18 records) investigating chronic NIV in stable COPD ([Bhatt 2013](#); [Cui 2019](#); [Duiverman 2008](#); [Eman Shebl 2015](#); [Garrod 2000](#); [Köhnlein 2014](#); [Ma 2019](#); [Martin-Marquez 2014](#); [Schneeberger 2017](#); [Zhou 2017](#)). Together with the seven studies from the original review, we included 17 studies on stable COPD in this review update. Additionally, we identified four studies (14 records) on chronic NIV following an acute exacerbation of COPD ([Cheung 2010](#); [De Backer 2011](#); [Murphy 2017](#); [Struik 2014](#)). In total, we included 21 studies in this review update.

[Figure 1](#) presents the PRISMA-IPD flowchart.

Figure 1. PRISMA flow diagram

Figure 1. (Continued)

Included studies

The [Characteristics of included studies](#) table shows full details of the included studies.

Stable COPD

Seventeen studies met the inclusion criteria for the review (Bhatt 2013; Casanova 2000; Clini 2002; Cui 2019; Duiverman 2008; Eman Shebl 2015; Garrod 2000; Gay 1996; Köhnlein 2014; Ma 2019; Martin-Marquez 2014; McEvoy 2009; Meecham Jones 1995; Schneeberger 2017; Sin 2007; Strumpf 1991; Zhou 2017). Two of these studies used a cross-over in design (Meecham Jones 1995; Strumpf 1991), the remaining studies adopted a parallel design. Fourteen studies measured outcomes after three months and are classified as 'short-term', while five studies also measured outcomes after 12 months and are defined as 'long-term' (Clini 2002; Duiverman 2008; Köhnlein 2014; Ma 2019; McEvoy 2009). We obtained the IPD for the studies from the trial authors, except for four studies (Cui 2019; Eman Shebl 2015; Garrod 2000; Ma 2019). Of these four studies, we could only include the aggregated data of Garrod 2000 for the meta-analysis. In one study, the treatment arm received either NIV or CPAP, and the trial did not report the number of participants receiving each treatment (Cui 2019). One study only measured the outcomes after six months of NIV, so we did not use the data (Eman Shebl 2015). In the other trial, the study report did not present the data (Ma 2019).

Participants

The 17 included studies were based in different countries: Australia (McEvoy 2009), Canada (Sin 2007), China (Cui 2019; Ma 2019; Zhou 2017), Egypt (Eman Shebl 2015), Germany (Köhnlein 2014; Schneeberger 2017), the Netherlands (Duijerman 2008), Spain (Casanova 2000; Martin-Marquez 2014), Italy (Clini 2002), the UK (Garrod 2000; Meecham Jones 1995) and the USA (Bhatt 2013; Gay 1996; Strumpf 1991). All studies included people with COPD in a clinically stable condition and included both males and females.

In total, we obtained the IPD of 778 participants with stable COPD, representing 68% of the participants included in the studies. The mean age of all participants was 66 ± 8 years. All studies included males and females; 71% were males. Mean FEV₁ was 0.72 ± 0.27 L (28.2% predicted) and mean PaCO₂ was 7.3 ± 1.1 kPa.

Intervention and comparator

Eleven studies compared chronic NIV with standard treatment (Bhatt 2013; Casanova 2000; Clini 2002; Cui 2019; Eman Shebl 2015; Köhnlein 2014; Ma 2019; McEvoy 2009; Meecham Jones 1995; Strumpf 1991; Zhou 2017), and two studies compared chronic NIV with sham treatment in the form of continuous positive airway pressure (CPAP) at 2 cmH₂O and 4 cmH₂O (Gay 1996; Sin 2007). In four studies, NIV was applied in addition to a pulmonary rehabilitation or exercise training program and compared to a control group receiving only the rehabilitation or training program (Duijerman 2008; Garrod 2000; Martin-Marquez 2014; Schneeberger 2017).

Participants allocated to the NIV were initiated in-hospital (Casanova 2000; Clini 2002; Cui 2019; Duiverman 2008; Eman Shebl 2015; Gay 1996; Köhnlein 2014; McEvoy 2009; Meecham Jones 1995; Schneeberger 2017; Sin 2007), out-patient based (Strumpf 1991; Zhou 2017) or at home (Bhatt 2013). The remaining three studies did not report the site of initiation (Garrod 2000; Ma 2019; Martin-Marquez 2014). Bi-level pressure support ventilation was applied with a back-up rate in eight studies (Clini 2002; Cui 2019; Duiverman 2008; Gay 1996; Köhnlein 2014; Martin-Marquez 2014; Strumpf 1991; Zhou 2017), with no back-up rate (Casanova 2000; Garrod 2000; Meecham Jones 1995), or information on a back-up rate was not specified (Bhatt 2013; Eman Shebl 2015; McEvoy 2009; Schneeberger 2017; Sin 2007). The ventilation mode was unspecified in one study (Ma 2019). NIV was delivered by nasal masks in six studies (Casanova 2000; Clini 2002; Garrod 2000; Gay 1996; Meecham Jones 1995; Strumpf 1991), and by either nasal or oronasal masks in seven studies (Bhatt 2013; Duiverman 2008; Köhnlein 2014; Martin-Marquez 2014; McEvoy 2009; Sin 2007; Zhou 2017). In four studies the interface was not specified (Cui 2019; Eman Shebl 2015; Ma 2019; Schneeberger 2017).

At baseline, the mean IPAP and EPAP were 16.5 ± 4.7 cmH₂O and 4.7 ± 4.7 cmH₂O, respectively. The corresponding values after three months were 17.9 ± 5.2 cmH₂O and 4.6 ± 1.4 cmH₂O, respectively. After 12 months, mean IPAP was 16.8 ± 5.4 cmH₂O and mean EPAP was 4.9 ± 1.5 cmH₂O. Chronic NIV was used for a mean of 6.2 ± 2.8 hours after three months and 5.5 ± 3.2 hours after 12 months.

Post-exacerbation COPD

Four studies met the inclusion criteria for this review (Cheung 2010; De Backer 2011; Murphy 2017; Struik 2014). All studies used

a parallel design and measured outcomes after both three and 12 months. The authors of one study did not respond to our request for the IPD (De Backer 2011), so we did not include this study in the pooled IPD analysis. Since De Backer 2011 did not present results in their paper after three or 12 months, we were also unable to use the data from this study in the meta-analysis. The remaining three studies provided the IPD after both three and 12 months.

Participants

The four included studies were based in the following countries: Belgium (De Backer 2011), China (Cheung 2010), the Netherlands (Struik 2014), and the UK (Murphy 2017). The studies included people with COPD who were hospitalised due to an exacerbation (De Backer 2011) or who were hospitalised for an episode of ARF due to COPD (Cheung 2010; Murphy 2017; Struik 2014). All studies included both males and females.

We obtained IPD for 364 participants initiated on chronic NIV following an acute exacerbation, representing 96% of the participants included in the studies. The mean age was 65 ± 9 years, and 50% were females. In the year prior to randomisation, the median number of COPD exacerbations was two (interquartile range (IQR) one to three). The mean FEV₁ was 0.62 ± 0.23 L and mean (inclusion) PaCO₂ was 7.9 ± 1.1 kPa.

Intervention and comparator

In one study (Cheung 2010), chronic NIV was compared to sham treatment with CPAP at 5 cmH₂O, the remaining three studies compared NIV to standard treatment. Participants were initiated on chronic NIV if they had persistent hypercapnia on day five to 12 of the admission (De Backer 2011), or after they were weaned from acute NIV > 48 hours (Cheung 2010; Struik 2014) or two to four weeks (Murphy 2017). All participants were initiated in-hospital, and on bi-level pressure support ventilation with a backup rate in three studies (Cheung 2010; Murphy 2017; Struik 2014). The other

study did not report the mode of ventilation (De Backer 2011). NIV was delivered through oronasal masks (De Backer 2011), through either nasal or oronasal masks (Murphy 2017; Struik 2014), or was not specified (Cheung 2010).

The mean IPAP and EPAP at initiation were 20.0 ± 4.4 cmH₂O and 4.8 ± 0.9 cmH₂O, respectively. After three months, the mean IPAP was 20.8 ± 4.4 cmH₂O and the mean EPAP was 5.0 ± 1.0 cmH₂O. Mean IPAP after 12 months was 21.9 ± 4.3 cmH₂O, and the corresponding mean EPAP was 5.0 ± 1.1 cmH₂O. Chronic NIV was used for a mean of 6.5 ± 2.4 hours after three months and for 6.8 ± 2.7 hours after 12 months.

Funding of trial (all trials)

Thirteen studies were funded by their National Respiratory Society/Foundation (Casanova 2000; Cheung 2010; Clini 2002; Duiverman 2008; Gay 1996; Köhnlein 2014; Martin-Marquez 2014; McEvoy 2009; Meecham Jones 1995; Murphy 2017; Sin 2007; Struik 2014; Zhou 2017), of which six were also partly funded by an industrial company (Cheung 2010; Clini 2002; Köhnlein 2014; McEvoy 2009; Murphy 2017; Struik 2014). Four studies were funded by an industrial company alone (Bhatt 2013; Garrod 2000; Schneeberger 2017; Strumpf 1991), and four studies did not report any funding (Cui 2019; De Backer 2011; Eman Shebl 2015; Ma 2019).

Excluded studies

The [Characteristics of excluded studies](#) table provides full details of the 10 excluded studies.

Risk of bias in included studies

The [Characteristics of included studies](#) table provides details of risk of bias in the included studies. [Figure 2](#) shows a summary of our risk of bias judgements across studies.

Figure 2. Risk of bias summary: review authors' judgements about each methodological quality item for each included study Note: blank squares indicate that the outcome domain was not measured in the study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias): All outcomes	Blinding of outcome assessment (detection bias): Patient reported outcomes	Blinding of outcome assessment (detection bias): Lung function and exercise test	Blinding of outcome assessment (detection bias): Blood gases, hospitalisations and mortality.	Incomplete outcome data (attrition bias): All outcomes	Selective reporting (reporting bias)	Other bias
Bhatt 2013	+	+	-	-	?	+	?	+	-
Casanova 2000	+	+	-	-	+	+	+	?	+
Cheung 2010	+	+	-			-	-	-	-
Clini 2002	?	+	-	-	+	+	+	?	+
Cui 2019	?	?	-	-	?	+	+	?	-
De Backer 2011	?	?	-		?	+	?	-	-
Duiverman 2008	+	+	-	-	?	+	+	+	+
Eman Shebl 2015	+	?	-	-	?	+	?	?	+
Garrod 2000	?	+	-		?	+	+	+	-
Gay 1996	?	+	?		?	+	-	?	+
Köhnlein 2014	+	+	-	-	+	+	+	+	+
Ma 2019	?	?	-		?	+	?	?	-
Martin-Marquez 2014	+	?	-	-	?	+	+	+	+
McEvoy 2009	+	+	-	-	?	+	+	?	+
Meecham Jones 1995	+	+	-	-	?	+	+	?	+
Murphy 2017	+	+	-	-	+	+	+	+	+

Figure 2. (Continued)

Meecham Jones 1995	+	+	-	-	?	+	+	?	+
Murphy 2017	+	+	-	-	+	+	+	+	+
Schneeberger 2017	?	+	-	-	?	+	+	+	-
Sin 2007	?	+	+	+	+	+	+	?	+
Struik 2014	+	+	-	-	+	+	+	+	+
Strumpf 1991	+	+	-	-	+	+	+	?	?
Zhou 2017	+	+	-	-	+	+	+	+	+

Allocation

Random sequence generation (selection bias)

All studies were described as randomised. Thirteen studies described the method of the sequence generation adequately, so we judged these to be at low risk of bias. In the other eight studies, insufficient data were available, so we judged these to be at unclear risk of bias (Clini 2002; Cui 2019; De Backer 2011; Garrod 2000; Gay 1996; Ma 2019; Schneeberger 2017; Sin 2007).

Allocation concealment (selection bias)

We also deemed allocation concealment to be adequate in the majority of the studies; 10 studies described a centralised randomisation office or independent person. In six cases, sequentially numbered, opaque, sealed envelopes were used. Five studies provided insufficient data on the allocation concealment, so we judged them to be at unclear risk of bias in this domain (Cui 2019; De Backer 2011; Eman Shebl 2015; Ma 2019; Martin-Marquez 2014).

Blinding

Blinding of participants and personnel (performance bias)

Given the nature of the intervention it is difficult to blind participants, but three studies attempted to do so and used a sham-device (Cheung 2010; Gay 1996; Sin 2007). One study also blinded personnel to treatment allocation, making this the only study that we could classify as having a low risk of bias in this domain (Sin 2007). In one other study it was not clear whether personnel were blinded (Gay 1996). We judged all other studies to be at high risk of bias with respect to blinding.

Blinding of outcome assessment (detection bias)

Participant-reported outcomes

In the majority of the studies, participants were not blinded for treatment (e.g. did not receive sham NIV), so we judged that participant-reported outcomes (HRQL and dyspnoea measurements) were likely to be affected by detection bias. Therefore, we judged 15 studies to be at high risk of bias. The remaining studies did not measure any participant-reported outcomes of relevance to this review (Cheung 2010; De Backer 2011; Garrod 2000; Gay 1996; Ma 2019; Sin 2007).

Lung function, respiratory muscle and exercise capacity tests

Most studies did not provide sufficient data on these outcomes, so we judged them to be at unclear risk. Eight studies described the outcome assessors as being unaware of the treatment assignment,

so we judged these to be at low risk (Casanova 2000; Clini 2002; Köhnlein 2014; Murphy 2017; Sin 2007; Struik 2014; Strumpf 1991; Zhou 2017). The Cheung 2010 study did not measure these outcomes.

Arterial blood gases, hospitalizations and mortality

Except for one study, we judged all studies to be at low risk of bias as these are either objective measures (e.g. blood gases) or are unlikely to be affected by the outcome assessor (e.g. hospitalisations/mortality). We judged the study of Cheung 2010 as high risk as for the primary outcome, as outcome assessors had to rate whether there was an event in the NIV group. One study did not measure these outcomes (Schneeberger 2017).

Incomplete outcome data

Given the severity of the illness and nature of the intervention, dropouts are to be expected due to the inability of the participants to attend control visits, or because of intolerance to the intervention. Therefore, most studies experienced dropouts, and the majority described the reason for these dropouts adequately. Five studies did not perform intention-to-treat (ITT) analyses. We classified these studies as low risk as dropouts due to intolerance were small, baseline characteristics of dropouts did not differ from completers, and the studies presented a clear description of the reason for participants dropping out (Duiverman 2008; Garrod 2000; Martin-Marquez 2014; Meecham Jones 1995; Sin 2007). Eight studies reported ITT analyses (or stated that "Inclusion of the patients who did not complete the study (intent to treat) did not affect any of the outcomes" Casanova 2000), so we considered these to be at low risk of bias (Casanova 2000; Clini 2002; Cui 2019; Köhnlein 2014; McEvoy 2009; Murphy 2017; Struik 2014; Zhou 2017). In one of the cross-over studies, only seven out of 19 randomised participants completed both arms (Strumpf 1991). Another study reported that four out of seven participants randomised to NIV completed the study, as opposed to all six in the sham group (Gay 1996). One study performed an ITT analysis on the primary outcome, but participants were withdrawn from the study after the primary outcome was reached (Cheung 2010). We classified these three studies as high risk of attrition bias. We judged five studies to be at unclear risk of bias, as these studies did not provide sufficient data regarding the reasons for participants dropping out (Bhatt 2013; De Backer 2011; Eman Shebl 2015; Ma 2019; Schneeberger 2017).

Selective reporting

Most of the earlier studies were not registered, nor were the original protocols retrieved, so we were unable to check if

the prespecified outcomes were all reported in the articles. In this domain the risk of bias was unclear. However, all outcomes listed in the methods sections of the studies were reported in the results sections. One study was registered retrospectively, and we judged this as unclear (McEvoy 2009). One study was not registered and the paper only reported the outcome data of one follow-up visit, whilst measurements were taken during four follow-up visits (De Backer 2011). We therefore judged this study to be at high risk. We judged two other studies to be high risk after comparing the paper with the trial registry, due to a change in the primary outcome (Cheung 2010; Zhou 2017). We judged eight studies to be at low risk, as these studies were registered and the data were reported in the paper, or (in case that the data were not reported), the authors provided the IPD (Bhatt 2013; Duiverman 2008; Garrod 2000; Köhnlein 2014; Martin-Marquez 2014; Murphy 2017; Schneeberger 2017; Struik 2014).

Other potential sources of bias

For 13 of the studies, we did not find any other source of bias. In one study we found a difference in the number of (telephone) contacts with the caregivers between both study groups at the start of the study, but as it was unclear for how long this activity continued (and thus the likelihood of affecting the outcomes after three months), we judged this as an unclear risk of bias (Strumpf 1991). We also observed this in two other studies (Bhatt 2013; Garrod 2000), and the NIV group in one of these studies received NIV during the run-in period, which could potentially affect the outcomes (Garrod 2000). In two studies, there were concerns regarding the sample size; in one study financial restraint prevented the inclusion of more than 50 participants, and one study did not present a power calculation and the sample sizes of both groups were unequal (Cheung 2010; De Backer 2011). In one study, participants with both hypoxemic and hypercapnic respiratory failure were included and treated with either CPAP or NIV in the treatment arm (Cui 2019). The study did

not provide data on the number of participants treated with either treatment, so we judged this study to have a high risk of bias. Lastly, two studies were only available as meeting abstracts (Ma 2019; Schneeberger 2017). Therefore, we judged all seven of these studies to be at high risk of other bias (Bhatt 2013; Cheung 2010; Cui 2019; De Backer 2011; Garrod 2000; Ma 2019; Schneeberger 2017).

Effects of interventions

See: **Summary of findings 1** Summary of Findings Table - Chronic non-invasive ventilation compared to standard treatment for people with stable COPD; **Summary of findings 2** Summary of Findings Table - Chronic non-invasive ventilation compared to standard treatment following a severe exacerbation for people with severe COPD

There is a difference between the number of participants included in the studies in total and the number included in the analysis, as most of the data were only available from participants who completed that particular study period and dropouts were common in most studies. For the short-term follow-up, participants dropped out due to mask intolerance, intercurrent infections or participants no longer meeting the inclusion criteria after a stabilisation period. In the studies also investigating the long-term effects, dropping out was often due to progression of the disease or death, and reluctance of participants to return to hospital for follow-up measurements. Finally, not all parameters were measured in all participants and, therefore, there was a difference in number of participants per outcome.

Stable COPD — primary outcomes

In Table 1, the absolute changes in the outcomes are shown separately for the NIV and the control group. In Figure 3, the modelled means obtained from the linear mixed effect models are presented for the primary outcomes.

Figure 3. The modelled means of the adjusted mixed-effect models for the primary outcomes, separate for the NIV and the control group, in stable COPD Black triangles: NIV group; red squares: control group. * indicates that the 95% confidence interval of the treatment effect does not cross zero. For the HRQL outcome, a positive value indicates improved HRQL.

Daytime arterial blood gas tensions

Three months' follow-up

Eleven studies contributed IPD for this outcome (Bhatt 2013; Casanova 2000; Clini 2002; Duiverman 2008; Gay 1996; Köhnlein 2014; Martin-Marquez 2014; Meecham Jones 1995; Sin 2007; Strumpf 1991; Zhou 2017). In total, blood gases of 475 participants were analysed, of which 271 were arterial blood gases and contributed to the PaO₂ outcome. Participants treated with NIV showed an increase in PaO₂ whereas participants allocated to the control group showed a decrease (adjusted mean difference (AMD) 0.27 kPa, 95% CI 0.04 to 0.49; Table 1). A reduction in the PaCO₂ was

observed in participants in both groups, but the decrease was -0.61 kPa larger in participants allocated to NIV (95% CI -0.77 to -0.45; Table 1).

The meta-analyses of the blood gas outcomes included data from one additional study (Garrod 2000), and showed a larger treatment effect on the PaO₂ (MD 0.31 kPa, 95% CI 0.14 to 0.48; P = 0.44, I² = 0%; 10 studies, 308 participants; moderate-certainty evidence; Analysis 1.1). The funnel plot was asymmetrical to the right side and might indicate that a publication bias was present (Figure 4). A smaller treatment effect with substantial statistical heterogeneity between the studies was found for the PaCO₂ (MD -0.48 kPa, 95% CI -0.72 to

-0.25; $P = 0.001$, $I^2 = 65\%$; 12 studies, 512 participants; high-certainty evidence; [Analysis 1.2](#)). We conducted subgroup analysis to explore

the heterogeneity. These subgroup analyses seem to explain the heterogeneity and are presented later.

Figure 4. Funnel plot for the PaO₂ outcome after 3 months, in participants with stable COPD

12 months' follow-up

Four studies contributed blood gases of 232 participants ([Clini 2002](#); [Duiverman 2008](#); [Köhnlein 2014](#); [McEvoy 2009](#)). Of these blood gases, 171 were arterial and were used for the PaO₂ analysis. Both study groups showed a minor decrease in PaO₂ (AMD 0.09 kPa, 95% CI -0.23 to 0.42; [Table 1](#)). In contrast, a reduction in PaCO₂ was only present in participants allocated to NIV, whereas participants in the control group did not change (AMD -0.42 kPa, 95% CI -0.68 to -0.16; [Table 1](#)).

The meta-analyses did not include additional data and yielded results comparable to the pooled IPD analysis for the PaO₂ (MD 0.08 kPa, 95% CI -0.37 to 0.53; $P = 0.16$, $I^2 = 46\%$; 3 studies, 171 participants; low-certainty evidence; [Analysis 1.1](#)) and a slightly smaller effect of NIV on the PaCO₂ (MD -0.35 kPa, 95% CI -0.68 to -0.02; $P = 0.14$, $I^2 = 45\%$; 4 studies, 232 participants; high-certainty evidence; [Analysis 1.2](#)). Both outcomes showed moderate statistical heterogeneity between the studies, but as only four studies measured this outcome we could not conduct subgroup analysis.

