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## Nocturnal mechanical ventilation for chronic hypoventilation in patients with neuromuscular and chest wall disorders (Review)

Annane D, Orlikowski D, Chevret S

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[Intervention Review]

# Nocturnal mechanical ventilation for chronic hypoventilation in patients with neuromuscular and chest wall disorders

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## ABSTRACT

### Background

Chronic alveolar hypoventilation is a common complication of many neuromuscular and chest wall disorders. Long-term nocturnal mechanical ventilation is commonly used to treat it. This is a 2014 update of a review first published in 2000 and previously updated in 2007.

### Objectives

To examine the effects on mortality of nocturnal mechanical ventilation in people with neuromuscular or chest wall disorders. Subsidiary endpoints were to examine the effects of respiratory assistance on improvement of chronic hypoventilation, sleep quality, hospital admissions and quality of life.

### Search methods

We searched the Cochrane Neuromuscular Disease Group Specialized Register, CENTRAL, MEDLINE and EMBASE on 10 June 2014. We contacted authors of identified trials and other experts in the field.

### Selection criteria

We searched for quasi-randomised or randomised controlled trials of participants of all ages with neuromuscular or chest wall disorder-related stable chronic hypoventilation of all degrees of severity, receiving any type and any mode of long-term nocturnal mechanical ventilation. The primary outcome measure was one-year mortality and secondary outcomes were unplanned hospital admission, short-term and long-term reversal of hypoventilation-related clinical symptoms and daytime hypercapnia, improvement of lung function and sleep breathing disorders.

### Data collection and analysis

We used standard Cochrane methodology to select studies, extract data and assess the risk of bias in included studies.

### Main results

The 10 eligible trials included a total of 173 participants. Roughly half of the trials were at low risk of selection, attrition or reporting bias, and almost all were at high risk of performance and detection bias. Four trials reported mortality data in the long term. The pooled risk ratio (RR) of dying was 0.62 (95% confidence interval (CI) 0.42 to 0.91, P value = 0.01) in favour of nocturnal mechanical ventilation compared to spontaneous breathing. There was considerable and significant heterogeneity between the trials, possibly related to differences between

the study populations. Information on unplanned hospitalisation was available from two studies. The corresponding pooled RR was 0.25 (95% CI 0.08 to 0.82, P value = 0.02) in favour of nocturnal mechanical ventilation. For most of the outcome measures there was no significant long-term difference between nocturnal mechanical ventilation and no ventilation. Most of the secondary outcomes were not assessed in the eligible trials. Three out of the 10 trials, accounting for 39 participants, two with a cross-over design and one with two parallel groups, compared volume- and pressure-cycled non-invasive mechanical ventilation in the short term. From the only trial (16 participants) on parallel groups, there was no difference in mortality (one death in each arm) between volume- and pressure-cycled mechanical ventilation. Data from the two cross-over trials suggested that compared with pressure-cycled ventilation, volume-cycled ventilation was associated with less sleep time spent with an arterial oxygen saturation below 90% (mean difference (MD) 6.83 minutes, 95% CI 4.68 to 8.98, P value = 0.00001) and a lower apnoea-hypopnoea (per sleep hour) index (MD -0.65, 95% CI -0.84 to -0.46, P value = 0.00001). We found no study that compared invasive and non-invasive mechanical ventilation or intermittent positive pressure versus negative pressure ventilation.

### Authors' conclusions

Current evidence about the therapeutic benefit of mechanical ventilation is of very low quality, but is consistent, suggesting alleviation of the symptoms of chronic hypoventilation in the short term. In four small studies, survival was prolonged and unplanned hospitalisation was reduced, mainly in participants with motor neuron diseases. With the exception of motor neuron disease and Duchenne muscular dystrophy, for which the natural history supports the survival benefit of mechanical ventilation against no ventilation, further larger randomised trials should assess the long-term benefit of different types and modes of nocturnal mechanical ventilation on quality of life, morbidity and mortality, and its cost-benefit ratio in neuromuscular and chest wall diseases.

## PLAIN LANGUAGE SUMMARY

### Mechanical ventilation at night for people with nerve, muscle or chest wall disease who have persistent breathing problems

#### Review question

We reviewed the evidence about the effect of mechanical ventilation at night in people with chronic (i.e. persistent) difficulties with breathing spontaneously due to diseases of the nerves, muscles or chest wall.