Exercise capacity

Three months' follow-up

Exercise capacity was measured using the 6MWD in eight studies ([Bhatt 2013](#); [Duiverman 2008](#); [Gay 1996](#); [Köhnlein 2014](#); [Martin-Marquez 2014](#); [Meecham Jones 1995](#); [Sin 2007](#); [Zhou 2017](#)), and 330 participants contributed to the IPD. The MCID for the 6MWD in people with severe COPD is 26 m ([Puhan 2011](#)). Participants in both groups improved on the 6MWD on average, but there was no relevant effect of the NIV (AMD 15.5 m, 95% CI -0.8 to 31.7; [Table 1](#)). The meta-analysis did not include additional data and yielded a smaller effect compared to the pooled IPD analysis (MD 7.85 m, 95% CI -5.52 to 21.23; $P = 0.39$, $I^2 = 6\%$; 8 studies, 330 participants; low-certainty evidence; [Analysis 1.3](#)).

12 months' follow-up

The 6MWD was measured in 134 participants in three studies ([Clini 2002](#); [Duiverman 2008](#); [Köhnlein 2014](#)). An improvement in the 6MWD was seen in the NIV group, whereas the control group deteriorated (AMD 26.4 m, 95% CI -7.6 to 60.5; [Table 1](#)). The meta-analysis of data of the same three studies that provided IPD yielded similar results (MD 23.50 m, 95% CI -3.03 to 50.03; $P = 0.37$, $I^2 = 0\%$; 3 studies, 134 participants; very low-certainty evidence; [Analysis 1.3](#)).

Health-related quality of life

Three months' follow-up

Three studies measured HRQL using the SRI in 217 participants (Duiverman 2008; Köhnlein 2014; Zhou 2017). The SRI is reported on a 0 to 100 scale, with a higher score indicating better HRQL. An improvement of approximately five units has been established as the MCID (Raveling 2020). Three studies provided SGRQ data for an additional 42 participants (Köhnlein 2014; Meecham Jones 1995; Schneeberger 2017). Scores for the SGRQ are also reported on a 0 to 100 scale, but with a lower score indicating better HRQL. The MCID of the SGRQ in people with severe COPD is approximately seven units (Welling 2015). Participants treated with NIV showed a larger improvement both on the summary score of the SRI and on the total score of the SGRQ, compared to participants allocated to the control group (Table 1). After pooling of the SRI and SGRQ data, there was a benefit of NIV on HRQL (AMD 0.39, 95% CI 0.15 to 0.62). Given a SD of 12.0 and of 10.2 units for the SRI and SGRQ respectively, this would result in an improvement of 4.7 units on the SRI and of 4.0 units on the SGRQ.

Meta-analyses based on data of the same five studies that provided IPD yielded comparable results to the pooled IPD analysis (SMD 0.42, 95% CI 0.17 to 0.67; $P = 0.43$, $I^2 = 0\%$; 5 studies, 257 participants; very low-certainty evidence; Analysis 1.4).

12 months' follow-up

Two studies contributed to the SRI data of 84 participants (Duiverman 2008; Köhnlein 2014), and three studies to the SGRQ data of 116 participants (Köhnlein 2014; Clini 2002; McEvoy 2009). An improvement on the summary score of the SRI was observed in participants treated with NIV, but participants allocated to the control group showed no change. This was not observed in the studies that used the SGRQ, as both groups showed a small improvement (Table 1). After pooling of the SRI and SGRQ data, there was no effect of chronic NIV (AMD 0.15, 95% CI -0.13 to 0.43). Given a SD of 12.2 and of 14.6 units for the SRI and SGRQ respectively, this would result in an improvement of 1.8 units on the SRI and of 2.2 units on the SGRQ.

There were no additional data available for the aggregated meta-analyses, and this analysis yielded comparable results to the pooled IPD analysis (SMD 0.18, 95% CI -0.24 to 0.59; $P = 0.12$, $I^2 = 49\%$; 4 studies; 199 participants; very low-certainty evidence; Analysis 1.4).

Stable COPD — secondary outcomes

Lung function

In one study (Köhnlein 2014), only the percentage of predicted values were recorded. Absolute spirometry values were calculated using regression equations (Quanjer 1993).

Three months' follow-up

The FEV₁ and FVC were measured in 10 studies (Bhatt 2013; Casanova 2000; Duiverman 2008; Gay 1996; Köhnlein 2014; Martin-Marquez 2014; Meecham Jones 1995; Sin 2007; Strumpf 1991; Zhou 2017). Data were available for 383 participants for the FEV₁ and of 384 participants for the FVC. On average, the FEV₁ of participants in both groups remained unchanged (AMD 0.01 L, 95% CI -0.02 to 0.04; Table 1). Similar results were observed for the FVC

as participants in both groups showed a small but equal increase (AMD -0.01 L, 95% CI -0.09 to 0.07; Table 1). Aggregated data were available for one additional study (Garrod 2000), but this did not result in any new findings for either the FEV₁ (MD -0.00 L, 95% CI -0.04 to 0.03; $P = 0.18$, $I^2 = 28\%$; 11 studies, 420 participants; Analysis 1.5) or the FVC (MD 0.01 L, 95% CI -0.06 to 0.08; $P = 0.80$, $I^2 = 0\%$; 11 studies, 421 participants; Analysis 1.6).

Lung hyperinflation (RV/%TLC) was measured in three studies (Duiverman 2008; Köhnlein 2014; Martin-Marquez 2014), and 184 participants contributed to the IPD. There were only minor changes in RV/%TLC of participants in both study groups (AMD -0.6 %, 95% CI -2.6 to 1.4; Table 1). The meta-analysis of the RV/%TLC data yielded similar results to the pooled IPD analysis (MD -0.53%, 95% CI -2.77 to 1.71; $P = 0.30$, $I^2 = 17\%$; 3 studies, 184 participants; Analysis 1.7), based on data from the same studies.

12 months' follow-up

Four studies provided the IPD of 236 participants for the FEV₁ and of 235 participants for the FVC (Clini 2002; Duiverman 2008; Köhnlein 2014; McEvoy 2009). Participants in both groups showed no change in FEV₁ after 12 months (AMD 0.00 L, 95% CI -0.04 to 0.04; Table 1). For the FVC a comparable decrease was observed in participants of both groups (AMD -0.03 L, 95% CI -0.14 to 0.08; Table 1). The meta-analyses did not include any additional data and yielded similar results for the FEV₁ (MD 0.00 L, 95% CI -0.04 to 0.04; $P = 0.61$, $I^2 = 0\%$; 4 studies, 236 participants; Analysis 1.5), and for the FVC (MD -0.02 L, 95% CI -0.13 to 0.09; $P = 0.83$, $I^2 = 0\%$; 4 studies, 235 participants; Analysis 1.6).

The RV/%TLC was measured in 197 participants in four studies (Clini 2002; Duiverman 2008; Köhnlein 2014; McEvoy 2009), and no treatment effect could be observed (AMD 0.4 %, 95% CI -2.1 to 2.9; Table 1). The MD obtained from the meta-analysis of the RV/%TLC data was 0.27 % (95% CI -1.98 to 2.53; $P = 0.96$, $I^2 = 0\%$; 4 studies, 195 participants; Analysis 1.7), based on data of the same four studies.

Respiratory muscle function

Three months' follow-up

Five studies with a total of 123 participants measured the PEmax (Casanova 2000; Duiverman 2008; Gay 1996; Martin-Marquez 2014; Strumpf 1991). On average, the PEmax improved more in participants treated with NIV compared to participants allocated to the control group (AMD 3.7 cmH₂O, 95% CI -4.2 to 11.6; Table 1). The PImax was measured in one additional study (Bhatt 2013), so 152 participants contributed IPD to this outcome. Both groups also showed an increase for the PImax, but AMD was 6.9 cmH₂O (95% CI 2.3 to 11.5; Table 1) in favour of the NIV group.

Respiratory muscle function data were available from one additional study (Garrod 2000). In contrast to the pooled IPD analysis, the meta-analyses revealed a larger and statistically significant effect on the PEmax (MD 9.03 cmH₂O, 95% CI -1.51 to 19.58; $P = 0.07$, $I^2 = 50\%$; 6 studies, 160 participants; Analysis 1.8). This outcome showed substantial statistical heterogeneity between the studies, which could not be explored by subgroup analysis as we included fewer than 10 studies. The meta-analysis on the PImax showed comparable results to the pooled IPD analysis

(MD 6.99 cmH₂O, 95% CI 3.29 to 10.62, $P = 0.99$, $I^2 = 0\%$; 7 studies, 192 participants; [Analysis 1.9](#)).

12 months' follow-up

The PEmax was only measured in one study ([Duiverman 2008](#)), and 38 participants contributed to the IPD. Data from this study showed a larger increase in PEmax in participants allocated to the NIV group (AMD 3.2 cmH₂O, 95% CI -24.5 to 31.0; [Table 1](#)). Two studies measured the PImax ([Clini 2002](#); [Duiverman 2008](#)), and 92 participants contributed to the IPD. The effect after 12 months was comparable to the effect after three months, and was in favour of the NIV group (AMD 6.0 cmH₂O, 95% CI -0.9 to 12.8; [Table 1](#)).

There were no additional data available for the meta-analyses of these outcomes. The meta-analyses did not result in any new findings for the PEmax (MD 3.50 cmH₂O, 95% CI -23.70 to 30.70; 1 study, 38 participants; [Analysis 1.8](#)), nor for the PImax (MD 7.04 cmH₂O, 95% CI -12.29 to 26.37; $P = 0.008$, $I^2 = 86\%$; 2 studies, 92 participants; [Analysis 1.9](#)). The results showed considerable statistical heterogeneity between the two studies, but this heterogeneity could not be explored by subgroup analysis due to the low number of studies.

Dyspnoea

Three months' follow-up

Three studies provided the IPD of 174 participants for the TDI ([Bhatt 2013](#); [Duiverman 2008](#); [Zhou 2017](#)). One other study reported the TDI ([Strumpf 1991](#)), but we could not extract the aggregated data from the paper. The total score of the TDI ranges from -9 points (major deterioration) to +9 points (major improvement), and an improvement of one point has been established as clinically relevant ([Witek 2003](#)). On average, participants allocated to both groups showed minor improvements (AMD 0.7, 95% CI -0.8 to 1.5; [Table 1](#)). Meta-analysis yielded a comparable effect of NIV (MD 0.77, 95% CI 0.01 to 1.53; $P = 0.34$, $I^2 = 8\%$; 3 studies, 178 participants; [Analysis 1.10](#)) but in contrast to the pooled IPD analysis, this effect was statistically significant.

Four studies measured dyspnoea using the (modified)MRC ([Casanova 2000](#); [Clini 2002](#); [Duiverman 2008](#); [Martin-Marquez 2014](#)), and the IPD were available for 155 participants. The mMRC is reported on a 0 to 4 scale, with a score of 4 indicating severe dyspnoea. This outcome was not normally distributed, hence we could not conduct the linear mixed-effect models. We included summary data of the same four studies in the meta-analysis, which showed a decrease in the mMRC in participants allocated to NIV (MD -0.29, 95% CI -0.59 to 0.01; $P = 0.21$, $I^2 = 34\%$; 4 studies, 155 participants; [Analysis 1.11](#)). We observed some statistical heterogeneity between the studies, but this was not considered important.

12 months' follow-up

None of the studies measured the TDI. Two studies measured dyspnoea using a 6-point MRC ([Clini 2002](#); [Duiverman 2008](#)), and the IPD were available for 103 participants. Due to a non-normal distribution, we did not conduct the linear mixed-effects models. The meta-analysis of this data showed a decrease in dyspnoea in participants treated with NIV (MD -0.49, 95% CI -0.90 to -0.08; $P = 0.45$, $I^2 = 0\%$; 2 studies, 103 participants; [Analysis 1.11](#)).

Sleep efficiency

We did not find any new data since the original review was performed for this outcome. For consistency, we re-analysed the data using the current linear mixed-effect models.

Three months' follow-up

Three studies with 24 participants provided IPD for sleep efficiency ([Gay 1996](#); [Meecham Jones 1995](#); [Strumpf 1991](#)). Participants allocated to both groups showed an improvement in sleep efficiency, but the effect tended to be larger in participants allocated to the control group (AMD -7.9, 95% CI -21.6 to 5.8; [Table 1](#)). The meta-analysis of data from the same studies showed a MD of -2.86% (95% CI -8.76 to 3.04; $P = 0.37$, $I^2 = 0\%$; 3 studies, 24 participants; [Analysis 1.12](#)).

12 months' follow-up

None of the included studies measured sleep efficiency as "the percentage time asleep of the total time in bed", with a follow-up of 12 months.

COPD exacerbations and hospital admissions

Baseline hospital admission rates were not recorded, or were recorded over different time frames ([Bhatt 2013](#); [Clini 2002](#); [Duiverman 2008](#)). We were unable to perform the linear mixed-effect models as this outcome was not normally distributed.

Three months' follow-up

One study provided the IPD of 56 participants ([Duiverman 2008](#)). On average, exacerbations did not occur frequently in participants allocated to either group ([Table 1](#)). The number of participants that experienced an exacerbation was similar in participants allocated to the NIV group (12 of 24 participants (50%) ≥ 1 exacerbation) and the control group (19 of 32 participants (59%) ≥ 1 exacerbation) (OR 0.69, 95% CI 0.23 to 2.0). Aggregated exacerbation data from [Casanova 2000](#) were available for the meta-analysis. The OR for an exacerbation was 0.76 (95% CI 0.34 to 1.69; $P = 0.77$, $I^2 = 0\%$; 2 studies, 100 participants; [Analysis 1.13](#)), in favour of participants treated with NIV.

Four studies provided the IPD on hospital admissions of 268 participants ([Bhatt 2013](#); [Clini 2002](#); [Duiverman 2008](#); [Köhnlein 2014](#)). Hospital admissions for respiratory causes were rare in participants of both groups ([Table 1](#)). An equal number of participants had been admitted to the hospital (NIV group: 34 of 137 participants (25%) admitted; control group: 34 of 131 participants (26%) admitted) (OR 0.89, 95% CI 0.51 to 1.57). Aggregated data from one additional study were available for the meta-analysis ([Casanova 2000](#)). The OR for a hospitalisation was 0.64 (95% CI 0.26 to 1.60; $P = 0.10$, $I^2 = 49\%$; 5 studies, 312 participants; [Analysis 1.14](#)), in favour of participants treated with NIV. The results showed moderate statistical heterogeneity between the studies.

12 months' follow-up

One study provided the IPD on COPD exacerbations of 45 participants ([Duiverman 2008](#)). The median number of exacerbations was similar in both groups ([Table 1](#)). The number of participants that experienced an exacerbation appeared similar in participants allocated to the NIV group (15 of 18 participants (83%) ≥ 1 exacerbation) and the control group (25 of 27 participants (93%) ≥ 1 exacerbation) (OR 0.36, 95% CI 0.05 to 2.47). For

the meta-analysis, the aggregated data of [Casanova 2000](#) could be included. The OR for an exacerbation favoured participants allocated to NIV (OR 0.72, 95% CI 0.25 to 2.05; $P = 0.47$, $I^2 = 0\%$; 2 studies, 89 participants; [Analysis 1.13](#)).

Data on hospital admissions were provided for 138 participants ([Clini 2002](#); [Duiverman 2008](#); [Köhnlein 2014](#)). In the first study year, admissions for respiratory causes were rare ([Table 1](#)). A similar number of participants had been admitted to the hospital (NIV group: 30 of 71 participants (42%) admitted; control group: 26 of 67 participants (39%) admitted) (OR 1.14, 95% CI 0.58 to 2.25). For the meta-analysis, the aggregated data of [Casanova 2000](#) could be included. There was no effect of NIV (OR 1.06, 95% CI 0.46 to 2.44; $P = 0.18$, $I^2 = 39\%$; 4 studies, 182 participants; [Analysis 1.14](#)). There was some statistical heterogeneity between the studies, but we did not consider this to be important.

All-cause mortality

Three studies provided the mortality data of 405 participants, with a median follow-up of 30 months ([Duiverman 2008](#); [Köhnlein 2014](#); [McEvoy 2009](#)). There was a lower risk for all-cause mortality in participants treated with NIV (adjusted hazard ratio (AHR) 0.75, 95% CI 0.58 to 0.97). Mortality was reported by one additional study ([Casanova 2000](#)), but we could not extract the data or source it from the authors. The meta-analysis demonstrated a survival benefit for participants treated with NIV, but in contrast to the IPD analysis, this estimate was not statistically significant (HR 0.78, 95% CI 0.58 to 1.05; $P = 0.29$, $I^2 = 20\%$; 3 studies, 405 participants; moderate-certainty evidence; [Analysis 1.15](#)).

Post-exacerbation COPD — primary outcomes

The absolute changes in all outcomes of participants commenced on NIV following an acute exacerbation is presented in [Table 2](#). In [Figure 5](#), the modelled means obtained from the linear mixed-effect models are presented for the primary outcomes.

Figure 5. The modelled means of the adjusted mixed-effect models for the primary outcomes, separate for the NIV and the control group, in post-exacerbation COPD. Black triangles: NIV group; red squares: control group. * indicates that the 95% confidence interval of the treatment effect does not cross zero. For the HRQL outcome, a positive value indicates improved HRQL.

Daytime arterial blood gas tensions

Three months' follow-up

Three studies provided the IPD for the arterial blood gases of 234 participants for the PaO₂ and for 241 participants for the PaCO₂ (Cheung 2010; Murphy 2017; Struik 2014). There was no difference on the change in PaO₂ between participants allocated to NIV or standard care (AMD -0.10 kPa, 95% CI -0.65 to 0.45; Table 2). There were improvements in the PaCO₂ in both groups, but the effect was larger in participants treated with NIV (AMD -0.40 kPa, 95% CI -0.70 to -0.09; Table 2).

The meta-analyses of these outcomes were based on data of the same three studies and yielded comparable results to the pooled IPD analyses for both the PaO₂ (MD -0.08 kPa, 95% CI -0.58 to 0.41; P = 0.85, I² = 0%; 3 studies, 234 participants; low-certainty evidence; Analysis 2.1) and PaCO₂ (MD -0.42 kPa, 95% CI -0.72 to -0.12; P = 0.45, I² = 0%; 3 studies, 241 participants; low-certainty evidence; Analysis 2.2).

12 months' follow-up

The same three studies provided the IPD of 170 participants for the PaO₂ and of 175 participants for the PaCO₂ (Cheung 2010; Murphy 2017; Struik 2014). In the control group, PaO₂ tended to improve

more compared to participants in the NIV group (AMD -0.27 kPa, 95% CI -0.86 to 0.32; [Table 2](#)). In contrast, the PaCO₂ was reduced in both groups, but the effect was larger in the participants treated with NIV (AMD -0.52 kPa, 95% CI -0.87 to -0.18; [Table 2](#)).

The meta-analyses of these outcomes were based on data from the same three studies and yielded comparable results to the pooled IPD analyses for both the PaO₂ (MD -0.24 kPa, 95% CI -0.81 to 0.34; $P = 0.64$, $I^2 = 0\%$; 3 studies, 170 participants; moderate certainty evidence; [Analysis 2.1](#)) and PaCO₂ (MD -0.53 kPa, 95% CI -0.88 to -0.19; $P = 0.94$, $I^2 = 0\%$; 3 studies, 175 participants; high-certainty evidence; [Analysis 2.2](#)).

Health-related quality of life

Three months' follow-up

Two studies provided the IPD of 216 participants for the SRI ([Murphy 2017](#); [Struik 2014](#)). Additional IPD of the SGRQ were available for three participants ([Murphy 2017](#)), so we standardised and pooled the data of the SRI and SGRQ. Participants treated with NIV improved more on the summary score of the SRI compared to participants allocated to the control group ([Table 2](#)). After pooling of the SRI and SGRQ data, there was no added benefit of the NIV on HRQL (AMD 0.25, 95% CI -0.01 to 0.51). Given a SD of 11.2 units for the SRI, this would suggest an improvement of 2.8 units.

The meta-analysis of aggregated data from the same two studies showed a SMD in favour of the NIV group (SMD 0.27, 95% CI 0.01 to 0.54; $P = 0.63$, $I^2 = 0\%$; 2 studies, 216 participants; very low-certainty evidence; [Analysis 2.3](#)). In contrast to the pooled IPD analysis, this was statistically significant.

12 months' follow-up

SRI data were available for 162 participants of the same two studies ([Murphy 2017](#); [Struik 2014](#)). Participants treated with NIV showed, on average, a larger improvement on the summary score of the SRI ([Table 2](#)). Additional IPD of the SGRQ were available for two participants ([Murphy 2017](#)), so we standardised and pooled the data. In line with the three-month data, there was no added benefit of the NIV on HRQL (AMD 0.25, 95% CI -0.06 to 0.55). Given a SD of 11.9 units for the SRI, this would suggest an improvement of 3.0 units.

The meta-analysis yielded similar results to the pooled IPD analysis (SMD 0.27, 95% CI -0.04 to 0.58; $P = 0.34$, $I^2 = 0\%$; 2 studies, 162 participants; very low-certainty evidence; [Analysis 2.3](#)).

Admission-free survival

This outcome was measured as time from randomisation to readmission (for a pulmonary cause) or death (of any cause) in the first year after randomisation in two studies ([Murphy 2017](#); [Struik 2014](#)). The trials provided data from 317 participants. The admission-free survival was better in participants treated with NIV compared to participants allocated to the control group (AHR 0.71, 95% CI 0.54 to 0.94).

The meta-analysis of data of the same studies demonstrated an admission-free survival benefit favouring the NIV group, but in contrast to the pooled IPD analysis this effect was not statistically significant (HR 0.69, 95% CI 0.39 to 1.23; $P = 0.05$, $I^2 = 75\%$; 2 studies, 317 participants; low-certainty evidence; [Analysis 2.4](#)). The results

showed considerable statistical heterogeneity between the studies, but this heterogeneity could not be explored by subgroup analysis due to the low number of studies.

Post exacerbation COPD — secondary outcomes

Lung function

Three months' follow-up

Two studies provided the IPD of 204 participants for this outcome ([Murphy 2017](#); [Struik 2014](#)). For the FEV₁, both study groups showed only a minor increase, the increase probably being slightly larger in participants allocated to the control group (AMD -0.02 L, 95% CI -0.07 to 0.03; [Table 2](#)). In contrast, an increase in the FVC was only observed in participants allocated to the control group (AMD -0.11 L, 95% CI -0.28 to 0.06; [Table 2](#)). The meta-analyses were based on the same two studies that provided the IPD and did not reveal any new findings for both the FEV₁ (MD -0.03 L, 95% CI -0.09 to 0.03; $P = 0.28$, $I^2 = 14\%$; 2 studies, 201 participants; [Analysis 2.5](#)) and the FVC (MD -0.13 L, 95% CI -0.32 to 0.04; $P = 0.61$, $I^2 = 0\%$; 2 studies, 202 participants; [Analysis 2.6](#)).

12 months' follow-up

The results of the 157 participants from the same two studies yielded similar results. Both study groups showed only minor changes in the FEV₁ (AMD -0.03 L, 95% CI -0.09 to 0.04; [Table 2](#)). The change in the FVC tended to be in favour of the control group (AMD -0.09 L, 95% CI -0.29 to 0.12; [Table 2](#)), as the FVC in the NIV group seems not affected.

The meta-analyses yielded comparable results for the FEV₁ (MD -0.03 L, 95% CI -0.09 to 0.03; $P = 0.62$, $I^2 = 0\%$; 2 studies, 157 participants; [Analysis 2.5](#)) and the FVC (MD -0.11 L, 95% CI -0.32 to 0.10; $P = 0.29$, $I^2 = 9\%$; 2 studies, 158 participants; [Analysis 2.6](#)).

COPD exacerbations and hospital admissions

Baseline hospital admission rates were recorded in two studies ([Murphy 2017](#); [Struik 2014](#)) for the 12 months before inclusion in the study but in one study it was only recorded whether there were < 3 or ≥ 3 admissions. We were unable to perform the linear mixed effect models as this outcome was not normally distributed.

Three months' follow-up

One study provided the IPD of 139 participants ([Struik 2014](#)). On average, the total numbers of COPD exacerbations appear to be equal between both groups ([Table 2](#)). An equal proportion of participants had experienced one or more exacerbation (NIV group: 35 of 76 participants (46%); control group: 31 of 68 participants (46%) ≥ 1 exacerbation). The OR for an exacerbation was 0.93 (95% CI 0.47 to 1.81) in favour of participants in the NIV group. The meta-analysis of data of the same study yielded also an OR of 0.93 (95% CI 0.48 to 1.81; 1 study, 139 participants; [Analysis 2.7](#)).

Hospitalisation data were not available for any of the included studies after three months.

12 months' follow-up

Three studies contributed COPD exacerbation data of 181 participants ([Cheung 2010](#); [Murphy 2017](#); [Struik 2014](#)). There was an equal number of COPD exacerbations in both groups during the study period ([Table 2](#)). Also, exacerbation rates appeared similar

between participants allocated to NIV (73 of 95 participants (77%) ≥ 1 exacerbation) and to the control group (71 of 86 participants (83%) ≥ 1 exacerbation). The OR was in favour of participants allocated to NIV (OR 0.70, 95% CI 0.33 to 1.46). Meta-analysis of data of the same three studies showed a comparable result to the IPD analysis (OR 0.67, 95% CI 0.32 to 1.41; $P = 0.98$, $I^2 = 0\%$; 3 studies, 181 participants; [Analysis 2.7](#)).

IPD regarding hospital admissions were available for 193 participants of the same three studies. There was no difference in the number of hospital admissions ([Table 2](#)). Admission rates appeared similar between participants treated with NIV (54 of 100 participants (54%) admitted) and participants allocated to the control group (53 of 93 participants (57%) admitted). The OR for a hospitalisation was 0.88 (95% CI 0.52 to 1.50) in favour of participants treated with NIV. In the meta-analysis, we observed a larger OR (OR 0.63, 95% CI 0.19 to 2.09; $P = 0.06$, $I^2 = 66\%$; 3 studies, 193 participants; [Analysis 2.8](#)). These results may represent substantial statistical heterogeneity between the studies, but this heterogeneity could not be explored due to the low number of studies.

All-cause mortality

All-cause mortality was measured in two studies ([Murphy 2017](#); [Struik 2014](#)), which provided the IPD of 317 participants. The

median follow-up of all participants was 21 months. The risk for all-cause mortality was not affected by NIV (AHR 0.97, 95% CI 0.74 to 1.28). The meta-analysis of the mortality data of the same two studies yielded similar results to the pooled IPD analysis (HR 0.98, 95% CI 0.74 to 1.29; $P = 0.96$, $I^2 = 0\%$; 2 studies, 317 participants; low-certainty evidence; [Analysis 2.9](#)).

Heterogeneity exploration in PaCO₂ response in stable state

In the stable population, the results of the PaCO₂ analysis after three months demonstrated substantial statistical heterogeneity ($P = 0.001$; $I^2 = 65\%$; [Analysis 1.2](#)). Subgroup analysis based on the mean baseline PaCO₂ of the study revealed a significant subgroup difference (test for subgroup differences: $P = 0.001$; $I^2 = 91\%$; [Analysis 1.16](#); [Figure 6](#)). In the PaCO₂ < 7.3 kPa subgroup, heterogeneity was reduced to 0%, but remained substantial in the ≥ 7.3 kPa subgroup. As seen in [Figure 6](#), the study by [Clini 2002](#) seems to cause this heterogeneity. This was the only study in this subgroup adopting low ventilator pressures (mean IPAP < 18 cmH₂O), and when this study was removed from the subgroup, the heterogeneity was reduced to 0% ($P = 0.64$).

Figure 6.

Additional subgroup analysis based on mean IPAP also found significant subgroup differences (test for subgroup differences: $P = 0.005$, $I^2 = 88\%$; [Analysis 1.17](#); [Figure 7](#)). In the IPAP < 18 cmH₂O subgroup, the heterogeneity was reduced to 0% ($P = 0.55$), whilst

in the IPAP ≥ 18 cmH₂O subgroup, the heterogeneity remained substantial. As seen in [Figure 7](#), the study by [Duiverman 2008](#) seems to cause this heterogeneity. This study mainly included participants with moderate hypercapnia (mean baseline PaCO₂ < 7.3 kPa), and

removal of this study from the subgroup reduced the heterogeneity to 0% ($P = 0.64$).

Figure 7.

Lastly, subgroup analysis based on compliance also showed significant subgroup differences (test for subgroup differences: $P = 0.04$, $I^2 = 77\%$; [Analysis 1.18](#)), but the heterogeneity in the good compliance subgroup remained substantial ($P = 0.01$, $I^2 = 59\%$).

Sensitivity analysis

For the sensitivity analysis we excluded seven studies on stable COPD as we had judged these to be at high or unclear risk of bias for the selection or attrition domain (or both) ([Bhatt 2013](#); [Clini 2002](#); [Gay 1996](#); [Martin-Marquez 2014](#); [Schneeberger 2017](#); [Sin 2007](#); [Strumpf 1991](#)). Removal of these studies from the analysis resulted in a slightly larger treatment effect for PaO₂ after three months of NIV (AMD 0.31 kPa, 95% CI 0.02 to 0.62, 103 participants), but did not affect the PaO₂ results after 12 months. The treatment effect of NIV on PaCO₂ increased both after three months' follow-up (AMD -0.76 kPa, 95% CI -0.98 to -0.55, 304 participants) and 12 months' follow-up (AMD -0.55 kPa, 95% CI -0.84 to -0.27, 174 participants). The sensitivity analysis also revealed a larger and statistically significant effect of NIV on the 6MWD, both after three months (AMD 22.3 m, 95% CI 2.1 to 42.5, 245 participants) and after 12 months (AMD 44.0m, 95% CI 0.2 to 87.8, 88 participants). Lastly, a larger effect of NIV was observed on HRQL at both follow-ups (three months: AMD 0.44, 95% CI 0.18 to 0.68, 229 participants; 12 months: AMD 0.26, 95% CI -0.05 to 0.55; 169 participants).

We excluded one post-exacerbation study due to high or unclear risk of bias ([Cheung 2010](#)). When limiting the analysis to the

remaining high-quality studies, the treatment effects for all primary outcomes were in line with the overall treatment effect in this cohort.

DISCUSSION

Summary of main results

In people with severe COPD in a stable condition, the addition of chronic NIV to standard treatment improves diurnal hypercapnia (high-certainty evidence) for up to 12 months. Additionally, chronic NIV seems to improve short-term diurnal PaO₂ and all-cause mortality (moderate-certainty evidence) and might result in a relevant improvement in HRQL at three months (very low-certainty evidence). In people who have COPD with persistent hypercapnia following a severe COPD exacerbation with AHRF, the added benefit of chronic NIV seems to be more limited. In this population, chronic NIV seems to improve daytime hypercapnia (moderate to high-certainty evidence) and might prolong the time to readmission or death (low-certainty evidence), without a beneficial effect on HRQL. Although the targets of this treatment seem to differ between these populations, the results of this systematic review seem to confirm the application of chronic NIV in people with COPD in a stable clinical state, and might support the initiation of chronic NIV in people who have COPD with persistent hypercapnia after an acute exacerbation of COPD.

Interpretation of the main findings

Gas exchange

The evidence indicates that regardless of the timing of chronic NIV initiation, relevant improvements in hypercapnia may be achieved with chronic NIV. Additionally, the PaO_2 of people with stable COPD seems to improve with NIV after three months. Our results again indicate that in stable COPD, the effect of NIV on diurnal ventilation seems to be larger in people with more severe hypercapnia ($\text{PaCO}_2 \geq 7.3$ kPa) and a better treatment compliance (≥ 5 hours per night) (Struik 2014). Hypercapnia also seems to improve more in people treated with an IPAP ≥ 18 cmH_2O . This finding supports the application of NIV adopting high IPAP to target nocturnal PaCO_2 reduction, which has become a major NIV strategy during the past decade (Dreher 2010; Windisch 2009). However, it remains uncertain to what extent these improvements in gas exchange contribute to the beneficial effect on individual-centred outcomes such as HRQL and survival. A better understanding of these mechanisms could improve selection of people with COPD for NIV, and could optimise the titration of the individual's NIV settings. Therefore, we emphasise this should be an aim of future studies.

Exercise capacity

Evidence that chronic NIV improves exercise capacity is currently insufficient. However, if only high-quality studies are included, it seems that there is a benefit of chronic NIV on the exercise capacity at both three months (AMD 22.3 m, 95% CI 2.1 to 42.5) and 12 months' follow-up (AMD 44.0 m, 95% CI 0.2 to 87.8). Given the MCID of 26 m identified in this population of people with very severe COPD (Puhan 2011), this improvement only seems to be of relevance after 12 months. We acknowledge that the uncertainty in these estimates is high, as the 95% CI are wide. So although there might be a positive effect, a definite conclusion about the effect of chronic NIV on exercise capacity cannot be drawn at this moment.

Health-related quality of life

Improving HRQL should be a major target of any treatment in severe or end-stage COPD. Acknowledging that our confidence in the evidence is very low, the results do indicate that the initiation on chronic NIV might have a beneficial effect on HRQL in people with stable COPD in the short term. This treatment effect after three months seems to reach clinical relevance, at least when measured with the change responsive SRI. The contrasting results at the 3- and 12-month follow-up periods are interesting. We emphasise that different proportions of studies contributed to either follow-up, possibly with different treatment and participant characteristics, which might explain these different results. For participants initiated following an exacerbation, there seems to be no benefit of NIV on HRQL and only the upper range of the 95% CI seems to be of clinical relevance for the total score of the SRI. Future studies should therefore continue to investigate the effect of post-exacerbation chronic NIV on HRQL and identify which individual is most likely to experience a HRQL benefit. Lastly, given the result of the meta-analysis on the dyspnoea outcomes, there may be a small beneficial effect on dyspnoea, but the data are sparse and the effect estimate does not seem to reach clinical relevance (Witek 2003).

Exacerbations and (re)hospitalisations

We found that chronic NIV might prolong the admission-free survival in people initiated on NIV following a severe COPD exacerbation. However, continuing NIV after an exacerbation did not affect the total number of COPD admissions in the first year, and did not affect mortality. We hypothesise that, although the first readmission might have been postponed, eventually these people with severe COPD suffer from frequent exacerbations and related mortality despite the chronic NIV. Furthermore, admission-free survival was investigated in the total population, while exacerbation and admission rates were investigated only in the participants who completed the study period of one year. To conclude, at this moment there is insufficient evidence that chronic NIV following a severe COPD exacerbation reduces the number of COPD exacerbations and admissions, and mortality in these patients remains high.

Mechanisms

It has been hypothesised that chronic NIV achieves its beneficial effect though improvements in respiratory mechanics, such as stabilisation of FEV_1 and a reduction in residual volume. The results of this review do not seem to be supportive of these hypotheses. We did not show an effect of NIV on different lung function outcomes in either of our cohorts. A second hypothesis concerns an improved function of the respiratory muscles that might be obtained by chronic NIV. The results of our analyses indicate an improved P_{lmax}. In people with severe COPD, P_{lmax} is known to be related to dyspnoea, HRQL and even survival (Ottenheijm 2008), so an improved respiratory muscle function could contribute to the improved outcomes of NIV. It should, however, be noted that P_{lmax} measures maximum inspiratory pressure, which is a derivative of respiratory muscle strength and importantly also affected by hyperinflation (Rochester 1985). However, we did not show an improvement in hyperinflation with NIV. In addition, due to its voluntary nature, these measurements are affected not only by strength but also by motivation (Ottenheijm 2008). These caveats prevent strong conclusions regarding improved respiratory function by NIV, but our results do at least not refute this hypothesis. Finally, an effect on sleep quality might be an important aspect in improving HRQL. However, this has unfortunately seldom been investigated, and no additional data could be added to this meta-analysis to support this hypothesis.

Overall completeness and applicability of evidence

This review included 21 RCTs investigating chronic NIV for people with severe COPD. Fortunately, the trial authors of 16 studies responded to our request to share their trial data, enabling the investigation of the IPD of 1142 participants. We could not obtain the IPD from five trials. Therefore, we also conducted a meta-analysis of the summary trial data from all trials. For the majority of the outcomes, the results of the meta-analysis were in line with the IPD results, except for expiratory muscle strength after three months, which became significant after additional data were added (Garrod 2000). In the post-exacerbation population, the IPD of the admission-free survival and mortality outcomes were not fully obtained, as these IPD were not provided for the study by Cheung 2010. This trial might bias the results, as participants were excluded from the trial once the primary outcome ("an episode recurrent AHRF requiring acute NIV or intubation, or death") was reached.

Additionally, it remains unclear if the trial by [Xiang 2007](#) could be included, as we were unable to contact the trial authors.

The inclusion criteria were generally consistent between the studies, and all studies only included participants with severe COPD. The vast majority included participants with chronic hypercapnia; only 61 participants (8%) without hypercapnia were included. We therefore emphasise that the results apply primarily to people with COPD who experience chronic hypercapnia. In the stable population, 72% of the participants were male, which could reflect the higher prevalence of COPD in males ([GOLD 2021](#); [Terzikhan 2016](#)). In contrast to the 2013 update, this review also included studies that investigated chronic nocturnal NIV in addition to a pulmonary rehabilitation or exercise training program. This increased the body of evidence as it resulted in the inclusion of four additional studies ([Duiverman 2008](#); [Garrod 2000](#); [Martin-Marquez 2014](#); [Schneeberger 2017](#)), including the IPD of 127 participants. Our results cannot automatically be extended to overlap people who have COPD with concomitant obstructive sleep apnea, as most studies excluded people with concomitant sleep apnea or a very high BMI. Although this might limit the generalisability of our conclusions, in the present analysis effects for people with COPD are reliably displayed without overestimating the effects due to concomitant sleep apnea or serious obesity hypoventilation.

It should also be noted the majority of the studies, especially the larger studies and studies with positive outcomes, have been conducted in Europe. This could limit the generalisability of the results to other regions as expertise and organisation of care might differ, which could lead to differences in treatment characteristics, adherence and effectiveness.

Quality of the evidence

Overall, the certainty of the evidence for the main comparisons was moderate to very low, according to the [GRADE 2013](#) recommendations. The PaCO₂ outcome was the only outcome that we judged to be of high certainty, and it is believed that the observed treatment effect lies close to the true treatment effect of NIV. Risk of bias was a major reason for downgrading the certainty, as the unblinded design of the included studies is likely to affect outcomes such as the 6MWD and HRQL. We decided not to downgrade the blood gas and survival outcomes on this domain, as we judged that the unblinded design is unlikely to affect these outcomes. Inconsistency was observed in two outcomes, but we did not consider this a reason to downgrade the certainty. First, we observed substantial statistical heterogeneity between the studies for the PaCO₂ outcome ($P = 0.001$, $I^2 = 65\%$), but this could be explained by the subgroup analysis. Second, the admission-free survival demonstrated considerable heterogeneity ($P = 0.005$, $I^2 = 75\%$). As only two studies provided data for this outcome, we were unable to conduct subgroup analysis to explore this heterogeneity. Nevertheless, this heterogeneity may be explained by differences in the timing of NIV initiation and participant selection, as in both studies the intervention targeted nocturnal correction of hypoventilation and was initiated in highly experienced centres. Another major reason to downgrade the certainty was serious imprecision. For most outcomes, the number of studies was low, resulting in wide 95% CIs. Thus, the possibility of harm or no treatment effect could not be excluded for outcomes such as the 6MWD, HRQL and the survival outcomes. Lastly, we did not observe indirectness or publication bias in our results.

Potential biases in the review process

Limitations regarding the setup of the analyses

Our protocol limited the follow-up duration to three or 12 months of NIV. Two studies measured or reported trial outcomes only after six months of NIV, and we did not use these data ([De Backer 2011](#); [Eman Shebl 2015](#)). The results of these two studies seem in line with the results of our review, with the exception that a relevant benefit was found on the 6MWD in stable COPD ([Eman Shebl 2015](#)). Although only 45 participants were included in these two studies, we acknowledge that this a limitation as it reduced the body of evidence. Another limitation is that we did not investigate serious or rare adverse effects. However, the (serious) adverse effects of chronic NIV are well known and are usually related to intolerance to the device or mask, leakage of the air delivered or facial irritation due to mask pressures. A recent review on chronic NIV supports this as it found an incidence rate of 0 per person (95% CI 0.00 to 0.01) for severe adverse events and of 0.21 per person (95% CI 0.12 to 0.37) for adverse events, acknowledging that a majority of the trials did not report adverse events ([Wilson 2020](#)). Lastly, we could not assess the risk of publication bias as the only outcome with more than 10 included studies (PaCO₂) demonstrated heterogeneity between the studies.

Limitations regarding the included studies

We encountered several limitations regarding the included studies. The major limitation concerns the unblinded nature of the vast majority of the trials. Although some trials used a continuous positive airway pressure as sham device ([Cheung 2010](#); [Gay 1996](#); [Sin 2007](#)), an optimal sham treatment is not available as these approaches could increase anatomical dead space or alter respiratory mechanisms, possibly also affecting the respiratory failure ([Rodway 2010](#); [Saatci 2004](#)). The extent to which the unblinded nature of the trials influences the outcomes differs; e.g. blood gases, hospitalisations and mortality are unlikely to be affected, whilst participant-reported outcomes are likely affected to a larger extent. Secondly, we have also included trials investigating chronic NIV applied during the night in addition to a training or rehabilitation program. It is, however, difficult to study the additional benefit of these training programs as for the majority of the included studies, it was unclear if participants were allowed to follow such a program, as studies did not record this adequately. Third, data on the actual timing of NIV initiation were missing in the post-exacerbation trials. This data would be of value to estimate the optimal timing of chronic NIV initiation shortly following an episode of AHRF. Fourth, exacerbations and hospitalisation frequency proved difficult to investigate adequately. Many studies did not report these numbers prior to trial inclusion, pre-study numbers were not always objectively assured and so could have been affected by recall bias, or studies reported exacerbations and hospitalisations over a different time frame (e.g. one or three years). It was therefore difficult to investigate whether NIV actually reduced the number of exacerbations. Additionally, nine of the included studies investigated HRQL but used multiple tools to assess this. We chose to consider only the disease-specific SRI and the SGRQ, as these tools have shown good validity and reliability, especially in people with COPD in a stable phase ([Struik 2013](#)). We therefore recommend future trials to use disease-specific HRQL tools such as the SRI. Lastly, one trial only reported the percentage predicted values of the lung function outcomes. Using the regression equations, we were able to calculate the absolute

values, but we acknowledge that this could introduce uncertainty and is sensitive to errors.

Agreements and disagreements with other studies or reviews

In recent years, two systematic reviews and meta-analyses have been conducted. Inclusion criteria appear similar to our review, except that both these reviews included observational or non-RCTs, and also included trials that compared different NIV strategies. Comparison of mortality and admission outcomes is difficult, as no review has been published that studied these outcomes as time-to-event data.

Recently, a systematic review and meta-analysis was published that included 51,085 people with COPD who experience chronic hypercapnia (33 studies), investigating the effect of chronic home NIV on mortality, all-cause hospital admissions and quality of life (Wilson 2020). As compared to our systematic review, this review included both RCTs and observational studies, and did not differentiate according to the timing of NIV initiation. However, the review authors also conducted subgroup analysis based on the timing of NIV initiation. These results are, in general, consistent with our finding; a significantly lower mortality risk (OR 0.62, 95% CI 0.42 to 0.92) and no effect on hospital admissions (RR 0.84, 95% CI 0.59 to 1.18) for people initiated in a stable phase, and no significant effect on mortality (OR 0.66, 95% CI 0.41 to 1.06) or HRQL (standardised MD -0.03, 95% CI -0.25 to 0.20) in people initiated following an acute exacerbation. They did not find a beneficial effect on HRQL in the stable subgroup. This difference might be explained by the tools used in the review by Wilson 2020; the COPD assessment test, the Chronic Respiratory disease Questionnaire, the SGRQ and the Short-form 36. HRQL tools designed specifically for people with respiratory failure, such as the SRI that was used for this review, might be more sensitive to change (Struik 2013). In addition, we have also used the HRQL data of the RCTs of Clini 2002 and McEvoy 2009, which could explain the observed difference.

In 2016, Dretzke 2016 published their systematic review of both RCTs and non-RCTs (31 studies), also grouping studies into stable and post-exacerbation populations. When the Dretzke 2016 review was published, some large trials included in the present review had not yet been published (Murphy 2017; Zhou 2017), possibly explaining the observed differences. They did not find a survival benefit of NIV in either the stable participants (RR 0.88, 95% CI 0.55 to 1.43) or the post-exacerbation population (RR 0.89, 95% CI 0.53 to 1.49). Results on the blood gases were not included in the meta-analysis but support our findings as they suggest improved blood gases (PaCO₂ and PaO₂) in the stable population, and a potential benefit on PaCO₂ in the post-exacerbation cohort.