#### Background

Weakness of muscles of breathing or changes in the control of breathing are major complications of diseases of the nerves or muscles and of the chest wall. These problems can lead to hypoventilation, which is a state in which not enough air enters the lungs. People may then need devices to help them breathe (mechanical ventilation). Mechanical ventilation is widely offered to people with nerve and muscle diseases or chest wall deformities who develop chronic hypoventilation. We wanted to discover whether mechanical ventilation at night improved survival and symptoms of hypoventilation in this group and to compare different types of ventilation.

#### Study characteristics

This review includes 10 clinical trials involving 173 participants with persistent, stable hypoventilation. Three trials included only participants with motor neuron diseases, in three all participants had chest wall deformation only, and one trial included only participants with Duchenne muscular dystrophy. The other three trials had mixed populations.

The trials were comparisons of mechanical ventilation and standard care (five trials), different methods of ventilation (four trials) or both (one trial).

#### Key results and quality of the evidence

We found that mechanical ventilation at night may relieve the symptoms of chronic hypoventilation and prolong survival. However, the quality of the studies was very low. The benefit of long-term mechanical ventilation should be confirmed in further trials.

The evidence is current to June 2014.

## SUMMARY OF FINDINGS

### Summary of findings for the main comparison. Nocturnal ventilation versus no ventilation for chronic hypoventilation in patients with neuromuscular and chest wall disorders

#### Nocturnal ventilation versus no ventilation for chronic hypoventilation in patients with neuromuscular and chest wall disorders

**Patient or population:** patients with neuromuscular and chest wall disorders and chronic hypoventilation

**Settings:** ambulatory patients

**Intervention:** nocturnal ventilation versus no ventilation

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No ventilation	Nocturnal ventilation				
<b>Mortality at 1 year (or more)</b>	<b>Study population</b>		<b>RR 0.62</b> (0.42 to 0.91)	99 (4 studies)	⊕⊕⊕⊕ <b>very low</b> <sup>1,2</sup>	
	<b>521 per 1000</b>	<b>323 per 1000</b> (219 to 474)				
	<b>Moderate</b>					
	<b>421 per 1000</b>	<b>261 per 1000</b> (177 to 383)				
<b>Unplanned admission to hospital</b>	<b>Study population</b>		<b>RR 0.25</b> (0.08 to 0.82)	38 (2 studies)	⊕⊕⊕⊕ <b>very low</b> <sup>1,2</sup>	
	<b>526 per 1000</b>	<b>132 per 1000</b> (42 to 432)				
	<b>Moderate</b>					
	<b>517 per 1000</b>	<b>129 per 1000</b> (41 to 424)				
<b>No improvement of hypoventilation symptoms: long-term</b>	<b>Study population</b>		<b>RR 0.43</b> (0.18 to 1.03)	51 (3 studies)	⊕⊕⊕⊕ <b>very low</b> <sup>1,2</sup>	
	<b>885 per 1000</b>	<b>380 per 1000</b> (159 to 911)				
	<b>Moderate</b>					

	<b>900 per 1000</b>	<b>387 per 1000</b> (162 to 927)			
<b>No improvement of daytime hypercapnia: long-term</b>	<b>Study population</b>		<b>RR 0.59</b> (0.41 to 0.86)	58 (3 studies)	⊕⊕⊕⊕ <b>very low</b> <sup>1,2</sup>
	<b>828 per 1000</b>	<b>488 per 1000</b> (339 to 712)			
	<b>Moderate</b>				
	<b>778 per 1000</b>	<b>459 per 1000</b> (319 to 669)			

\*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in a footnote<sup>3</sup>. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

<sup>1</sup>Small unblinded trials.

<sup>2</sup>There was strong heterogeneity across the trials, possibly related to populations with very different severity of illness.

<sup>3</sup>Assumed control risk is based on actual control group risk as reported in included trials.

## Summary of findings 2. Volume-cycled ventilation versus pressure-cycled ventilation for chronic hypoventilation in patients with neuromuscular and chest wall disorders

### Volume-cycled ventilation versus pressure-cycled ventilation for chronic hypoventilation in patients with neuromuscular and chest wall disorders

**Patient or population:** patients with neuromuscular and chest wall disorders and chronic hypoventilation

**Settings:** ambulatory patients

**Intervention:** volume-cycled ventilation versus pressure-cycled ventilation

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				

	Volume-cycled ventilation	Pressure-cycled ventilation			
<b>Mortality at 1 year (or more)</b> Not measured - data reported for mortality at 3 months	<b>111 per 1000</b>	<b>143 per 1000</b> (11 to 1000)	<b>RR 1.29</b> (0.1 to 17.14)	16 (1 study)	⊕⊕⊕⊕ <b>very low</b> <sup>1</sup>
<b>Unplanned admission to hospital</b> - not measured	-	-	Not estimable	-	-
<b>No improvement of hypoventilation symptoms: long-term</b> - not measured	-	-	Not estimable	-	-
<b>No improvement of daytime hypercapnia: long-term</b> - not measured	-	-	Not estimable	-	-

\*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes<sup>2</sup>. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

<sup>1</sup>Only one small sized and unblinded study with few events (one death in each group).