Lastly, the results of our review on COPD exacerbation in the post-exacerbation cohort contradict a major finding of Murphy 2017, who found a reduced exacerbation rate favouring the NIV group. In contrast to Murphy, we conducted our analysis only on participants who completed the 12-month follow-up ('completers'). Dropouts could be unequally distributed between both study arms, and the 'time at risk' for an exacerbation could therefore differ between both arms, introducing bias. Although including only completers reduced statistical power, there was not even a trend towards a reduced exacerbation rate in our

analysis. We acknowledge that this analysis setup could explain the observed difference.

AUTHORS' CONCLUSIONS

Implications for practice

The results of this systematic review and individual participant data (IPD) analysis provide sufficient evidence for the routine application of chronic NIV in people with severe chronic obstructive pulmonary disease (COPD) who have chronic hypercapnic respiratory failure (CHRF), while its place remains uncertain for people who remain hypercapnic shortly after a severe COPD exacerbation. The benefits and goals of chronic non-invasive ventilation (NIV) seem to differ between different COPD populations. For people initiated in a stable clinical state, significant and relevant improvements in diurnal hypercapnia can be achieved, and oxygenation, health-related quality of life (HRQL) and all-cause mortality might improve. In contrast, people who remain hypercapnic after a severe COPD exacerbation seem to benefit mostly in terms of a reduction in hypercapnia, and a prolonged time to readmission or death, but without relevant improvements in HRQL. Evidence also suggests that the effect of NIV on gas exchange is largest when the NIV is applied with sufficiently high pressures and for at least five hours of NIV use per night.

Currently, the application of chronic NIV in people with COPD varies greatly between different healthcare providers (Crimi 2016). Considering the results of the participant-centred outcomes of this review, reluctance towards the initiation of NIV in stable hypercapnic COPD may no longer be warranted, whilst the application of chronic NIV post-exacerbation can be discussed. Consistent with the guideline recommendations of the European Respiratory Society and the American Thoracic Society, the findings of this review support the application of this treatment in people with severe end-stage COPD (Ergan 2019; Macrea 2020).

Implications for research

Given that the certainty of the evidence on the participant-centred outcomes is moderate to very low, there is a need for new randomised controlled trials (RCTs) that investigate chronic NIV in people with stable COPD to strengthen the evidence. For future studies it should be taken into consideration that these people are severely limited by their disease and have poor prognosis and a limited number of other treatment options. Therefore, ethical concerns might arise when withholding NIV from a control group. In contrast, there remains a need for additional RCTs that investigate chronic NIV shortly after a severe exacerbation. Nevertheless, not all people eventually benefit from NIV, and the initiation of this treatment can be challenging and stressful. Therefore, future studies may focus on the identification of the person with COPD who is most likely to benefit from this treatment. Large observational studies may identify different COPD phenotypes based on individual and disease characteristics, and try to identify the underlying cause of chronic hypercapnic respiratory failure in the individual person. Furthermore, studies are needed to further elucidate what pathophysiological mechanisms are improved by NIV (and in what way), so that more goal-directed therapy can be provided. The evidence regarding respiratory muscle functioning improvement is limited, as is the evidence regarding sleep quality improvement. Treatment targets are needed for the different

phenotypes, and optimal criteria to start and continue NIV are to be identified, realising that these targets and criteria might differ substantially between different phenotypes. Lastly, the current aim of chronic NIV is to reduce the partial pressure of carbon dioxide (PaCO_2) by improving nocturnal ventilation. Evidence that only this reduction is responsible for the improved outcomes is insufficient, and there is a need to unravel the mechanisms through which this intervention improves physiological and participant-centred outcomes.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Bhatt 2013

Study characteristics

Methods	Design: single centre randomised controlled study with parallel groups
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Bhatt 2013 (Continued)

Dates: study dates not reported

Setting: pulmonary clinic at the University of Iowa Hospital, USA

Follow-up: 6 weeks, 3 and 6 months

Participants	<p><u>Inclusion criteria</u></p> <ul style="list-style-type: none"> Stable COPD ($FEV_1/FVC < 0.70$), no exacerbations in the 4 weeks prior to initiation of the study At least 10 pack-year smoking history $PaCO_2 < 52$ mmHg (6.9 kPa) Low clinical probability of OSA (assessed using the Berlin Questionnaire) <p><u>Exclusion criteria</u></p> <ul style="list-style-type: none"> Diagnosed with congestive heart failure, OSA, chronic respiratory conditions other than COPD Age < 35 years Any disease limiting life expectancy to less than 2 years Active malignancy other than non-melanotic skin cancer in the previous 2 years Any anatomic variation or disease process that precluded wearing a nasal mask <p><u>Baseline characteristics (raw data of 33 participants)</u></p> <ul style="list-style-type: none"> Age 69.4 ± 8.3 years Sex (m/f) 25/8 FEV_1 0.73 ± 0.19 L (29 ± 8 %predicted) $PaCO_2$ 6.0 ± 1.1 kPa
Interventions	<p><u>Domiciliary NPPV (n = 15)</u></p> <ul style="list-style-type: none"> Interface: oronasal mask or nasal pillows Device: BiPAP Synchrony (Respironics Inc.) Target: titrated to final pressures of 15/5 cmH₂O within a week Initiation: at home by a respiratory therapist Ventilator settings: IPAP 15, EPAP 5 cmH₂O (all patients) Compliance: 3.1 ± 3.3 hours <p><u>Comparator (n = 15)</u></p> <p>Usual therapy (not specified)</p>
Outcomes	<p>Primary outcome: HRQL (CRQ), dyspnoea (TDI)</p> <p>Secondary outcomes: BGA, FEV_1, 6MWD, PImax</p>
Notes	<p>Conflicts of interest: none</p> <p>Funding: Respironics Inc.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised in a 1:1 ratio to receive NIV versus control treatment using a random number generator.
Allocation concealment (selection bias)	Low risk	Randomisation was done using opaque sealed envelopes which were opened during screening visits.

Bhatt 2013 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding performed.
Blinding of outcome assessment (detection bias) Patient reported outcomes	High risk	No blinding of participant performed so the TDI is at high risk of bias.
Blinding of outcome assessment (detection bias) Lung function and exercise test	Unclear risk	Unclear if personnel performing measurements were blinded.
Blinding of outcome assessment (detection bias) Blood gases, hospitalisations and mortality.	Low risk	BGA are objective measurements and unlikely to be affected by the assessor.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	3 participants dropped out of the control group, reasons for dropout not provided.
Selective reporting (reporting bias)	Low risk	Trial not registered, all primary and secondary outcomes reported.
Other bias	High risk	Baseline imbalance; unclear, no significance levels provided. Some data (FVC and 6MWD) seem to be not in balance. Differential attention paid by caregivers; NIV group: participants were called every day the first week and could be visited while the control group was not.

Casanova 2000

Study characteristics

Methods	<u>Design:</u> multicentre randomised controlled trial with parallel groups <u>Dates:</u> between 1995 and 1997 <u>Setting:</u> pulmonary clinics of two hospitals in the Canary Islands, Spain <u>Follow-up:</u> 3, 6 and 12 months
Participants	<u>Inclusion criteria</u> <ul style="list-style-type: none"> • Age 45 to 75 years • Smoking history of > 20 pack years • FEV₁ < 45% of predicted, FEV₁/FVC < 70%, TLC ≥ 80% predicted • A stable clinical state (no acute exacerbation for 3 months prior to the initiation of the study) <u>Exclusion criteria</u> <ul style="list-style-type: none"> • A 15% increase in FEV₁ after the administration of an inhaled bronchodilator • Refusal to stop smoking • OSA; AHI > 10 per hour

Casanova 2000 (Continued)

- Other etiologies of chronic airway obstruction (bronchiectasis and cystic fibrosis)
- Active and important coexisting medical conditions, such as left ventricular failure

Baseline characteristics (raw data of 36 participants)

- Age 66.6 ± 5.3 years
- Sex (m/f) 35/1
- FEV₁ 0.84 ± 0.22 L (31 ± 7 %predicted)
- PaCO₂ 6.8 ± 0.9 kPa

Interventions	<u>Nocturnal nasal non-invasive positive pressure ventilation plus standard care (n=26)</u> <ul style="list-style-type: none"> • Interface: nasal positive pressure mask • Device: bilevel pressure ventilation system (model DP-90; Taema), set in spontaneous mode • Target: targeted an EPAP of 4 cmH₂O and an IPAP of at least 8 cmH₂O above EPAP • Initiation: inpatient • Ventilator settings: IPAP 12 ± 2, EPAP 4 cmH₂O • Compliance: mean 6.2 hours <u>Comparator (n = 26)</u> Standard care alone, including LTOT
Outcomes	After 3 months: BGA, lung function, dyspnoea (MRC and Borg scale), PE/Plmax After 12 months: exacerbation rate, hospital admissions, intubations and mortality
Notes	Conflicts of interest: not reported Funding: supported in part by a grant from the Spanish Respiratory Society

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The 52 patients who met the study criteria were randomised by an independent office into two groups using a table of random numbers"
Allocation concealment (selection bias)	Low risk	Quote: "Randomised by an independent office using a table of random numbers"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants: no blinding for treatment
Blinding of outcome assessment (detection bias) Patient reported outcomes	High risk	Participants were not blinded for treatment.
Blinding of outcome assessment (detection bias) Lung function and exercise test	Low risk	Quote (from correspondence): "Blinded: for gas exchange and lung function"
Blinding of outcome assessment (detection bias)	Low risk	Quote (from correspondence): "Blinded: for gas exchange and lung function"

Chronic non-invasive ventilation for chronic obstructive pulmonary disease (Review)

Casanova 2000 (Continued)

Blood gases, hospitalisations and mortality.

Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Inclusion of the patients who did not complete the trial (intent to treat) did not affect any of the outcomes"
Selective reporting (reporting bias)	Unclear risk	Trial not registered, all outcomes listed in the Methods were reported
Other bias	Low risk	The study appears to be free of other source of bias

Cheung 2010

Study characteristics

Methods	<p><u>Design</u>: single centre randomised controlled trial with parallel groups</p> <p><u>Dates</u>: January 2007 to March 2009</p> <p><u>Setting</u>: United Christian Hospital, Hong Kong, China</p> <p><u>Follow-up</u>: 4 weeks, then every 12 weeks up to 52 weeks (participants were withdrawn from the study after reaching the primary outcome)</p>
Participants	<p><u>Inclusion criteria</u></p> <ul style="list-style-type: none"> People with COPD who survived an episode of ARF requiring NIV despite initial treatment with bronchodilators, corticosteroids, and antibiotics. <p><u>Exclusion criteria</u></p> <ul style="list-style-type: none"> Active smokers Respiratory failure due to non-COPD cause Radiological evidence of pneumonia Transmissible infection Requires long term systemic steroids Has serious comorbidity with an estimated life expectancy of < 1 year Has significant obstructive sleep apnoea (AHI # 10 per hour) Has an FEV₁ bronchodilator response > 15% Already on home NIV Inability of participant or caregiver to comply with the research protocol <p><u>Baseline characteristics (raw data of 47 participants)</u></p> <ul style="list-style-type: none"> Age 70.3 ± 7.7 years Sex (m/f) 43/4 FEV₁ 0.59 ± 0.17 L (30 ± 9 %predicted) Pre-randomisation PaCO₂ 7.5 ± 1.0 kPa
Interventions	<p>47 participants randomised to receive, in addition to optimised treatment:</p> <p><u>Nocturnal NIV (n = 23)</u></p> <ul style="list-style-type: none"> Interface: not reported

Cheung 2010 (Continued)

- Device: BiPAP Synchrony (Respironics Inc.) with IPAP titrated from 10 to 20 cmH₂O as tolerated and EPAP set at 5 cmH₂O. A backup rate of 14/min with an inspiratory time of 1 sec was used.
- Target: a tidal volume of 7 to 10 ml/kg
- Initiation: in-hospital
- Timing of initiation: after > 48 hours independence of acute NIV
- Ventilator settings: IPAP 14.8 ± 1.1 and EPAP 5 cmH₂O
- Compliance: 7 to 9 hours

Placebo home NIV (n = 24)

Delivered by the same ventilator using a CPAP of 5 cmH₂O

Outcomes	<p>Primary outcome: recurrent severe COPD exacerbation, resulting in repeat NIV, intubation or death in 1 year</p> <p>Secondary outcomes: compliance, BGA, readmission due to COPD exacerbation, all-cause mortality</p>
Notes	<p>Conflicts of interest: none</p> <p>Funding: partially sponsored by the Hong Kong Lung Foundation. Machines were free loans from Respironics Inc.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomisation was performed by drawing sequentially numbered and sealed opaque envelopes containing computer-generated random numbers by non-study personnel".
Allocation concealment (selection bias)	Low risk	Quote: "randomisation was performed by drawing sequentially numbered and sealed opaque envelopes containing computer-generated random numbers by non-study personnel".
Blinding of participants and personnel (performance bias) All outcomes	High risk	<p>Quote: "This was an open label study, but care had been taken to avoid biasing the patients into believing either mode was superior".</p> <p>Control group received sham ventilation. Unclear how they took care to avoid performance bias. Not mentioned if study personnel were blinded.</p>
Blinding of outcome assessment (detection bias) Blood gases, hospitalisations and mortality.	High risk	For primary outcome: there is a high risk of bias. The outcome assessors were aware of the treatment allocation as they had to rate whether there was an 'event' in the NIV group, which was defined as > 12 hours use of NIV because of symptom deterioration.
Incomplete outcome data (attrition bias) All outcomes	High risk	Intention to treat principle for primary outcome. In the control arm of 26 participants, 2 were not in the final analysis (because of a protocol violation and death before CPAP start). High proportion of dropouts, not equally divided (NIV 8 / CPAP 4). Reasons provided.
Selective reporting (reporting bias)	High risk	<p>Mortality not reported in the results.</p> <p>Comparison made with trial register: change in definition of primary outcome, intubation not presented.</p>
Other bias	High risk	No reliable sample size calculation based on previous data; financial constraints did not permit > 50 patients.

Clini 2002

Study characteristics

Methods	<p><u>Design</u>: multicentre randomised controlled trial with parallel groups</p> <p><u>Dates</u>: June 1996 to January 2000</p> <p><u>Setting</u>: 20 Italian and one French Respiratory Units</p> <p><u>Follow-up</u>: 1 month, followed by every 3 months up to 24 months</p>
Participants	<p><u>Inclusion criteria</u></p> <ul style="list-style-type: none"> • Age ≤ 75 years • LTOT for at least 6 months • Dyspnoea score as assessed by the mMRC score ≥ 2 • $FEV_1 < 1.5$ L, $FEV_1/FVC < 60\%$, total lung capacity $\geq 90\%$ predicted • $PaCO_2 > 6.6$ kPa (50 mmHg) and $PaO_2 < 7.8$ kPa (60 mmHg) breathing room air at rest <p><u>Exclusion criteria</u></p> <ul style="list-style-type: none"> • A 15% increase in FEV_1 after inhaled salbutamol (200 mg) • $pH \leq 7.34$ • Active smoking • Documented history of obstructive sleep apnoea syndrome as defined by an AHI > 10 per hour during polysomnography • Therapy with systemic steroids • Important concomitant chronic systemic diseases (i.e. chronic heart failure, diabetes, infections, neoplasm, etc) • Other chronic respiratory diseases (e.g. significant fibrothorax, bronchiectasis, cystic fibrosis) • Previous or concomitant NPPV or participation in any homecare program apart from LTOT <p><u>Baseline characteristics (raw data of 80 participants)</u></p> <ul style="list-style-type: none"> • Age 66.4 ± 6.1 years • Sex (m/f) 64/15 • FEV_1 0.72 ± 0.23 L ($29 \pm 10\%$ predicted) • $PaCO_2$ 7.5 ± 0.8 kPa
Interventions	<p><u>Nocturnal non-invasive positive pressure ventilation in addition to LTOT (n = 43)</u></p> <ul style="list-style-type: none"> • Interface: nasal mask • Device: BiPAP-ST30 (Respironics Inc.) set in spontaneous/timed mode at the maximal tolerated IPAP and an EPAP in the range of 2 to 5 cmH₂O with a back-up respiratory rate of 8 • Target: 5% decrease in $PaCO_2$ after 1 hour of continuous support and by nighttime oxymetry • Initiation: in-hospital • Ventilator settings: IPAP 14 ± 3 and EPAP 2 ± 1 cmH₂O • Compliance: 9 ± 2 hours <p><u>Comparator (n = 47)</u></p> <p>LTOT alone</p> <p>All patients received regular treatment (bronchodilators) adjusted to achieve optimal symptomatic control and were strongly encouraged to remain active.</p>

Clini 2002 (Continued)

Outcomes	<p>After 3 months: BGA, hospitalisations</p> <p>After 12 months: BGA, lung function, dyspnoea (MRC), 6MWD, PImax, sleep studies (4-point scale), HRQL (SGRQ and MRF-28) and hospitalisations</p>
Notes	<p>Conflicts of interest: not reported</p> <p>Funding: this study was supported by AIPO (Italian Association of Hospital Pulmonologists) and Markos-Mefar through Air Liquide Group Italia</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "... a centralised randomisation was used", but unclear how sequences were generated.
Allocation concealment (selection bias)	Low risk	Quote: "Because of the small number of eligible patients in each centre, a centralised randomisation was used. Blocks were used to provide balanced groups in the overall enrolment (not inside each centre)"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants: no blinding for treatment
Blinding of outcome assessment (detection bias) Patient reported outcomes	High risk	Participants were not blinded, PRO are at risk for detection bias.
Blinding of outcome assessment (detection bias) Lung function and exercise test	Low risk	Quote: "All physiological measurements were performed by personnel blind to treatment and not involved in the study"
Blinding of outcome assessment (detection bias) Blood gases, hospitalisations and mortality.	Low risk	Quote: "All physiological measurements were performed by personnel blind to treatment and not involved in the study"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Main parameters were evaluated both in terms of patient completers and of intention-to-treat"
Selective reporting (reporting bias)	Unclear risk	Trials not registered, all outcomes listed in the methods were reported
Other bias	Low risk	The study appears to be free of other source of bias

Cui 2019
Study characteristics

Methods	<p><u>Design</u>: randomised controlled trial with 3 parallel groups</p> <p><u>Dates</u>: February 2016 to April 2017</p>
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Chronic non-invasive ventilation for chronic obstructive pulmonary disease (Review)

Cui 2019 (Continued)

Setting: Binzhou People's Hospital, Shandong, China

Follow-up: 3 months

Participants	<p><u>Inclusion criteria</u></p> <ul style="list-style-type: none"> • Stable condition of COPD for at least 2 weeks • Having severity of pulmonary function at grade III or IV • Satisfying the diagnostic criteria described in the Guidelines for the Diagnosis and Treatment of COPD • Not having short-acting bronchodilators in 6h before trial and long-acting bronchodilators 12 hours before trial <p><u>Exclusion criteria</u></p> <ul style="list-style-type: none"> • Severe hepatic or renal disease • Cognitive impairment • Severe extremity function disturbance • Other respiratory tract diseases <p><u>Baseline characteristics (n = 59)</u></p> <ul style="list-style-type: none"> • Age 68.2 ± 5.5 years • Sex (m/f) 33/26 • FEV₁ 1.16 ± 0.13 L (42 ± 5 %predicted) • PaCO₂ 7.0 ± 0.6 kPa <p>Raw data not available.</p>
Interventions	<p><u>Nocturnal non-invasive positive pressure ventilation in addition to conventional medicine treatment (n = 30)</u></p> <ul style="list-style-type: none"> • Interface: not reported • Device: BiPAP synchrony (Respironics Inc.) set in spontaneous/timed mode, IPAP was set as 8 to 12 cmH₂O, and EPAP was set as 4 cmH₂O • The maximal tolerated IPAP and an EPAP in the range of 2 to 5 cmH₂O with a back-up respiratory rate of 15 • Target: not reported • Initiation: hospital • Ventilator settings: not reported • Compliance: not reported <p><u>Comparator (n = 29)</u></p> <p>All participants were given conventional drug treatment and oxygen therapy only</p> <p><u>Comparator (n = 29)</u></p> <p>Multidisciplinary comprehensive respiratory rehabilitation in addition to conventional drug treatment, oxygen therapy and NIV (not of interest to this review)</p>
Outcomes	Cardiopulmonary exercise testing, body mass index, FEV ₁ , dyspnoea (mMRC), HRQL (COPD-QOL scale), BGA
Notes	<p>Conflicts of interest: not reported</p> <p>Funding: not reported</p>

Risk of bias

Cui 2019 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote from abstract: "patients were enrolled en grouped ..., according to random sampling". Not mentioned how randomisation sequences were generated.
Allocation concealment (selection bias)	Unclear risk	Quote from abstract: "patients were enrolled and grouped, according to random sampling". Not mentioned how the randomisation was concealed.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were not blinded to treatment, investigators were not mentioned.
Blinding of outcome assessment (detection bias) Patient reported outcomes	High risk	Dyspnoea and HRQL are reported by the participants, who are not blinded to treatment.
Blinding of outcome assessment (detection bias) Lung function and exercise test	Unclear risk	Blinding of the outcome assessors of these outcomes is not reported.
Blinding of outcome assessment (detection bias) Blood gases, hospitalisations and mortality.	Low risk	BGA are unlikely affected by the outcome assessor.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts are not reported.
Selective reporting (reporting bias)	Unclear risk	Trial was not registered so we were unable to check with a protocol. However, except for the FVC, all outcomes mentioned in the method are reported.
Other bias	High risk	Both participants with hypoxemic and hypercapnic respiratory failure were included; CPAP and BiPAP were used, but data are not available for the separate groups, and these are completely different groups and therapies.

De Backer 2011
Study characteristics

Methods	<u>Design:</u> single centre randomised controlled trial with parallel groups <u>Dates:</u> study dates not reported <u>Setting:</u> University Hospital of Antwerp, Belgium <u>Follow-up:</u> after 1, 3 and 6 months (follow-up of NIV for 12 months)
Participants	<u>Inclusion criteria</u> <ul style="list-style-type: none"> 18 to 80 years of age COPD GOLD III or IV ($FEV_1 < 50\%$, $FEV_1/FVC < 0.7$) Hospitalised due to an exacerbation

Chronic non-invasive ventilation for chronic obstructive pulmonary disease (Review)

De Backer 2011 (Continued)

- Persistent hypercapnia ($\text{PaCO}_2 > 45 \text{ mmHg} / > 6.0 \text{ kPa}$) on day 5 to 12 under maximal pharmacological treatment
- Stopped smoking
- Not having had any treatment with home NIV before admission

Exclusion criteria

- Invasive ventilation
- Asthma
- People with restrictive lung diseases, malignancy, heart failure; OSA

Baseline characteristics (n = 15)

- Age 65.6 ± 6.9 years
- Sex (m/f) 10/5
- FEV_1 30 ± 7.8 %predicted
- Pre-randomisation PaCO_2 $7.3 \pm 1.0 \text{ kPa}$

Raw data not available.

Interventions	<u>Nocturnal NIV in addition to optimised pharmacological treatment (n = 10)</u> <ul style="list-style-type: none"> • Interface: oronasal mask • Device: Synchrony BiPAP (Respironics Inc.) • Target: oxygen saturation was $> 90\%$ during 90% of the time and PaCO_2 was decreased 5% in 1 hour • Initiation: in-hospital • Timing of initiation: 5 to 12 days after admission • Ventilator settings: not reported • Compliance: not reported <u>Comparator (n = 5)</u> Optimised pharmacological treatment (not specified)
Outcomes	Primary outcome: BGA Secondary outcomes: lung function, exercise tolerance (6MWD)
Notes	Conflicts of interest: not reported Funding: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentioned how sequences were generated.
Allocation concealment (selection bias)	Unclear risk	Not mentioned how randomisation was performed, so unclear if design was truly randomised.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants not possible, blinding of personnel not mentioned.
Blinding of outcome assessment (detection bias)	Unclear risk	No information.

De Backer 2011 (Continued)

Lung function and exercise
test

Blinding of outcome assessment (detection bias) Blood gases, hospitalisations and mortality.	Low risk	Primary outcome BGA is unlikely to be affected by the outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No flow diagram, no information about dropouts. In Figure 7 only 8 data points are available.
Selective reporting (reporting bias)	High risk	No comparison possible with trial register. All measurements mentioned in the method section are presented, but only for 1 visit (after 6 months, measurements taken after 1, 3, 6, (and 12) months).
Other bias	High risk	No power calculation; no equal randomisation (5 vs 10 participants), no detailed information about selection of participants (e.g. no information about participants who could not get used to NIV); no information about follow-up differences. No comparison of baseline characteristics of those 5 vs 10 participants.

Duiverman 2008
Study characteristics

Methods	<u>Design:</u> single centre randomised controlled trial with parallel groups <u>Dates:</u> September 2004 to January 2007 <u>Setting:</u> University Hospital in Groningen, the Netherlands <u>Follow-up:</u> after 3, 6, 12, 18 and 24 months
Participants	<u>Inclusion criteria</u> <ul style="list-style-type: none"> Participants with COPD GOLD stage III or IV ($FEV_1/FVC < 70\%$ and $FEV_1 < 50\%$ predicted) Aged 40 to 76 years Clinically stable (no exacerbations in the 4 weeks prior to study participation) with $pH > 7.35$ Chronic hypercapnic respiratory failure ($PaCO_2 > 6.0$ kPa, at rest breathing room air) <u>Exclusion criteria</u> <ul style="list-style-type: none"> Cardiac or neuromuscular diseases limiting exercise tolerance Previous exposure to a pulmonary rehabilitation program during the previous 18 months Previous exposure to chronic NIV at any time $AHI \geq 10$ per hour <u>Baseline characteristics (raw data of 66 participants)</u> <ul style="list-style-type: none"> Age 61.9 ± 8.7 years Sex (m/f) 31/35 FEV_1 0.80 ± 0.33 L ($30 \pm 12\%$ predicted) $PaCO_2$ 6.8 ± 0.7 kPa
Interventions	72 participants randomised to receive nocturnal non-invasive positive pressure ventilation in addition to pulmonary rehabilitation or to receive pulmonary rehabilitation alone.

Chronic non-invasive ventilation for chronic obstructive pulmonary disease (Review)

Duiverman 2008 (Continued)

Nocturnal non-invasive positive pressure ventilation (n = 37, 31 participants started NPPV after a run-in period)

- Interface: nasal or oronasal mask
- Device: BiPAP Synchrony (Respironics Inc.), in spontaneous/timed mode
- Target: optimal correction of nocturnal arterial blood gases ($\text{PaCO}_2 < 6.0 \text{ kPa}$ and $\text{PaO}_2 > 8.0 \text{ kPa}$)
- Initiation: in-hospital
- Ventilator settings: IPAP 23 ± 4 and EPAP $6 \pm 2 \text{ cmH}_2\text{O}$
- Compliance: 7.7 (5.8 to 8.5) hours

Pulmonary rehabilitation (n = 35)

A 12-week multidisciplinary in-hospital rehabilitation program. The programme consisted of strength training, cycling, walking, inspiratory muscle training, education and psychological and/or nutritional support if necessary. Participants trained 3 times a week for 1 hour and each session was fully supervised. After the 1-week program, all participants continued with physiotherapy at a community practice 1 to 2 times a week.

Outcomes	Primary outcome: HRQL (CRQ, MRF-28, SRI) Secondary outcomes: BGA, 6MWD, lung function, PI/PEmax, exacerbations
Notes	Conflicts of interest: 1 author received research grants from Respironics Funding: Dutch Asthma Foundation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was computerised.
Allocation concealment (selection bias)	Low risk	Randomisation performed by an independent statistician.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of subjects was not performed, blinding of investigators not mentioned.
Blinding of outcome assessment (detection bias) Patient reported outcomes	High risk	Primary endpoint and some secondary endpoints were PRO (CRQ/MRF36/SRI).
Blinding of outcome assessment (detection bias) Lung function and exercise test	Unclear risk	Blinding of personnel performing the lung function and exercise tests is not mentioned.
Blinding of outcome assessment (detection bias) Blood gases, hospitalisations and mortality.	Low risk	BGA and exacerbations are objective measures or not at risk for assessors bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Full data set analysis, with all data of all participants available at the start of the home-based period included for analyses and all available data used for analyses until participants dropped out.

Duiverman 2008 (Continued)

		Dropouts were reported, and there was no difference in dropout rates between groups.
Selective reporting (reporting bias)	Low risk	Checked with trial registry. All outcomes reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Eman Shebl 2015
Study characteristics

Methods	<u>Design:</u> single centre randomised controlled trial with parallel groups <u>Enrolment:</u> June 2012 to May 2014 <u>Setting:</u> Egypt <u>Follow-up:</u> 6 months
Participants	<u>Inclusion criteria</u> <ul style="list-style-type: none"> Hypercapnic COPD patients (diagnosis of COPD was based on clinical history, physical examinations, and spirometry criteria according to the GOLD guidelines) Stable clinical state, free of exacerbations at least 4 weeks prior to recruitment <u>Exclusion criteria</u> <ul style="list-style-type: none"> Sleep apnoea syndrome Other etiologies of chronic airway obstruction (e.g. bronchiectasis) Significant coexisting medical conditions, such as left ventricular failure <u>Baseline characteristics (n = 30)</u> <ul style="list-style-type: none"> Age 65.5 ± 6.7 years Sex (m/f) 25/5 FEV₁ 30.6 ± 11.5 %predicted PaCO₂ 7.3 ± 0.9 kPa Raw data not available.
Interventions	<u>Nocturnal non-invasive positive pressure ventilation in addition to standard treatment (n = 15)</u> <ul style="list-style-type: none"> Interface: not reported Device: BiPAP Vision (Respironics Inc.), IPAP and EPAP were titrated according to the patient's comfort and synchrony with the ventilator and a marked reduction in the use of accessory muscles Target: a decrease in PaCO₂ values > 5% after 1 hour Initiation: in-hospital Ventilator settings: IPAP 19.7 ± 2.4 and EPAP 6.8 ± 1.7 cmH₂O Compliance: not reported <u>Comparator (n = 15)</u> Standard treatment alone <ul style="list-style-type: none"> Consisting of bronchodilators, inhaled corticosteroids, supplemental oxygen, antibiotic, and systemic corticosteroids during episodes of acute exacerbation.

Eman Shebl 2015 (Continued)

Outcomes	BGA, spirometry, 6MWD, dyspnoea (MRC), HRQL (SF-12V2)
Notes	Conflicts of interest: none Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (from correspondence): "by random number table".
Allocation concealment (selection bias)	Unclear risk	There was insufficient information on the allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of subjects was not performed, investigators were blinded for the treatment (from correspondence)
Blinding of outcome assessment (detection bias) Patient reported outcomes	High risk	Participants were aware of their treatment as NIV can not be blinded, therefore PRO are at high risk of assessor bias.
Blinding of outcome assessment (detection bias) Lung function and exercise test	Unclear risk	No information presented.
Blinding of outcome assessment (detection bias) Blood gases, hospitalisations and mortality.	Low risk	BGA and mortality are unlikely affected by outcome assessor.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data on follow-up or dropouts are not presented.
Selective reporting (reporting bias)	Unclear risk	Trial was not registered. All outcomes mentioned in the method section are reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Garrod 2000
Study characteristics

Methods	<u>Design</u> : single centre randomised controlled trial with parallel groups <u>Dates</u> : not reported <u>Setting</u> : London Chest Hospital, UK <u>Follow-up</u> : 4 and 8 weeks
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Garrod 2000 (Continued)

Participants	<p><u>Inclusion criteria</u></p> <ul style="list-style-type: none"> • A history of severe COPD with FEV₁ < 50 %predicted, and less than 15% reversibility of FEV₁ to inhaled Salbutamol (400 mg) • No reported exacerbations in the past 4 weeks • Limited exercise tolerance due to dyspnoea • No previous exposure to NIPPV <p><u>Exclusion criteria</u></p> <ul style="list-style-type: none"> • Unstable angina pectoris • Intermittent claudication • Other mobility limiting conditions <p><u>Baseline characteristics (n = 45)</u></p> <ul style="list-style-type: none"> • Age 65 (range 38 to 84) years • Sex (m/f) 28/17 • FEV₁ 0.93 ± 0.29 L (34 ± 8.5 %predicted) • PaCO₂ 6.1 ± 1.1 kPa <p>Raw data not available.</p>
Interventions	<p><u>Nocturnal non-invasive positive pressure ventilation in addition to the exercise training program (n = 23)</u></p> <ul style="list-style-type: none"> • Interface: nasal mask • Device: BiPAP ST 30 ventilator in the spontaneous mode • Target: maximal pressure tolerated. All participants on NPPV then had resting earlobe gases taken after 1 hour on the ventilator. • Initiation: not reported • Ventilator settings: IPAP 16 (IQR 13 to 24) and EPAP 4 (IQR 4 to 6) cmH₂O • Compliance: 2.1 (range 0 to 11.4) hours <p><u>Comparator (n = 22)</u></p> <p>Exercise training program alone</p> <ul style="list-style-type: none"> • The pulmonary rehabilitation program consisted of 16 hourly sessions of physical training supervised by an experienced physiotherapist, followed by an education program standardised for both groups.
Outcomes	BGA, spirometry, PE/Plmax, HRQL (CRQ)
Notes	<p>Conflicts of interest: not reported</p> <p>Funding: educational grant from Respironics Inc</p>
Risk of bias	
Bias	Authors' judgement Support for judgement
Random sequence generation (selection bias)	Unclear risk Not mentioned how sequences were generated.
Allocation concealment (selection bias)	Low risk Randomisation using sealed envelopes.

Garrod 2000 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants, blinding of personnel not mentioned/unclear.
Blinding of outcome assessment (detection bias) Lung function and exercise test	Unclear risk	No information provided on blinding of the assessors of these outcomes.
Blinding of outcome assessment (detection bias) Blood gases, hospitalisations and mortality.	Low risk	BGA are not influenced by outcome assessor.
Incomplete outcome data (attrition bias) All outcomes	Low risk	In total 8 participants dropped out of the study (NIV+ET 5/ET 3), clear information given about dropouts; no differences in baseline variables between completers and dropouts.
Selective reporting (reporting bias)	Low risk	Trial not registered. All outcomes mentioned in the method section are reported for the baseline and final measurements.
Other bias	High risk	NIV + ET group contacted twice weekly for the first 4 weeks, the control group contacted only once in this period. During the run-in period (after randomisation, but prior to the 8-week ET program), the NIV + ET group already received NIV.

Gay 1996

Study characteristics

Methods	<u>Design:</u> sham controlled, single blind randomised controlled trial with parallel groups <u>Dates:</u> study dates not reported <u>Setting:</u> USA <u>Follow-up:</u> 3 months
Participants	<u>Inclusion criteria</u> <ul style="list-style-type: none"> FEV₁ < 40 % predicted PaCO₂ > 45 mmHg (6.0 kPa) during quiet breathing Age < 80 years BMI ≤ 30 kg/m² <u>Exclusion criteria</u> <ul style="list-style-type: none"> Had been activated for a lung transplantation Had active psychiatric disease that necessitated sedative or hypnotic medications Were currently using nocturnal ventilation or CPAP Had major illness that were likely to preclude completion of a prolonged clinical trial <u>Baseline characteristics (raw data of 10 participants)</u> <ul style="list-style-type: none"> Age 67.6 ± 7.8 years

Gay 1996 (Continued)

- Sex (m/f) 8/2
- FEV₁ 0.68 ± 0.21 L
- PaCO₂ 6.9 ± 1.1 kPa

Interventions	<p>13 participants randomised to receive, in addition to maximal medical care:</p> <p><u>Nocturnal nasal ventilation (n = 7)</u></p> <ul style="list-style-type: none"> • Interface: nasal mask • Device: BiPAP device (Respironics Inc.), set in spontaneous/timed mode with initial timed rate set to 2 breaths below the observed spontaneous rate • Goal: IPAP of 10 cmH₂O and the lowest possible EPAP • Initiation: in-hospital • Ventilator settings: IPAP 10, EPAP 2 cmH₂O (all participants) • Compliance: 5.1 ± 3.8 hours <p><u>Sham NNV (n = 6)</u></p> <p>Participants were fitted with the same equipment but with the lowest EPAP and no added IPAP or timed breaths</p>
Outcomes	BGA, lung function, 6MWD, sleep study (sleep efficiency), PE/Plmax
Notes	<p>Conflicts of interest: not reported</p> <p>Funding: this study was supported in part by Grant MOI RR 00585 from the National Institutes of Health, Public Health Service, and the Mayo Foundation</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentioned how sequences were generated.
Allocation concealment (selection bias)	Low risk	Quote (from correspondence): "It was done with a sealed envelope randomisation technique"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	<p>Participants: blinded for intervention as sham NIV was used.</p> <p>Personnel: unknown</p>
Blinding of outcome assessment (detection bias) Lung function and exercise test	Unclear risk	Blinding not mentioned.
Blinding of outcome assessment (detection bias) Blood gases, hospitalisations and mortality.	Low risk	Arterial blood gases are unlikely to be affected by the outcome assessor.
Incomplete outcome data (attrition bias) All outcomes	High risk	Final analysis was done with only the completers; 4 out of 7 people who were still using ventilation and all the 6 people in sham group

Gay 1996 (Continued)

Selective reporting (reporting bias)	Unclear risk	Trial not registered, all outcomes listed in the Methods were reported
Other bias	Low risk	The study appears to be free of other source of bias

Köhnlein 2014

Study characteristics

Methods	<p><u>Design:</u> multicentre randomised controlled trial with parallel groups</p> <p><u>Dates:</u> October 2004 to July 2011</p> <p><u>Settings:</u> 36 respiratory units in Germany and Austria</p> <p><u>Follow-up:</u> visits were scheduled at 14 days, and 3, 6, 9, and 12 months after randomisation</p>
Participants	<p><u>Inclusion criteria</u></p> <ul style="list-style-type: none"> Clinically stable, hypercapnic COPD patients in GOLD stage IV, no acute exacerbation (defined as an increase in or new onset of more than one respiratory symptom lasting 2 days or more and requiring any change of pharmacological treatment) during the 4-week run-in period Age ≥ 18 years Baseline $\text{PaCO}_2 \geq 7$ kPa (51.9 mmHg) and $\text{pH} > 7.35$, after > 30 minutes breathing room air in a sitting position, participants on long-term oxygen treatment inhaled oxygen with the previously prescribed dose Written informed consent obtained <p><u>Exclusion criteria</u></p> <ul style="list-style-type: none"> Abnormalities of the thorax or the lung other than COPD (e.g., pneumonia, pulmonary fibrosis, severe bronchiectasis, active tuberculosis, post tuberculosis syndrome, severe kyphoscoliosis, history of asthma, tracheostoma) $\text{PaCO}_2 > 10$ kPa (74 mmHg) BMI of ≥ 35 kg/m² Obesity hypoventilation syndrome or other conditions resulting in hypercapnia Previously initiated NPPV Malignant comorbidities Severe heart failure in NYHA stage IV, unstable angina, and severe arrhythmia. Permanent atrial fibrillation was not an exclusion criterion Neuromuscular diseases and/or impairment of basal brain nerve function with disturbed swallowing and choking Skin lesions of the face, or abnormalities of the upper airways Impaired general condition that could preclude regular follow-up visits <p><u>Baseline characteristics (raw data of 195 participants)</u></p> <ul style="list-style-type: none"> Age 63.2 ± 8.4 years Sex (m/f) 121/74 FEV_1 27.1 ± 10.1 %predicted PaCO_2 7.8 ± 0.7 kPa
Interventions	<p><u>Nocturnal non-invasive positive pressure ventilation in addition to optimised COPD therapy (n = 102)</u></p> <ul style="list-style-type: none"> Interface: nasal or face masks

Köhnlein 2014 (Continued)

- Device: ventilators from ResMed, Weinmann or Tyco, set in pressure support mode with high back-up rate to achieve controlled ventilation
- Target: reduce baseline PaCO₂ by 20% or more, or achieve PaCO₂ < 6.5 kPa (48.1 mmHg)
- Initiation: in-hospital
- Ventilator settings: IPAP 21.6 ± 4.7 and EPAP 4.8 ± 1.6 cmH₂O
- Compliance: 5.9 ± 3.1 hours

Comparator (n = 93)

Optimised COPD therapy, with acute NPPV allowed temporarily in case of acute exacerbation with an increase in PaCO₂ > 10 kPa.

Outcomes	Primary outcome: 1 year all-cause mortality Secondary outcomes: BGA, lung function and volumes, 6MWD, HRQL (SF-36, SGRQ, SRI)
Notes	Conflicts of interest: nine authors have reported conflicts of interest Funding: German Lung Foundation, ResMed, Tyco Healthcare, Weinmann

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated randomisation list.
Allocation concealment (selection bias)	Low risk	Randomisation performed centrally by an independent statistician.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants not blinded; PROBE design applied, staff members who performed NIV were the only group aware of treatment assignment.
Blinding of outcome assessment (detection bias) Patient reported outcomes	High risk	Participants were aware of their treatment as NIV can not be blinded, therefore PRO are at high risk of assessors bias.
Blinding of outcome assessment (detection bias) Lung function and exercise test	Low risk	Outcome assessors were unaware of treatment assignment throughout the study.
Blinding of outcome assessment (detection bias) Blood gases, hospitalisations and mortality.	Low risk	BGA and mortality are unlikely affected by outcome assessor.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention to treat analysis on all outcomes. In the one year observation period, 9 participants discontinued NIV (reasons provided). 2 participants were lost to follow-up, both in the NIV group.
Selective reporting (reporting bias)	Low risk	All outcomes reported, including additional outcomes not mentioned in the trial registry.
Other bias	Low risk	The study appears to be free of other sources of bias.

Ma 2019

Study characteristics

Methods	<u>Design:</u> randomised controlled trial <u>Dates:</u> January 2015 to June 2016 <u>Settings:</u> hospital, China <u>Follow-up:</u> 12 months
Participants	<u>Inclusion criteria</u> <ul style="list-style-type: none"> COPD accompanied by respiratory failure (type II) Quote from conclusion of the abstract: "... to treatment of <u>stationary</u> COPD cases". <u>Exclusion criteria</u> Not reported <u>Baseline characteristics</u> Not reported
Interventions	<u>Non-invasive positive pressure ventilation in addition to oxygen treatment (n = 90)</u> Not further specified <u>Comparator (n = 90)</u> Chronic oxygen treatment via a nasal catheter
Outcomes	BGA, lung function, 6MWD and acute recurrence
Notes	Conference meeting abstract, no full-text or trial registry available Conflicts of interest: not reported Funding: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote from abstract: "were randomly distributed in a ..." No further information present on the generation of the randomisation sequences. No full text or trial registry available.
Allocation concealment (selection bias)	Unclear risk	Quote from abstract: "were randomly distributed in a ..." No further information present on the allocation concealment. No full text or trial registry available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Patients were not blinded to treatment, sham treatment was not used. Blinding of personnel not mentioned.
Blinding of outcome assessment (detection bias)	Unclear risk	Not reported in the conference meeting abstract, full text or trial registry not available.

Ma 2019 (Continued)

Lung function and exercise test

Blinding of outcome assessment (detection bias) Blood gases, hospitalisations and mortality.	Low risk	BGA are unlikely to be affected by the outcome assessor.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient data are reported in the conference meeting abstract. Due to the number of participants and duration of the study, it is likely that dropouts have occurred.
Selective reporting (reporting bias)	Unclear risk	All outcomes reported in the methods are reported. We were unable to check with a trial registry as it seems not to be registered.
Other bias	High risk	Only the conference meeting abstract with no data or numbers is present.

Martin-Marquez 2014

Study characteristics

Methods	<p><u>Design</u>: single centre randomised controlled trial with three parallel groups</p> <p><u>Dates</u>: May 2007 to September 2011</p> <p><u>Setting</u>: University Hospital in Spain</p> <p><u>Follow-up</u>: 3 months</p>
Participants	<p><u>Inclusion criteria</u></p> <ul style="list-style-type: none"> Being an adult with a diagnosis of COPD, as defined by the GOLD criteria Having been clinically stable for at least the previous three months Airflow obstruction with $FEV_1 < 50\%$ Chronic respiratory failure with hypoxaemia ($PaO_2 < 60$ mmHg (8.0 kPa)) and hypercapnia ($PaCO_2 > 45$ mmHg (6.0 kPa)) <p><u>Exclusion criteria</u></p> <ul style="list-style-type: none"> An unwillingness to participate in the study A history of recent exacerbation (< 3 months) requiring systemic corticosteroids or antibiotics Any contraindication or inability to perform the study tests (including a history of uncontrolled heart disease or the presence of acute respiratory conditions) The presence of obstructive sleep apnoea requiring NIV <p><u>Baseline characteristics (raw data of 30 participants)</u></p> <ul style="list-style-type: none"> Age 68.3 ± 8.2 years Sex (m/f) 29/1 FEV_1 0.93 ± 0.27 L ($35 \pm 9\%$ predicted) $PaCO_2$ 6.7 ± 0.6 kPa
Interventions	<p><u>Nocturnal NIV in addition to a training program (n = 15)</u></p> <ul style="list-style-type: none"> Interface: nasal mask Device: BiPAP ventilator (Respironics Inc.), set in S/T mode, with the respiratory rate set at 12 breaths and initially provided: 10 cmH₂O IPAP and 4 cmH₂O EPAP

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Martin-Marquez 2014 (Continued)

- Target: IPAP was increased progressively to a maximum of 20 cmH₂O, depending on patient tolerance, clinical response and arterial oxygen saturation
- Initiation: not reported
- Ventilator settings: median IPAP 16 and EPAP 4 cmH₂O
- Compliance: 7 (6.5 to 9) hours

Comparator (n = 15)

Training program alone

- Training sessions were carried out on three non-consecutive days every week for 12 weeks. Sessions lasted for 40 min plus a 10-min warm-up and 10-min cool down. The programme consisted of a combination of resistance and strength training.