<sup>2</sup>Assumed control risk is based on actual control group risk as reported in included trials.

## BACKGROUND

Long-term mechanical ventilation in people with neuromuscular conditions was first introduced between 1950 and 1960 in France and Sweden, as a consequence of the poliomyelitis epidemics. During the following decades, the concept of home mechanical ventilation expanded rapidly. Long-term mechanical ventilation was implemented in many other countries, and for many other conditions including neuromuscular or chest wall disorders, spinal cord injury and chronic obstructive pulmonary disease. Long-term mechanical ventilation can be delivered via a canula directly inserted into the trachea (invasive mechanical ventilation) or more frequently via face or nasal mask, or via a mouth piece (non-invasive mechanical ventilation). At the beginning of the 1990s, 26,000 people in France and 11,419 in the USA were receiving long-term respiratory assistance. About 10% presented with neuromuscular or chest wall disorders (Chailleux 1996; Milligan 1991). A European survey conducted between July 2001 and June 2002 reported the use of home mechanical ventilation in 483 centres in 16 countries (Lloyd-Owen 2005). That study identified 27,118 participants with long-term mechanical ventilation for lung or neuromuscular diseases related chronic respiratory failure. Then, the estimated prevalence was 6.6 per 100,000 people. In 2010, the estimated number of ventilator users in the USA was about 11,000, with three-quarters receiving invasive mechanical ventilation (King 2012). The estimated prevalence of children receiving home mechanical ventilation ranged from 4.7 to 6.4 per 100,000 children, that is a total of 3500 to 4800 children. Prolonged mechanical ventilation is a life-sustaining technology, which can be delivered at home, and is the fastest growing sector of the home health care economy (Arras 1995; Lewarski 2007). In 1990, the cost in the USA was estimated to be USD 789 per day for each ventilator-assisted patient by the American Association for Respiratory Care and the Gallup Organization (Milligan 1991). In the USA, a Medicare rough estimate of total payment for home mechanical ventilation was over USD 35 million for 2005 (Lewarski 2007). The average payment for home mechanical ventilation by Medicare, Medicaid or other private insurances varies from USD 500 to 1000 per month (Lewarski 2007).

Chronic alveolar hypoventilation is a state characterised by reduced arterial oxygen tension ( $\text{PaO}_2$ ) and increased carbon dioxide tension ( $\text{PaCO}_2$ ), which the patient may correct at least partially by voluntary hyperventilation (Newsom-Davis 1980). In most cases, chronic alveolar hypoventilation leads to daytime fatigue, hypersomnia and changes in psychological function. The mechanisms underlying hypercapnia in people with neuromuscular or chest wall disorders are multiple and not yet fully understood. They may involve impairment of lung mechanics or airway function and cough, ventilation-perfusion mismatch, blunted central ventilatory drive or respiratory-muscle fatigue. Abnormalities may occur while awake or during sleep (Loh 1979; Newsom-Davis 1980; Raphaël 1987; Skatrud 1980; Smith 1987). Numerous observational and uncontrolled studies suggest that nocturnal mechanical ventilation at least partially improves lung mechanics, respiratory muscle strength, or respiratory drive, or reduces ventilation-perfusion mismatch, by day as well as night (Annane 1999; Bach 1987; Barbé 1996; Carroll 1988; Ellis 1987; Heckmatt 1990; Hoepfner 1984). A multicentre randomised trial of preventive nocturnal non-invasive positive pressure ventilatory assistance in 70 participants with moderate pulmonary insufficiency due to Duchenne muscular