Comparator (n = 15)

Nocturnal NIV alone (not of relevance to this review)

Outcomes	Primary outcome: exercise capacity (submaximal exercise test) Secondary outcomes: BGA, HRQL (CRQ), lung function, 6MWD
Notes	Conflicts of interest: none Funding: supported by the Health Research Fund (FIS) of the Spanish Ministry of Science and Innovation, NEUMOSUR foundation and SEPAR grant

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated random number table.
Allocation concealment (selection bias)	Unclear risk	Not mentioned if table was open to investigator, or who conducted the randomisation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants not performed as blinding for treatment with NIV is not possible, blinding of investigators is not mentioned.
Blinding of outcome assessment (detection bias) Patient reported outcomes	High risk	Participants were not blinded to treatment.
Blinding of outcome assessment (detection bias) Lung function and exercise test	Unclear risk	Not mentioned if personnel performing the measurements were blinded.
Blinding of outcome assessment (detection bias) Blood gases, hospitalisations and mortality.	Low risk	BGA are not at risk for assessors bias.
Incomplete outcome data (attrition bias)	Low risk	2 participants dropped out (1 in the NIV group and 1 in the NIV + ET group), reasons for dropout were provided.

Martin-Marquez 2014 (Continued)

All outcomes

Selective reporting (reporting bias)	Low risk	All outcomes were reported, and absolute values were presented in the online supplement. Compared to trial register: BGA not mentioned but presented in the paper.
Other bias	Low risk	This study appears to be free of other sources of bias.

McEvoy 2009
Study characteristics

Methods	<u>Design:</u> multicentre randomised controlled trial with parallel groups <u>Dates:</u> between June 1998 and 2004 <u>Setting:</u> 4 Australian university hospitals <u>Follow-up:</u> 6 monthly intervals
Participants	<u>Inclusion criteria</u> <ul style="list-style-type: none"> Men and women aged < 80 years Severe COPD secondary to smoking ($FEV_1 < 1.5$ L or < 50 %predicted, < 20% improvement in FEV_1 following aerosol bronchodilator, and ratio of $FEV_1/FVC < 60\%$) Stable hypercapnic ventilatory failure ($PaCO_2 > 46$ mmHg (6.1 kPa) at least twice in the previous 6 months during periods of clinical stability On LTOT for at least 3 months and, as required for LTOT prescription, not currently smoking <u>Exclusion criteria</u> <ul style="list-style-type: none"> Significant comorbidity such as malignancy, left ventricular heart failure or unstable angina likely to affect survival in the 2-year follow-up period Severe psychiatric disorder likely to impair ability to comply with NIV BMI > 40 kg/m² Polysomnographic evidence of sleep apnoea (AHI > 20 per hour) <u>Baseline characteristics (raw data of 144 participants)</u> <ul style="list-style-type: none"> Age 68.0 ± 7.7 years Sex (m/f) 94/50 FEV_1 0.64 ± 0.25 L (26 ± 11 %predicted) $PaCO_2$ 7.3 ± 1.1 kPa
Interventions	<u>Nocturnal non-invasive ventilation in addition to usual care and LTOT (n = 72)</u> <ul style="list-style-type: none"> Interface: nasal or full-face mask Device: VPAPs device (ResMed) with IPAP gradually increased to the maximum tolerated with a target IPAP — EPAP difference of ≥ 10 cmH₂O Target: at least 3 hours of sleep were confirmed on NIV at an IPAP — EPAP difference of at least 5 cmH₂O Initiation: in-hospital Ventilator settings: IPAP 12.9 ± 1.8 and EPAP 5.1 ± 1.1 cmH₂O Compliance: 4.5 ± 3.2 hours <u>Comparator (n = 72)</u>

McEvoy 2009 (Continued)

Usual care and LTOT alone

Outcomes	BGA, lung function, sleep studies (total sleep time, only in NIV group), HRQL (SGRQ and SF-36), hospitalisation rates (days on trial: days in hospital rate), survival
Notes	Conflicts of interest: none Funding: Australian National Health and Medical Research Council, Air Liquide Healthcare, Australian Lung Foundation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The central study coordinator generated a random sequence of treatment assignments".
Allocation concealment (selection bias)	Low risk	Quote: "The central study coordinator generated a random sequence of treatment assignments that were stratified by centre and distributed in blocks of 10 sealed opaque envelopes to centres".
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding for participants, intervention or personnel.
Blinding of outcome assessment (detection bias) Patient reported outcomes	High risk	Participant-reported outcomes are at high risk for detection bias as participants were not blinded to treatment.
Blinding of outcome assessment (detection bias) Lung function and exercise test	Unclear risk	Not mentioned if personnel performing lung function test were aware of treatment allocation.
Blinding of outcome assessment (detection bias) Blood gases, hospitalisations and mortality.	Low risk	ABG and mortality are unlikely affected by the outcome assessor.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All primary analyses were conducted on an intention-to-treat basis. However, since a proportion of patients assigned to NIV treatment did not use the treatment regularly or abandoned it altogether after a time, a planned per protocol sub analysis was conducted comparing outcomes of patients in the treatment arm who used NIV consistently (defined as average > 4 hours per night) with patients in the control arm".
Selective reporting (reporting bias)	Unclear risk	Trial was registered retrospectively, all outcomes listed in the methods and registry were reported.
Other bias	Low risk	The study appears to be free of other source of bias.

Meecham Jones 1995

Study characteristics

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Meecham Jones 1995 (Continued)

Methods	<u>Design:</u> single centre randomised controlled cross-over study <u>Dates:</u> study dates not reported <u>Setting:</u> UK <u>Follow-up:</u> 4-weekly intervals up to 6 months (cross-over after 3 months)	
Participants	<u>Inclusion criteria</u> <ul style="list-style-type: none">• Age < 75 years• FEV₁ < 50 %predicted• Resting daytime PaO₂ < 60 mmHg (8.0 kPa), PaCO₂ > 45mmHg (6.0 kPa)• Stable clinical state• Establishment on domiciliary LTOT <u>Exclusion criteria</u> <ul style="list-style-type: none">• Deteriorating clinical state• Significant obstructive sleep apnea <u>Baseline characteristics (raw data of 14 participants)</u> <ul style="list-style-type: none">• Age 65.9 ± 8.6 years• Sex (m/f) 12/2• FEV₁ 0.84 ± 0.34 L• PaCO₂ 7.4 ± 0.5 kPa	
Interventions	18 participants received, in randomised order: <u>Nocturnal nasal pressure support ventilation in addition to oxygen therapy</u> <ul style="list-style-type: none">• Interface: nasal mask• Device: BIPAP ventilator (Respironics Inc.) in S mode, IPAP being increased gradually to obtain the highest level tolerated. EPAP levels were adjusted according to patient comfort.• Target: maximum IPAP/EPAP gradient• Initiation: in-hospital• Ventilator settings (median): IPAP 18 and EPAP 2 cmH₂O• Compliance: 6.9 (range 4.2 to 10.8) hours <u>Comparator</u> Oxygen therapy alone <ul style="list-style-type: none">• Oxygen therapy was delivered through a nasal cannulae at a constant flow of 2 L/min.	
Outcomes	BGA, lung function, 6MWD, HRQL (SGRQ), sleep study (sleep efficiency)	
Notes	Conflicts of interest: not reported Funding: supported by a grant from the British Lung Foundation	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “Randomization was achieved with a previously generated randomised sequence”

Meecham Jones 1995 (Continued)

Allocation concealment (selection bias)	Low risk	Quote from correspondence: "The sequence was kept by another research fellow unconnected with the study, and I was made aware of the randomisation as patients were recruited"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participant was not performed. Personnel was not described.
Blinding of outcome assessment (detection bias) Patient reported outcomes	High risk	As participants were not blinded to treatment, the St George Respiratory Questionnaire is at risk of bias.
Blinding of outcome assessment (detection bias) Lung function and exercise test	Unclear risk	Not mentioned if personnel performing these measurements were blinded to treatment.
Blinding of outcome assessment (detection bias) Blood gases, hospitalisations and mortality.	Low risk	ABGs are unlikely to be affected by outcome assessor.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Fourteen of the 18 patients completed all stages of the study" Reasons for withdrawal for all 4 participants were mentioned. One patient did not tolerate NIV. Final analysis was done with the 14 completers.
Selective reporting (reporting bias)	Unclear risk	Trial was not registered, all outcomes listed in the methods were reported.
Other bias	Low risk	The study appears to be free of other source of bias

Murphy 2017
Study characteristics

Methods	<u>Design:</u> multicentre randomised controlled trial with parallel groups <u>Dates:</u> February 2010 to April 2015 <u>Setting:</u> 13 home ventilation centres in the UK <u>Follow-up:</u> 6 weeks, 3, 6, and 12 months
Participants	<u>Inclusion criteria</u> <ul style="list-style-type: none"> • People admitted with acute decompensated hypercapnic exacerbations of COPD requiring acute NIV, and 2 to 4 weeks after resolution of decompensated acidosis (arterial pH > 7.30) were required to have persistent hypercapnia (PaCO₂ > 53 mmHg (7.1 kPa)) and hypoxaemia (PaO₂ < 55 mmHg (7.3 kPa) or < 60 mmHg (8.0 kPa); ≥ 1 of polycythemia, pulmonary hypertension, or cor pulmonale; > 30% of sleep time with oxygen saturation < 90% as measured by pulse oximetry). • Arterial pH > 7.30 while breathing room air • With > 20 pack year smoking history <u>Exclusion criteria</u>

Murphy 2017 (Continued)

- Not assessed within 4 weeks of resolution of the index COPD exacerbation
- Required intubation and invasive mechanical ventilation during the index exacerbation
- Currently using non-invasive home mechanical ventilation
- Exhibited cognitive impairment or unstable psychiatric morbidity
- Undergoing renal replacement therapy
- Active unstable coronary artery syndrome
- Younger than 18 years
- homeless
- BMI > 35 kg/m²
- OSA
- Neuromuscular or chest-wall disease

Baseline characteristics (raw data of 116 participants)

- Age 66.6 ± 9.6 years
- Sex (m/f) 55/61
- FEV₁ 0.57 ± 0.22 L (23 ± 9 %predicted)
- PaCO₂ 7.9 ± 0.9 kPa

Interventions	<p><u>Nocturnal NIV (n = 57) in addition to home oxygen therapy</u></p> <ul style="list-style-type: none">• Interface: nasal, oronasal or total face mask• Device: Harmony 2 (Philips Respironics Inc) or VPAP IIISTa (ResMed), in pressure support mode• Target: control hypoventilation and hypoxemia aiming to maintain SpO₂ >88% and to reduce TcCO₂ by at least 4 mmHg, aiming to reach a target IPAP of ≥ 25cmH₂O• Initiation: in-hospital• Timing of initiation: 2 to 4 weeks after resolution of respiratory acidemia• Ventilator settings (median (interquartile range)): IPAP 24 (22-26) and EPAP 4 (4-5) cmH₂O <p><u>Home oxygen therapy (n = 59)</u></p> <p>Oxygen therapy was initiated at the lowest flow rate required to increase the PaO₂ level to greater than 60 mmHg (8.0 kPa) without producing decompensated respiratory failure, which was defined as an arterial pH < 7.30 on the morning blood gas measurement after overnight use of oxygen without NIV.</p>	
Outcomes	<p>Primary outcome: time to readmission or death within 12 months</p> <p>Secondary outcomes: all-cause mortality, exacerbation frequency, BGA, dyspnoea (MRC), HRQL (SRI/SGRQ)</p>	
Notes	<p>Conflicts of interest: Lane Fox Clinical Respiratory Physiology Research Centre has received unrestricted research grants. An additional 13 authors reported conflicts of interest.</p> <p>Funding: unrestricted educational grant funding from Philips Respironics, ResMed, the ResMed Foundation, and the Guy's and St Thomas' Charity. The study was supported by Guy's and St Thomas' NHS Foundation Trust and King's College London, the National Institute of Health Research Comprehensive Biomedical Research Centre, and the NIHR Respiratory Disease Biomedical Research Unit at the Royal Brompton and Harefield NHS Foundation Trust and Imperial College London</p>	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “randomized by the Oxford Clinical Trials Unit using computer-based minimisation software”

Murphy 2017 (Continued)

Allocation concealment (selection bias)	Low risk	Randomisation performed centrally. Quote: “randomized by the Oxford Clinical Trials Unit using computer-based minimisation software”
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: “Although there was no suitable sham option for non- invasive ventilation, and the supervising clinicians were un-blinded to treatment allocation”
Blinding of outcome assessment (detection bias) Patient reported outcomes	High risk	Participants were not blinded to treatment.
Blinding of outcome assessment (detection bias) Lung function and exercise test	Low risk	Quote: “the trial staff conducting the outcome assessments were blinded for treatment allocation”
Blinding of outcome assessment (detection bias) Blood gases, hospitalisations and mortality.	Low risk	Quote: “the trial staff conducting the outcome assessments were blinded for treatment allocation” Primary outcome (time to readmission or death) and BGA are unlikely to be affected by the outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analyses on primary outcome. Clear description of dropouts. Number of participants given for all outcomes at each time point, dropout inherent to the studied population.
Selective reporting (reporting bias)	Low risk	Checked with trial registry and method; not all outcomes presented (MRC, nocturnal SaO ₂ , ISWT spirometry), but these data are either irrelevant (SaO ₂) or the IPD were provided by the authors (MRC / spirometry). ISWT not measured as participants were too weak to conduct this test.
Other bias	Low risk	The study appears to be free of other sources of bias.

Schneeberger 2017

Study characteristics

Methods	<u>Design:</u> randomised controlled trial with parallel groups <u>Dates:</u> January 2011 to September 2013 <u>Setting:</u> hospital, Germany <u>Follow-up:</u> 3 weeks and 3 months (HRQL)
Participants	<u>Inclusion criteria</u> <ul style="list-style-type: none"> Confirmed diagnosis of COPD in stages GOLD III/ IV Receiving optimised medical treatment and long term oxygen therapy if needed Consent to participate in this trial No treatment with NIV in the last 4 weeks Treatment with NIV in the last 4 weeks due to an acute exacerbation

Schneeberger 2017 (Continued)

Exclusion criteria

- Treatment with NIV in the last 4 weeks (except due to an acute exacerbation)
- Intolerance to perform NIV
- Acute exacerbation at baseline or during pulmonary rehabilitation
- Hypercapnia > pCO₂ 55 mmHg (7.3 kPa)
- Inability to perform a 6MWD

Baseline characteristics (raw data of 31 participants)

- Age 62.3 ± 7.5 years
- Sex (m/f) 19/12
- FEV₁ 0.85 ± 0.25 L (31 ± 7 %predicted)
- PaCO₂ 6.2 ± 0.5 kPa

Interventions	<u>Pulmonary rehabilitation with nocturnal NIV (n = 13)</u> <ul style="list-style-type: none"> • Interface: not reported • Device: not reported • Target: not reported • Initiation: in-hospital • Ventilator settings: IPAP 20 ± 4 and EPAP 5 ± 1 cmH₂O • Compliance: 6 ± 2 hours <u>Pulmonary rehabilitation alone (n = 18)</u> 3 weeks, not further specified
Outcomes	Primary outcome: 6MWD Secondary outcomes: nocturnal transcutaneous PCO ₂ , HRQL (CRQ & SGRQ), Hospital Anxiety and Depression Scale
Notes	Trial was terminated due to recruitment difficulties. Conflict of interest: not reported Funding: ResMed Inc.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote from abstract: "were randomly assigned to ..." No further information present on the generation of the randomisation sequence.
Allocation concealment (selection bias)	Low risk	Quote from correspondence: "the randomization was conducted by an independent person and group allocation was put in sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	No masking, study was open-label (from trial registry). Quote from correspondence: "the investigators and the statistician were blind-ed to the treatment"
Blinding of outcome assessment (detection bias) Patient reported outcomes	High risk	Participants were not blinded to treatment allocation.

Schneeberger 2017 (Continued)

Blinding of outcome assessment (detection bias) Lung function and exercise test	Unclear risk	Participants were not blinded to treatment allocation (open-label design), but the outcome assessors for the lung function and exercise tests are not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote from correspondence: "The study was terminated due to recruitment difficulties. 44 patients were randomized and 13 patients dropped out of the study for several reasons". Reasons and the distribution between the NIV and control group is unclear.
Selective reporting (reporting bias)	Low risk	Comparison made to trial registry. All outcomes measured are reported in the meeting abstract.
Other bias	High risk	Only abstract available. Trial registry: terminated (major problems in recruiting participants due to very strict inclusion criteria).

Sin 2007

Study characteristics

Methods	<u>Design:</u> single centre randomised double-blind controlled trial with parallel groups <u>Dates:</u> not reported <u>Setting:</u> specialists' clinics at the University of Alberta Hospital, Canada <u>Follow-up:</u> 3 months
Participants	<u>Inclusion criteria</u> <ul style="list-style-type: none"> Clinical diagnosis of COPD Age ≥ 40 years old ≥ 10-pack-year history of cigarette smoking FEV₁/FVC ratio $< 70\%$ and post-bronchodilator FEV₁ $< 70\%$ of predicted <u>Exclusion criteria</u> <ul style="list-style-type: none"> Coexisting medical conditions that made survival for at least 6 months unlikely Refusal to participate Cognitive impairment that made it impossible to obtain informed consent Clinical history of left ventricular heart failure AHI ≥ 20 per hour on a home-based sleep apnoea test <u>Baseline characteristics (raw data of 17 participants)</u> <ul style="list-style-type: none"> Age 65.4 ± 9.7 years Sex (m/f) 9/8 FEV₁ 0.88 ± 0.31 L ($32 \pm 16\%$ predicted) PaCO₂ 5.8 ± 1.3 kPa
Interventions	In addition to standard medical treatment, participants were randomised to receive: <u>Non-invasive mechanical ventilation (n = 11)</u> <ul style="list-style-type: none"> Interface: nasal or oronasal mask Device: VPAP II device (ResMed), initially started on an IPAP of 8 cmH₂O and an EPAP of 4 cmH₂O

Chronic non-invasive ventilation for chronic obstructive pulmonary disease (Review)

Sin 2007 (Continued)

- Target: titrated up until the highest IPAP tolerated by the patient or 20 cmH₂O was reached, EPAP remained at 4 cmH₂O
- Initiation: in-hospital
- Ventilator settings: IPAP 15.5 ± 4.2 and EPAP fixed at 4 cmH₂O
- Compliance: 3.7 ± 3.4 hours

Sham treatment (n = 12)

Control participants were treated using a CPAP device (S7 Elite, ResMed) set at 4 cmH₂O

Outcomes	BGA, lung function and 6MWD
Notes	Conflicts of interest: not reported Funding: this project is supported by Canadian Institutes of Health Research (clinical trials), The Institute of Health Economics, and the University of Alberta Hospital Foundation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentioned how sequences were generated.
Allocation concealment (selection bias)	Low risk	Quote: "Randomization occurred at a central site by one individual who was unaware of patients' clinical status".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind design. Participants were blind to intervention treatment (NIV versus sham) and: "All outcome measurements were performed and interpreted by personnel who were blinded to treatment allocation of patients".
Blinding of outcome assessment (detection bias) Lung function and exercise test	Low risk	Quote: "All outcome measurements were performed and interpreted by personnel who were blinded to treatment allocation of patients".
Blinding of outcome assessment (detection bias) Blood gases, hospitalisations and mortality.	Low risk	Quote: "All outcome measurements were performed and interpreted by personnel who were blinded to treatment allocation of patients".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Two out of eleven subjects refused any nocturnal therapy following randomisation and were excluded from the main analysis".
Selective reporting (reporting bias)	Unclear risk	Trial not registered, all outcomes listed in the methods were reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Struik 2014

Study characteristics

Methods	<u>Design</u> : multicentre randomised controlled trial with parallel groups
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Chronic non-invasive ventilation for chronic obstructive pulmonary disease (Review)

Struik 2014 (Continued)

Dates: December 2007 to July 2012

Setting: three specialised home mechanical ventilation centres in the Netherlands

Follow-up: 3, 6 and 12 months. Survival data up to 68 months

Participants	<p><u>Inclusion criteria</u></p> <ul style="list-style-type: none"> • COPD, GOLD severity stage 3 and 4 • Minimally 48 hours without ventilatory support after invasive or non-invasive ventilatory support during an acute respiratory failure and maximally until discharge • Persistent hypercapnia ($\text{PaCO}_2 > 6.0 \text{ kPa}$) during daytime at rest without ventilatory support <p><u>Exclusion criteria</u></p> <ul style="list-style-type: none"> • Age < 18 or ≥ 75 years • Significant bronchiectasis with recurrent infections • Significant heart failure • Kyphoscoliosis • Neuromuscular disease • Obstructive sleep apnea ($\text{AHI} > 15$ per hour) • Current use of CPAP or BiPAP • Insufficient motivation for chronic ventilatory support • Social circumstances making chronic ventilatory support impossible • Other disease factors limiting life limitations <p><u>Baseline characteristics (raw data of 201 participants)</u></p> <ul style="list-style-type: none"> • Age 63.4 ± 8.2 years • Sex (m/f) 83/118 • FEV_1 $0.66 \pm 0.23 \text{ L}$ ($26 \pm 8 \%$ predicted) • PaCO_2 $7.8 \pm 1.2 \text{ kPa}$
Interventions	<p><u>Nocturnal NIV in addition to standard treatment (n = 101)</u></p> <ul style="list-style-type: none"> • Interface: nasal or oronasal mask • Device: Synchrony (Respironics Inc.), set in S/T mode • Target: (1) maximally support respiration and (2) and achieve normocapnia, which was measured during the night with transcutaneous monitoring • Initiation: in-hospital • Timing of initiation: after > 48 hours independence from ventilatory support (invasive or non-invasive) • Ventilator settings: IPAP 19.2 ± 3.4 and EPAP $4.8 \pm 1.0 \text{ cmH}_2\text{O}$ • Compliance: 6.3 ± 2.4 hours <p><u>Comparator (n = 100)</u></p> <p>Standard treatment alone</p> <ul style="list-style-type: none"> • Optimal medical treatment + LTOT if indicated
Outcomes	<p>Primary outcome: time to readmission or death within 12 months</p> <p>Secondary outcomes: daytime BGA, lung function, HRQL (SRI, MRF-28, CCQ, CRQ), dyspnoea (MRC), exacerbation frequency, survival</p>
Notes	<p>Conflicts of interest: four authors reported conflicts of interest</p> <p>Funding: Dutch Lung foundation, Philips/Respironics, Mediq TEFA and Stichting Astma Bestrijding</p>

Struik 2014 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomized ... by a computer with minimisation".
Allocation concealment (selection bias)	Low risk	Quote: "randomized ... by a computer with minimisation".
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants is not possible as sham treatment is not available. No information on blinding of study personnel.
Blinding of outcome assessment (detection bias) Patient reported outcomes	High risk	Participants were not blinded, so the PRO (SRI/MRC) are subjective measurements at high risk.
Blinding of outcome assessment (detection bias) Lung function and exercise test	Low risk	Not mentioned if staff performing these measurements were blinded to treatment.
Blinding of outcome assessment (detection bias) Blood gases, hospitalisations and mortality.	Low risk	Primary outcome and BGA are unlikely to be affected by the outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Flowchart presented: similar number of dropout in both group. (NIV 25/controls 24), reasons for dropout are provided in online supplement. ITT analysis on primary outcome, secondary outcomes assessed complete case analysis.
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in method section are presented fully. Comparison made with trial register: medical costs/exercise tolerance/inflammation markers/muscle strength and nutritional status not presented in paper (only exercise tolerance relevant to this review, not performed as participants were too weak to conduct the 6MWT).
Other bias	Low risk	The study appears to be free of other sources of bias.

Strumpf 1991
Study characteristics

Methods	<u>Design:</u> multicentre randomised controlled cross-over study <u>Dates:</u> study dates not reported <u>Setting:</u> pulmonary clinics at two US hospitals <u>Follow - up:</u> 6 months, cross-over after 3 months
Participants	<u>Inclusion criteria</u> <ul style="list-style-type: none"> FEV₁ < 1.0 L, a FEV₁/FVC ratio < 0.75 and TLC > 80% predicted

Strumpf 1991 (Continued)

Exclusion criteria

- > 15% increase in FEV₁ after the administration of an inhaled bronchodilator
- An exacerbation on their airway disease within the previous month
- Obstructive sleep apnea
- Coexisting medical conditions such as uncontrolled coronary heart disease, malignancy, or cardiac failure, or any condition that might hamper their ability to participate in a long-term trial

Baseline characteristics (raw data of 7 participants)

- Age 65.6 ± 5.6 years
- Sex (m/f) 5/2
- FEV₁ 0.54 ± 0.07 L (32 ± 4 %predicted)
- PaCO₂ 6.2 ± 0.9 kPa

Interventions	<p>23 participants received, in randomised order:</p> <p><u>Nocturnal nasal ventilation</u></p> <ul style="list-style-type: none"> • Interface: nasal mask • Device: BiPAP ventilator (Respironics Inc.), tidal volume was augmented by increasing the IPAP, EPAP was kept at 2 cmH₂O. • Target: settings were adjusted to match the patient's spontaneous breathing rate and to provide a 20 to 50% augmentation of resting minute ventilation and reduction of at least 5 mmHg in end-tidal PCO₂. • Initiation: out-patient • Ventilator settings: IPAP 15 ± 1 and EPAP fixed at 2 cmH₂O • Compliance: 6.7 ± 0.6 hours <p><u>Comparator</u></p> <p>Optimal medical care</p> <ul style="list-style-type: none"> • Consisted of optimised medication and oxygen supplementation to patients with severe hypoxemia. Participants were encouraged to remain active, but no specific rehabilitation program was offered to them.
Outcomes	BGA, lung function, PE/Plmax, sleep study (sleep efficiency), walking test (treadmill walking time), dyspnoea (TDI)
Notes	<p>Conflicts of interest: not reported</p> <p>Funding: supported in part by a grant from Respironics, Inc., Monroeville, Pennsylvania</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (from correspondence): "Computer-generated random number sequence".
Allocation concealment (selection bias)	Low risk	Quote (from correspondence): "Computer-generated random number sequence placed in envelopes that were opened as patients were enrolled".
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants: no blinding for treatment (cross-over).

Strumpf 1991 (Continued)

Blinding of outcome assessment (detection bias) Patient reported outcomes	High risk	TDI at risk for detection bias as participants were not blinded to treatment.
Blinding of outcome assessment (detection bias) Lung function and exercise test	Low risk	Quote: "All physiological measurements were performed by personnel blind to treatment and not involved in the study".
Blinding of outcome assessment (detection bias) Blood gases, hospitalisations and mortality.	Low risk	Quote: "All physiological measurements were performed by personnel blind to treatment and not involved in the study".
Incomplete outcome data (attrition bias) All outcomes	High risk	Reasons for withdrawal from study were mentioned for every participant. Seven people withdrew due to intolerance, five of intercurrent illness. Final analysis in article was done with the seven people who completed both arms.
Selective reporting (reporting bias)	Unclear risk	Trial was not registered, all outcomes listed in the methods were reported.
Other bias	Unclear risk	Quote: "respiratory therapist ... visited the home three times weekly until the patients had successfully adapted to the device" Unclear for how long these visits continued and if they could affect the outcomes after three months.

Zhou 2017
Study characteristics

Methods	<u>Design:</u> multicentre randomised controlled trial with parallel groups <u>Dates:</u> October 2015 to May 2016 <u>Setting:</u> 20 respiratory units in China <u>Follow - up:</u> 3 months
Participants	<u>Inclusion criteria</u> <ul style="list-style-type: none"> Clinically stable, hypercapnic GOLD stage III and IV COPD (no acute exacerbation, which was defined as an increase in or new onset of more than one respiratory symptom lasting ≥ 2 days and requiring any change of pharmacological treatment) Chronic hypercapnia (prolonged hypercapnia during daytime at rest without oxygen or ventilatory support for at least 3 months) Aged > 40 years <u>Exclusion criteria</u> <ul style="list-style-type: none"> Abnormalities of the thorax or the lung other than COPD Previously initiated NPPV Obstructive sleep apnoea COPD with OSA overlap syndrome Severe heart failure in NYHA stage IV, unstable angina, and severe arrhythmia, Malignant co-morbidities Impaired general condition that could preclude regular follow-up visits

Zhou 2017 (Continued)

Baseline characteristics (raw data of 115 participants):

- Age 67.7 ± 6.8 years
- Sex (m/f) 99/16
- FEV₁ 0.59 ± 0.20 L (26 ± 10 %predicted)
- PaCO₂ 8.0 ± 1.1 kPa

Interventions	<u>Nocturnal NIV in addition to optimised medical treatment (n = 57)</u> <ul style="list-style-type: none"> • Interface: face (not further specified) or nasal mask • Device: Flexo ST30 NIV (Curative Co), in S/T mode, EPAP set at 4 cmH₂O and backup frequency at 16 breaths/min • Target: IPAP to the maximally tolerated level and IPAP – EPAP difference more than 10 cmH₂O • Initiation: out-patient • Ventilator settings: IPAP 17.8 ± 2.1 and EPAP 4.2 ± 0.1 cmH₂O • Compliance: 5.6 ± 1.4 hours <u>Comparator (n = 58)</u> Optimised medical treatment including LTOT
Outcomes	Primary outcome: BGA Secondary outcomes: HRQL (SRI), lung function, 6MWD, dyspnoea (TDI)
Notes	Conflicts of interest: the authors received financial support from Curative Medical Co. China for the re-search Funding: Natural Science Foundation of China, Science and Technology Project of Guangdong Province

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated sequence.
Allocation concealment (selection bias)	Low risk	Computerised block randomisation, performed by a central independent statistician.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants not blinded, effective sham treatment not available. Probe design used but not mentioned if investigators were blinded to treatment.
Blinding of outcome assessment (detection bias) Patient reported outcomes	High risk	HRQL and dyspnoea measurements (SRI/TDI) are PRO, these are at risk for outcome assessors bias as participants were not blinded.
Blinding of outcome assessment (detection bias) Lung function and exercise test	Low risk	Outcome assessors were unaware of treatment assignment throughout the study.
Blinding of outcome assessment (detection bias)	Low risk	BGA not at risk for outcome assessor.

Zhou 2017 (Continued)

Blood gases, hospitalisations and mortality.

Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed. Dropout similar between group, reasons of 2 participants not provided. In total 5 participants did not complete the trial. 2 in the NIV group, due to discontinuation of NIV (mask problems and lack of effect), and 3 in the control group (1 participant died, 2 participants dropped out).
Selective reporting (reporting bias)	High risk	Outcomes described were checked with trial register. Primary outcome in trial register was SRI, in paper it was PaCO ₂ . Exacerbation frequency and survival rate were not reported in the paper, whilst they were described in the trial register as secondary outcomes.
Other bias	Low risk	No baseline imbalance although no absolute P values are given.

Data are reported as mean ± standard deviation or median (interquartile range (IQR)), unless otherwise stated.

6MWD: 6-minute walking distance; AHI: apnoea hypopnoea index; ARF: acute respiratory failure; BGA: blood gas analysis; BiPAP: Bilevel Positive Airway Pressure; COPD: chronic obstructive pulmonary disease; CRQ: chronic respiratory disease questionnaire; EPAP: expiratory positive airway pressure; FEV₁: forced expiratory volume in 1 second; HRQL: health-related quality of life; IPAP: inspiratory positive airway pressure; LTOT: long-term oxygen therapy; (m)MRC: (modified) Medical Research Council scale; MRF-28: Mageri Respiratory failure questionnaire-28; NIV: non-invasive ventilation; OSA: obstructive sleep apnea; PaCO₂: arterial carbon dioxide tension; PEmax: maximal expiratory pressure; PImax: maximal inspiratory pressure; PRO: participant-reported outcome; SD: standard deviation; SF36: short form — 36 items; SGRQ: St. George's Respiratory Questionnaire; SRI: severe respiratory insufficiency questionnaire; TDI: transition dyspnoea index; TLC: total lung capacity.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Ali 2012	Conference abstract. Allocation of participants was not randomised. Outcomes irrelevant to this review.
Chiang 2004	Mixed population of people with obstructive lung diseases, not only people with COPD.
Clini 1998	The assignment of the participants to the 2 groups was not randomised.
Diaz 1999	This study did not meet the inclusion criteria that NIV should be applied during the night for at least 5 hours, as participants received NIV for 3 hours a day.
Funk 2011	Ineligible study design. All included participants were initiated on NIV and then randomised to either continue NIV or to withdraw from NIV.
Kamei 1999	The assignment of participants to either NIV or long-term oxygen therapy groups was not randomised.
Lin 1996	Participants received NIV for only 2 weeks. It is difficult to start NIV in people with COPD, therefore, it is necessary to determine the effects after a longer period so the participants can adjust to the ventilator.
Nicolini 2014	Intervention group received inspiratory positive pressure breathing during the daytime.

COPD: chronic obstructive pulmonary disease; NIV: non-invasive ventilation.

Characteristics of studies awaiting classification [ordered by study ID]

Baturova 2013

Methods	Randomised trial.
Participants	25 people with COPD who have persistent nocturnal desaturation with basal SpO ₂ 88%.
Interventions	NIV in addition to standard care compared to standard treatment.
Outcomes	After 6 months: HRQL (SF36), exacerbation frequency and time to exacerbation.
Notes	Abstract of the European Respiratory Society Annual Congress, 2013 Barcelona, no full-text could be retrieved. Authors did not respond to clarify uncertainties in the study design and outcomes.

Guan 2018

Methods	Multicentre, prospective, randomised, controlled trial.
Participants	165 people with stable hypercapnic COPD
Interventions	Non-invasive ventilation
Outcomes	Primary outcome: HRQL (SRI) Secondary outcomes: BGA, 6MWD, lung function, dyspnoea (TDI)
Notes	There was a high suspicion that this trial was an extension of the included study by Zhou 2017 . Unfortunately, authors did not respond to clarify this.

Xiang 2007

Methods	Randomised, parallel controlled study
Participants	40 people with COPD
Interventions	Nocturnal-NIV and long-term oxygen therapy versus long-term oxygen therapy alone for 2 years
Outcomes	BGA, lung function, dyspnoea, 6MWD, respiratory muscle score, mortality, hospital admissions, dropout rate, anxiety scores
Notes	The article was written in Chinese. This study probably meets the review eligibility criteria, but verifying how the study was conducted based on the English information available was not possible, as authors did not respond to clarify important issues. Update 2020: a second attempt was made to contact the authors, but no response was received.

6MWD: 6-minute walking distance; AHRF: acute hypercapnic respiratory failure; BGA: blood gas analysis; COPD: chronic obstructive pulmonary disease; HRQL: health-related quality of life; NIV: non-invasive ventilation; SF36: short form — 36 items; SGRQ: St. George's respiratory questionnaire; SRI: severe respiratory insufficiency questionnaire; TDI: transition dyspnoea index.

Characteristics of ongoing studies *[ordered by study ID]*

Ankjaergaard

Study name	Home Non-Invasive Ventilation (NIV) Treatment for COPD-patients After a NIV-treated Exacerbation
Methods	Multicentre randomised controlled trial
Participants	150 participants having survived an admission with non-invasive ventilatory treatment of AHRF due to COPD.
Interventions	Nocturnal NIV for >6h per night + usual care compared to a control group receiving only usual care.
Outcomes	Primary outcome: time to death or repeat AHRF with need of NIV (within 12 months). Secondary outcomes: hospitalizations, HRQL (CAT, SRI), medication status, dyspnoea (MRC), number of contacts with emergency room or general practitioner, days admitted, 1-year mortality, number of repeat AHRF.
Starting date	July 2013
Contact information	Kasper Linde Ankjærgaard, Department of Pulmonary Medicine, Gentofte Hospital, Kildegårdsvej 28, 2900, Hellerup, Denmark
Notes	

Beth Israel Deaconess Medical Center

Study name	Sleep Ventilation for Patients with Advanced Hypercapnic COPD
Methods	Prospective, randomised, comparative effectiveness clinical trial
Participants	300 participants with advanced hypercapnic COPD
Interventions	Usual care plus home nocturnal NIV
Outcomes	Primary outcome: time to readmission or death within 12 months Secondary outcomes: HRQL (SF36 and SGRQ), dyspnoea (MRC), BGA
Starting date	Not yet recruiting (updated June 123, 2020)
Contact information	Melanie S. Pogach, MD; mpogach@bidmc.harvard.edu Robert J. Thomas, MD; rthomas1@bidmc.harvard.edu
Notes	

Gonzales

Study name	Respiratory Support in Chronic Obstructive Pulmonary Disease (COPD) Patients.
Methods	Open-label, prospective randomised, controlled, superiority clinical trial consisting of 4 arms with a 1:1:1:1 distribution.
Participants	400 people who have COPD with AHRF, treated > 24 hours with ventilation, with a pH > 7.35 and Pa-CO ₂ > 6kPa during daytime at rest, measured 48h to 2 weeks after NIV withdrawal.

Gonzales (Continued)

Interventions	Home non-targeted NIV, home targeted NIV and rescue home NIV
Outcomes	Primary outcome: admission-free survival within 0 to 36 months Secondary outcomes: overall survival; exacerbation frequency, HRQL (SGRQ, SRI, SF36, EQ5D, CCI, CAT), sleep quality (PSQI, ESS), dyspnoea (mMRC), adverse event.
Starting date	July 2019
Contact information	Angèle Guilbot; mailto:angele.guilbot%40multihealthgroup.com?subject=NCT03890224 , R2M, Respiratory Support in Chronic Obstructive Pulmonary Disease (COPD) Patients Nathalie Gagne; mailto:nathalie.gagne%40clinact.com?subject=NCT03890224 , R2M, Respiratory Support in Chronic Obstructive Pulmonary Disease (COPD) Patients Principal Investigator: Jesus Gonzalez, MDHôpital Pitié Salpêtrière-Charles Foix, Paris, France.
Notes	

Lamia

Study name	Home Non Invasive Ventilation for COPD Patients (NIVOLD).
Methods	Randomized controlled trial, parallel group.
Participants	86 people with COPD who survived after an episode of AHRF, weaned from mechanical ventilation-prescribed for acute episode since at least five days with following arterial blood gas: pH > 7.35 and PCO ₂ ≥ 45 mmHg.
Interventions	Home NIV compared to long term oxygen therapy
Outcomes	Primary outcome: first episode of AHRF Secondary outcomes: AHRF rate, lung function, 6MWD, HRQL, cardiac function (echocardiography), cost-effectiveness, mortality, BGA
Starting date	December 2011
Contact information	Bouchra Lamia, MD, MPH, PhD, University Hospital, Rouen; mailto:bouchra.lamia%40chu-rouen.fr?subject=NCT03221101 , 2013-AO1276-39 2010/080/HP, Home Non Invasive Ventilation for COPD Patients
Notes	

Pepin

Study name	Innovation in Non Invasive Ventilation in COPD Patients Treated by Long Term Oxygen Therapy (INOV-LTOT)
Methods	Prospective, randomised, parallel, open-labelled study
Participants	45 people with COPD on long-term oxygen therapy, affiliated to French social security system or equivalent.

Pepin (Continued)

Interventions	Respiratory assistance by a facial mask without intubation or tracheotomy, versus standard treatment without NIV
Outcomes	Primary outcome: nocturnal transcutaneous pressure of CO ₂ Secondary outcomes: HRQL (SGRQ), lung function, BGA, physical activity, 3 min chair rise test, venous cardiovascular risk parameters.
Starting date	June 2018
Contact information	Jean-Louis Pépin, Pr, PhD, University Grenoble Hospital
Notes	

Wijkstra

Study name	The Effects of Nocturnal Non-invasive Ventilation in Stable COPD (RECAPTURE)
Methods	Parallel group non-blinded randomised controlled trial
Participants	116 people with COPD who have an indication for chronic NIV (PaCO ₂ >6.0kPa), in stable condition (no COPD exacerbations in the past 4 weeks).
Interventions	Nocturnal NIV + standard care versus a control group that will receive standard care and postpone NIV for 3 months.
Outcomes	Primary outcome: change in FEV ₁ after 3 months, HRQL (SRI) Secondary outcomes: adverse events, HRQL (SF36, CCQ), mood status, activities and restrictions; dyspnoea (MRC), daytime & nocturnal gas exchange, 6MWD, lung function and volumes, respiratory muscle activity, venous blood and urine samples, high resolution computed tomography, patient-ventilator asynchrony, ventilation compliance.
Starting date	December 2017
Contact information	Principal investigator: Peter J. Wijkstra, University Medical Center Groningen; p.j.wijkstra@umcg.nl.
Notes	

6MWD: 6-minute walking distance; AHRF: acute hypercapnic respiratory failure; BGA: blood gas analysis; CAT: COPD assessment test; CCI: Charlson comorbidity index; COPD: chronic obstructive pulmonary disease; EQ5D: 5 level EuroQol; ESS: Epworth sleepiness scale; FEV₁: forced expiratory volume in 1 second; HRQL: health-related quality of life; (m)MRC: (modified) medical research council scale; NIV: non-invasive ventilation; PSQI: Pittsburgh Sleep Quality Index; SF36: short form 36 items; SGRQ: St. George's respiratory questionnaire; SRI: severe respiratory insufficiency questionnaire.

DATA AND ANALYSES

Comparison 1. Comparison 1: NIV vs standard care in stable COPD

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Stable COPD: PaO₂	11		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1.1 follow-up: 3 months	10	308	Mean Difference (IV, Random, 95% CI)	0.31 [0.14, 0.48]
1.1.2 follow-up: 12 months	3	171	Mean Difference (IV, Random, 95% CI)	0.08 [-0.37, 0.53]
1.2 Stable COPD: PaCO₂	13		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.2.1 follow-up: 3 months	12	512	Mean Difference (IV, Random, 95% CI)	-0.48 [-0.72, -0.25]
1.2.2 follow-up: 12 months	4	232	Mean Difference (IV, Random, 95% CI)	-0.35 [-0.68, -0.02]
1.3 Stable COPD: 6-minute walking distance	9		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.3.1 follow-up: 3 months	8	330	Mean Difference (IV, Random, 95% CI)	7.85 [-5.52, 21.23]
1.3.2 follow-up: 12 months	3	134	Mean Difference (IV, Random, 95% CI)	23.50 [-3.03, 50.03]
1.4 Stable COPD: HRQL	7		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.4.1 follow-up: 3 months	5	257	Std. Mean Difference (IV, Random, 95% CI)	0.42 [0.17, 0.67]
1.4.2 follow-up: 12 months	4	199	Std. Mean Difference (IV, Random, 95% CI)	0.18 [-0.24, 0.59]
1.5 Stable COPD: FEV₁	13		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.5.1 follow-up: 3 months	11	420	Mean Difference (IV, Random, 95% CI)	-0.00 [-0.04, 0.03]
1.5.2 follow-up: 12 months	4	236	Mean Difference (IV, Random, 95% CI)	0.00 [-0.04, 0.04]
1.6 Stable COPD: FVC	13		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.6.1 follow-up: 3 months	11	421	Mean Difference (IV, Random, 95% CI)	0.01 [-0.06, 0.08]
1.6.2 follow-up: 12 months	4	235	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.13, 0.09]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.7 Stable COPD: RV/%TLC	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.7.1 follow-up: 3 months	3	184	Mean Difference (IV, Random, 95% CI)	-0.53 [-2.77, 1.71]
1.7.2 follow-up: 12 months	4	195	Mean Difference (IV, Random, 95% CI)	0.27 [-1.98, 2.53]
1.8 Stable COPD: PEmax	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.8.1 follow-up: 3 months	6	160	Mean Difference (IV, Random, 95% CI)	9.03 [-1.51, 19.58]
1.8.2 follow-up: 12 months	1	38	Mean Difference (IV, Random, 95% CI)	3.50 [-23.70, 30.70]
1.9 Stable COPD: PImax	8		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.9.1 follow-up: 3 months	7	192	Mean Difference (IV, Random, 95% CI)	6.96 [3.29, 10.62]
1.9.2 follow-up: 12 months	2	92	Mean Difference (IV, Random, 95% CI)	7.04 [-12.29, 26.37]
1.10 Stable COPD: Transition Dyspnoea Index	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.10.1 follow-up: 3 months	3	178	Mean Difference (IV, Random, 95% CI)	0.77 [0.01, 1.53]
1.11 Stable COPD: (modified) Medical Research Council dyspnoea scale	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.11.1 follow-up: 3 months	4	155	Mean Difference (IV, Random, 95% CI)	-0.29 [-0.59, 0.01]
1.11.2 follow-up: 12 months	2	103	Mean Difference (IV, Random, 95% CI)	-0.49 [-0.90, -0.08]
1.12 Stable COPD: sleep efficiency	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.12.1 follow-up: 3 months	3	24	Mean Difference (IV, Random, 95% CI)	-2.86 [-8.76, 3.04]
1.13 Stable COPD: exacerbations	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.13.1 follow-up: 3 months	2	100	Odds Ratio (M-H, Random, 95% CI)	0.76 [0.34, 1.69]
1.13.2 follow-up: 12 months	2	89	Odds Ratio (M-H, Random, 95% CI)	0.72 [0.25, 2.05]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.14 Stable COPD: hospitalisations	5		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.14.1 follow-up: 3 months	5	312	Odds Ratio (M-H, Random, 95% CI)	0.64 [0.26, 1.60]
1.14.2 follow-up: 12 months	4	182	Odds Ratio (M-H, Random, 95% CI)	1.06 [0.46, 2.44]
1.15 Stable COPD: all-cause mortality	3	405	Hazard Ratio (IV, Random, 95% CI)	0.78 [0.58, 1.05]
1.16 PaCO ₂ after 3 months - subgroup PaCO ₂ (stable COPD)	12	512	Mean Difference (IV, Random, 95% CI)	-0.48 [-0.72, -0.25]
1.16.1 Baseline PaCO ₂ <7.3 kPa	8	217	Mean Difference (IV, Random, 95% CI)	-0.25 [-0.43, -0.06]
1.16.2 Baseline PaCO ₂ ≥7.3 kPa	4	295	Mean Difference (IV, Random, 95% CI)	-0.82 [-1.10, -0.53]
1.17 PaCO ₂ after 3 months - subgroup IPAP (stable COPD)	12	512	Mean Difference (IV, Random, 95% CI)	-0.48 [-0.72, -0.25]
1.17.1 mean IPAP <18 cmH ₂ O	8	241	Mean Difference (IV, Random, 95% CI)	-0.26 [-0.45, -0.07]
1.17.2 mean IPAP ≥18 cmH ₂ O	4	271	Mean Difference (IV, Random, 95% CI)	-0.80 [-1.12, -0.48]
1.18 PaCO ₂ after 3 months - subgroup compliance (stable COPD)	12	512	Mean Difference (IV, Random, 95% CI)	-0.48 [-0.72, -0.25]
1.18.1 Mean compliance <5 hours per night	3	81	Mean Difference (IV, Random, 95% CI)	-0.15 [-0.50, 0.19]
1.18.2 Mean compliance ≥5 hours per night	9	431	Mean Difference (IV, Random, 95% CI)	-0.60 [-0.84, -0.36]

Analysis 1.1. Comparison 1: Comparison 1: NIV vs standard care in stable COPD, Outcome 1: Stable COPD: PaO₂ **Analysis 1.2. Comparison 1: Comparison 1: NIV vs standard care in stable COPD, Outcome 2: Stable COPD: PaCO₂**

Analysis 1.3. Comparison 1: Comparison 1: NIV vs standard care in stable COPD, Outcome 3: Stable COPD: 6-minute walking distance **Analysis 1.4. Comparison 1: Comparison 1: NIV vs standard care in stable COPD, Outcome 4: Stable COPD: HRQL**

Analysis 1.5. Comparison 1: Comparison 1: NIV vs standard care in stable COPD, Outcome 5: Stable COPD: FEV₁ **Analysis 1.6. Comparison 1: Comparison 1: NIV vs standard care in stable COPD, Outcome 6: Stable COPD: FVC**

Analysis 1.7. Comparison 1: Comparison 1: NIV vs standard care in stable COPD, Outcome 7: Stable COPD: RV/%TLC

Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias): Lung function and exercise test
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

Analysis 1.8. Comparison 1: Comparison 1: NIV vs standard care in stable COPD, Outcome 8: Stable COPD: PEmax

Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias): Lung function and exercise test
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

Analysis 1.9. Comparison 1: Comparison 1: NIV vs standard care in stable COPD, Outcome 9: Stable COPD: PImax **Risk of bias legend**

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias): Lung function and exercise test
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

Analysis 1.10. Comparison 1: Comparison 1: NIV vs standard care in stable COPD, Outcome 10: Stable COPD: Transition Dyspnoea Index **Risk of bias legend**

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias): Patient reported outcomes
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

**Analysis 1.11. Comparison 1: Comparison 1: NIV vs standard care in stable COPD,
Outcome 11: Stable COPD: (modified) Medical Research Council dyspnoea scale** **Analysis 1.12. Comparison 1: Comparison 1: NIV vs standard
care in stable COPD, Outcome 12: Stable COPD: sleep efficiency**

Analysis 1.13. Comparison 1: Comparison 1: NIV vs standard care in stable COPD, Outcome 13: Stable COPD: exacerbations

Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias): Blood gases, hospitalisations and mortality.
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

Analysis 1.14. Comparison 1: Comparison 1: NIV vs standard care in stable COPD, Outcome 14: Stable COPD: hospitalisations

Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias): Blood gases, hospitalisations and mortality.
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

Analysis 1.15. Comparison 1: Comparison 1: NIV vs standard care in stable COPD, Outcome 15: Stable COPD: all-cause mortality

Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias): Blood gases, hospitalisations and mortality.
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

Analysis 1.16. Comparison 1: Comparison 1: NIV vs standard care in stable COPD, Outcome 16: PaCO₂ after 3 months - subgroup PaCO₂ (stable COPD) **Analysis 1.17. Comparison 1: Comparison 1: NIV vs standard care in stable COPD, Outcome 17: PaCO₂ after 3 months - subgroup IPAP (stable COPD)**

Analysis 1.18. Comparison 1: Comparison 1: NIV vs standard care in stable COPD, Outcome 18: PaCO₂ after 3 months - subgroup compliance (stable COPD) **Comparison 2. Comparison 2: NIV vs standard care in post-exacerbation COPD**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Post-exacerbation COPD: PaO ₂	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1.1 follow-up: 3 months	3	234	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.58, 0.41]
2.1.2 follow-up: 12 months	3	170	Mean Difference (IV, Random, 95% CI)	-0.24 [-0.81, 0.34]
2.2 Post-exacerbation COPD: PaCO ₂	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.2.1 follow-up: 3 months	3	241	Mean Difference (IV, Random, 95% CI)	-0.42 [-0.72, -0.12]
2.2.2 follow-up: 12 months	3	175	Mean Difference (IV, Random, 95% CI)	-0.53 [-0.88, -0.19]
2.3 Post-exacerbation COPD: HRQL	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.3.1 follow-up: 3 months	2	216	Std. Mean Difference (IV, Random, 95% CI)	0.27 [0.01, 0.54]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3.2 follow-up: 12 months	2	162	Std. Mean Difference (IV, Random, 95% CI)	0.27 [-0.04, 0.58]
2.4 Post-exacerbation COPD: admission-free survival	2	317	Hazard Ratio (IV, Random, 95% CI)	0.69 [0.39, 1.23]
2.5 Post-exacerbation COPD: FEV ₁	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.5.1 follow-up: 3 months	2	201	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.09, 0.03]
2.5.2 follow-up: 12 months	2	157	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.09, 0.03]
2.6 Post-exacerbation COPD: FVC	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.6.1 follow-up: 3 months	2	202	Mean Difference (IV, Random, 95% CI)	-0.13 [-0.30, 0.04]
2.6.2 follow-up: 12 months	2	158	Mean Difference (IV, Random, 95% CI)	-0.11 [-0.32, 0.10]
2.7 Post-exacerbation COPD: exacerbations	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.7.1 follow-up: 3 months	1	139	Odds Ratio (M-H, Random, 95% CI)	0.93 [0.48, 1.81]
2.7.2 follow-up: 12 months	3	181	Odds Ratio (M-H, Random, 95% CI)	0.67 [0.32, 1.41]
2.8 Post-exacerbation COPD: hospitalisations	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.8.1 follow-up: 12 months	3	193	Odds Ratio (M-H, Random, 95% CI)	0.63 [0.19, 2.09]
2.9 Post-exacerbation COPD: all-cause mortality	2	317	Hazard Ratio (IV, Random, 95% CI)	0.98 [0.74, 1.29]

Analysis 2.1. Comparison 2: Comparison 2: NIV vs standard care in post-exacerbation COPD, Outcome 1: Post-exacerbation COPD: PaO₂ **Analysis 2.2. Comparison 2: Comparison 2: NIV vs standard care in post-exacerbation COPD, Outcome 2: Post-exacerbation COPD: PaCO₂**

Analysis 2.3. Comparison 2: Comparison 2: NIV vs standard care in post-exacerbation COPD, Outcome 3: Post-exacerbation COPD: HRQL

Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias): Patient reported outcomes
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

Analysis 2.4. Comparison 2: Comparison 2: NIV vs standard care in post-exacerbation COPD, Outcome 4: Post-exacerbation COPD: admission-free survival

Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Incomplete outcome data (attrition bias)
- (E) Selective reporting (reporting bias)
- (F) Other bias

Analysis 2.5. Comparison 2: Comparison 2: NIV vs standard care in post-exacerbation COPD, Outcome 5: Post-exacerbation COPD: FEV₁

Analysis 2.6. Comparison 2: Comparison 2: NIV vs standard care in post-exacerbation COPD, Outcome 6: Post-exacerbation COPD: FVC

Analysis 2.7. Comparison 2: Comparison 2: NIV vs standard care in post-exacerbation COPD, Outcome 7: Post-exacerbation COPD: exacerbations

Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias): Blood gases, hospitalisations and mortality.
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

Analysis 2.8. Comparison 2: Comparison 2: NIV vs standard care in post-exacerbation COPD, Outcome 8: Post-exacerbation COPD: hospitalisations

Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias): Blood gases, hospitalisations and mortality.
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

Analysis 2.9. Comparison 2: Comparison 2: NIV vs standard care in post-exacerbation COPD, Outcome 9: Post-exacerbation COPD: all-cause mortality

Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias): Blood gases, hospitalisations and mortality.
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

ADDITIONAL TABLES

Table 1. Absolute changes in the outcomes after three and 12 months in stable COPD, separate for the NIV and the control group

Outcome	3 months		12 months				
	n	Change in NIV group	n	Change in control group	n	Change in NIV group	Change in control group
PaO₂ (kPa)	131	0.17 ± 0.95	140	-0.07 ± 0.99	88	-0.03 ± 1.07	-0.06 ± 1.12
PaCO₂ (kPa)	238	-0.81 ± 1.01	237	-0.17 ± 0.93	123	-0.46 ± 1.10	-0.05 ± 0.98
6MWD (m)	167	32.2 ± 73.9	163	16.0 ± 75.6	67	15.0 ± 105.9	-10.7 ± 94.8
SRI , summary score	108	7.5 ± 12.5	109	2.2 ± 11.0	42	6.1 ± 14.2	0.5 ± 9.3
SGRQ , total score	20	-3.2 ± 9.3	20	-0.2 ± 8.9	62	-0.2 ± 14.0	-0.9 ± 15.3
FEV₁ (l)	194	0.01 ± 0.15	189	0.01 ± 0.14	125	-0.01 ± 0.17	-0.01 ± 0.15
FVC (l)	196	0.05 ± 0.40	188	0.05 ± 0.38	125	-0.07 ± 0.43	-0.05 ± 0.46
RV/TLC (%)	93	-0.6 ± 6.8	91	-0.05 ± 6.8	101	0.6 ± 8.0	0.07 ± 9.0
PEmax (cmH ₂ O)	60	8.7 ± 24.6	63	3.0 ± 23.6	16	17.4 ± 46.2	13.9 ± 36.1
Plmax (cmH ₂ O)	76	9.2 ± 16.7	76	2.2 ± 12.5	45	8.0 ± 16.9	2.0 ± 16.5
TDI	84	1.2 ± 2.7	94	0.5 ± 2.7	0	—	—
(m)MRC	68	-0.7 ± 1.0	87	-0.4 ± 0.9	49	-0.6 ± 1.2	-0.1 ± 1.0
Sleep efficiency	13	7.0 ± 23.2	11	12.6 ± 16.8	0	—	—
COPD exacerbations^a	24	0.5 (0 to 1.8)	32	1.0 (0 to 2.0)	18	3.0 (2.8 to 4.0)	3.0 (2.0 to 5.0)
COPD hospitalisations^a	137	0 (0 to 0.5)	131	0 (0 to 1.0)	71	0 (0 to 2.0)	0 (0 to 2.0)

Data are based on the studies that provided the IPD, and are presented as mean ± standard deviation or median (interquartile range).

^a absolute number of exacerbations or hospitalisations.

6MWD: 6-minute walking distance; CI: confidence interval; COPD: Chronic Obstructive Pulmonary Disease; FEV₁: forced expiratory volume in 1 second; FVC: forced vital capacity; (m)MRC: (modified) Medical Research Council dyspnoea scale, a decrease indicates an improvement in dyspnoea; NIV: noninvasive ventilation; PaCO₂: arterial carbon dioxide tension; PaO₂: arterial oxygen tension; PEmax: peak expiratory pressure; PImax: peak inspiratory pressure; RV/TLC: residual volume/total lung capacity; SGRQ: St. George's Respiratory Questionnaire, a decrease indicates an improved health-related quality of life; SRI: Severe Respiratory Insufficiency questionnaire, an increase indicates an improved health-related quality of life; TDI: transitional dyspnoea index, a positive value indicates an improvement in dyspnoea.

Table 2. Absolute changes in the outcomes after three and 12 months in post-exacerbation COPD, separate for the NIV and the control group

Outcome	3 months				12 months			
	n	Change in NIV group	n	Change in control group	n	Change in NIV group	n	Change in control group
PaO₂ (kPa)	120	0.08 ± 2.33	114	0.19 ± 2.12	86	0.21 ± 1.96	84	0.48 ± 2.10
PaCO₂ (kPa)	127	-0.99 ± 1.24	114	-0.59 ± 1.19	90	-1.12 ± 1.15	85	-0.61 ± 1.20
SRI, summary score	115	4.7 ± 10.6	101	1.7 ± 11.7	85	4.8 ± 11.9	77	1.7 ± 11.8
FEV₁ (l)	108	0.02 ± 0.19	93	0.04 ± 0.20	82	0.01 ± 0.21	75	0.03 ± 0.22
FVC (l)	108	-0.01 ± 0.66	93	0.12 ± 0.63	83	-0.01 ± 0.64	75	0.08 ± 0.68
COPD exacerbations^a	72	0 [0 to 1.0]	67	0 [0 to 1.0]	95	2.0 [1.0 to 4.0]	86	2.0 [1.0 to 4.0]
COPD hospitalisations^a	0	—	0	—	100	0 (0 to 2.0)	93	0 (0 to 2.0)

Data are based on the studies that provided the IPD, and are presented as mean ± standard deviation or median (interquartile range).

^a absolute number of exacerbations or hospitalisations.

CI: confidence interval; COPD: Chronic Obstructive Pulmonary Disease; FEV₁: forced expiratory volume in 1 second; FVC: forced vital capacity; NIV: noninvasive ventilation; PaCO₂: arterial carbon dioxide tension; PaO₂: arterial oxygen tension; SRI: Severe Respiratory Insufficiency questionnaire, an increase indicates an improved health-related quality of life.

APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways Register of Trials

Electronic searches: core databases

Database	Dates searched	Frequency of search
CENTRAL (<i>via the Cochrane Register of Studies</i>)	From inception	Monthly
MEDLINE (Ovid) ALL	1946 onwards	Weekly
Embase (Ovid)	1974 onwards	Weekly
PsycINFO (Ovid)	1967 onwards	Monthly
CINAHL (EBSCO)	1937 onwards	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respiriology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

COPD search

1. Lung Diseases, Obstructive/
2. exp Pulmonary Disease, Chronic Obstructive/
3. emphysema\$.mp.
4. (chronic\$ adj3 bronchiti\$).mp.
5. (obstruct\$ adj3 (pulmonary or lung\$ or airway\$ or airflow\$ or bronch\$ or respirat\$)).mp.
6. COPD.mp.
7. COAD.mp.

8. COBD.mp.

9. AECB.mp.

10. or/1-9

Filter to identify RCTs

1. exp "clinical trial [publication type]"/

2. (randomised or randomised).ab,ti.

3. placebo.ab,ti.

4. dt.fs.

5. randomly.ab,ti.

6. trial.ab,ti.

7. groups.ab,ti.

8. or/1-7

9. Animals/

10. Humans/

11. 9 not (9 and 10)

12. 8 not 11

(The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases)

Appendix 2. Search strategies - original search (2002 and 2013)

The original version of this review carried out a search on all COPD records in the Cochrane Airways Group Specialised Register using the terms: nasal ventilat* OR positive pressure OR NIPPV. For this update, a search was done in all COPD records in the Register using the following search string: (nasal OR mechanical OR noninvasive OR non-invasive or "non invasive" or positive OR intermittent OR bi-level OR "bi level" OR airway* OR controlled OR pressure OR support AND (ventilat*)) OR (NIPPV). The latest search for the 2013 update was conducted in August 2012.

Appendix 3. Search strategy - current update

Search strategy to identify relevant trials from the Cochrane Airways Trials Register

#1 MeSH DESCRIPTOR Pulmonary Disease, Chronic Obstructive Explode All

#2 MeSH DESCRIPTOR Bronchitis, Chronic

#3 (obstruct*) near3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)

#4 COPD:MISC1

#5 (COPD OR COAD OR COBD):TI,AB,KW

#6 #1 OR #2 OR #3 OR #4 OR #5

#7 nasal* near3 ventilat*

#8 mechanical* near3 ventilat*

#9 (noninvasive or non-invasive) near3 ventilat*

#10 positive* near3 ventilat*

#11 intermittent* near3 ventilat*

#12 (bi-level or bi-level) near3 ventilat*

Chronic non-invasive ventilation for chronic obstructive pulmonary disease (Review)

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- #13 airway* near3 ventilat*
- #14 controlled near3 ventilat*
- #15 pressure near3 ventilat*
- #16 support near3 ventilat*
- #17 NIPPV
- #18 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17
- #19 #6 and #18

Search strategy to identify relevant trials from online trial registries

ClinicalTrials.gov (www.ClinicalTrials.gov)

Study type: intervention

Condition: COPD

Intervention: ventilation OR noninvasive OR bi-level OR bilevel OR NIPPV

[World Health Organization \(WHO\) trials portal](http://www.who.int/ictrp/en/) (www.who.int/ictrp/en/)

Condition: COPD

Intervention: ventilation OR noninvasive OR bi-level OR bilevel OR NIPPV

WHAT'S NEW

Date	Event	Description
21 December 2020	New citation required and conclusions have changed	The PICO was changed; standard care was redefined and all trials that investigate chronic NIV in COPD were to be included. This resulted in the inclusion of 12 new studies which enabled the investigation of additional outcomes.
21 December 2020	New search has been performed	New literature search run

HISTORY

Protocol first published: Issue 2, 2001

Review first published: Issue 2, 2002

Date	Event	Description
4 June 2014	Amended	Plain language summary title amended
1 February 2013	New search has been performed	New literature search done
28 January 2013	New citation required but conclusions have not changed	A new search was performed which identified 3 new eligible studies (Clini 2002 ; McEvoy 2009 ; Sin 2007). One trial is listed as 'awaiting classification' until we can clarify the methods used in their study. The review has been re-written and there has been a change to the list of authors and the review now also contains long-term data (after 12 months).

Date	Event	Description
13 August 2008	Amended	Converted to new review format.
2 January 2002	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Raveling and Duiverman: searched and reviewed relevant papers, collected IPD of the newly included RCTs, authors of the review. Vonk: supervised statistical analysis of IPD, co-author of the review; Struik, Goldstein, Kerstjens and Wijkstra: review development, co-authors of the review.

Contributions of editorial team

Rebecca Fortescue (Co-ordinating Editor): edited the review update; advised on methodology interpretation and content; approved the review prior to publication.

Christian Osadnik (Contact Editor): edited the review; advised on methodology, interpretation and content.

Emma Dennett (Managing Editor): co-ordinated the editorial process; advised on interpretation and content; edited the review.

Emma Jackson (Assistant Managing Editor): conducted peer review; edited the references and other sections of the review.

Elizabeth Stovold (Information Specialist): designed the search strategy; ran the searches; edited the search methods section.

DECLARATIONS OF INTEREST

T Raveling: none known.

J Vonk: none known.

FM Struik: none known.

R Goldstein: none known.

HAM Kerstjens: none known.

PJ Wijkstra: none known.

ML Duiverman: none known.

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External sources

- All, UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Update 2013: We selected three of the primary outcomes from the last update as our primary outcomes, in consultation with the Cochrane Airways Group.

Update 2020: after consultation with the Cochrane Airways Group, we extended the PICO and reran the original search to also include trials that:

- 1) investigated nocturnal NIV in addition to pulmonary rehabilitation or an exercise program, as this may now be considered standard of care in severe COPD (studies investigating NIV during exercise training were excluded);
- 2) investigated chronic NIV at home following an episode of acute respiratory failure.

INDEX TERMS

Medical Subject Headings (MeSH)

Diaphragm [physiopathology]; Hypercapnia [etiology] [physiopathology] [*therapy]; Partial Pressure; Positive-Pressure Respiration [*methods]; Pulmonary Disease, Chronic Obstructive [complications] [physiopathology] [*therapy]; Pulmonary Gas Exchange; Quality of Life; Sleep [physiology]; Time Factors; Walking

MeSH check words

Humans