dystrophy (DMD) showed that survival was significantly worse in participants receiving preventive nocturnal ventilatory assistance, although daytime blood gases were improved (Raphaël 1994). Several other randomised trials, performed on parallel groups (Bourke 2006; Pinto 1995; Ward 2005), or based on a cross-over design and small samples (Ambrosino 1997; Ellis 1987; Laserna 2003; Restrict 1993; Willson 2004), suggested that nocturnal ventilation had beneficial effects on arterial blood gases or sleep parameters. Several reviews emphasise that nocturnal ventilatory assistance may be effective in reducing daytime hypoventilation, improving quality of life and prolonging survival in people with chronic alveolar hypoventilation (Claman 1996; Orlikowski 2005; Simonds 2003). A recent observational study highlighted that ventilator users deserve close monitoring (Chatwin 2010). In that study, 1211 patients requiring home mechanical ventilation had access to online support. There were about 500 patient calls each month, and close to 200 home emergency visits, identifying a ventilator dysfunction in about one-quarter of cases. A Consensus Conference of the American College of Chest Physicians recommended the implementation of long-term ventilation in patients with chronic hypercapnia during the day and in those with symptomatic nocturnal hypercapnia, particularly when secondary to neuromuscular or skeletal disorders (Make 1998). Another recent experts' consensus recommended the use of non-invasive bilevel positive ventilation either part time (< 23 hours) or full time (> 23 hours) in patients with end-stage chronic respiratory failure related to neuromuscular or chest wall disorders (Bach 2013).

The determination of the size of any beneficial effect of nocturnal mechanical ventilation on daytime hypoventilation in patients with neuromuscular or chest wall disorders and the comparative effects of different modes of ventilation requires a systematic review.

The primary aim of the present review was to search systematically for, and combine all evidence from, randomised trials relating to the effects of nocturnal mechanical ventilation in people with neuromuscular or chest wall disorders in order to supply the best evidence currently available on which to base recommendations for clinical practice and further research. This is a 2014 update of a review first published in 2000 and previously updated in 2007.

## OBJECTIVES

To examine the effects on mortality of nocturnal mechanical ventilation in people with neuromuscular or chest wall disorders. Subsidiary endpoints were to examine the effects of respiratory assistance on improvement of chronic hypoventilation, sleep quality, hospital admissions and quality of life.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We examined all randomised and quasi-randomised trials with or without blinding (although blinding seems unlikely to be feasible).

#### Types of participants

Participants with stable chronic hypoventilation, defined by an arterial  $\text{CO}_2$  tension above 6 kPa during the day, or symptoms of nocturnal hypercapnia (i.e. any of the following: diurnal hypersomnia, headaches, nightmares, enuresis), including



children and adults of all degrees of severity, whether living in institutions or in the community. We excluded studies reporting results for people with chronic obstructive pulmonary disease. We included data from studies of mixed populations if separate data were available from the participants with neuromuscular or chest wall disorders, or when contact with the authors resulted in the provision of the data.

We considered chronic hypoventilation due to one of the following medical conditions, according to the classification of the Consensus Conference of the American College of Chest Physicians.

1. Central nervous system disorders: Arnold-Chiari malformation, central nervous system trauma, cerebrovascular disorders, disorders of congenital and acquired central control of breathing, myelomeningocele, spinal cord traumatic injuries.
2. Neuromuscular disorders: amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), polio and postpolio syndrome, congenital childhood hypotonia, Guillain-Barré syndrome, infantile botulism, muscular dystrophy, myotonic dystrophy, phrenic nerve paralysis, myasthenia gravis.
3. Skeletal disorders: kyphoscoliosis, thoracic wall deformities, thoracoplasty.

#### Types of interventions

1. Long-term treatment (at least four weeks) with nocturnal mechanical ventilation (for at least three hours per night) versus no ventilation.
2. Type of ventilation: invasive techniques, i.e. tracheostomy (intermittent positive pressure) versus non-invasive techniques using negative pressure or positive pressure. For negative pressure, we considered the four available types of body enclosures, (i) body tanks (iron lungs), (ii) chest shells (rigid domes that fit over the chest and abdomen), (iii) body wraps (nylon or plastic jackets that surround the chest and abdomen), and (iv) abdominal pneumobelts (inflatable rubber bladders held firmly against the abdomen by nylon corsets). For non-invasive positive pressure ventilation, nasal, mouthpiece and oronasal interfaces were all considered.
3. Mode of ventilation: volume-cycled, pressure-cycled mechanical ventilation or bilevel positive airway pressure (BiPAP).

#### Types of outcome measures

##### Primary outcomes

Mortality at one year.

##### Secondary outcomes

1. Admission to hospital (other than routine visits).
2. Reversal of daytime hypoventilation-related clinical symptoms, i.e. diurnal hypersomnia, headaches, nightmares, enuresis.
3. Reversal of daytime hypercapnia, i.e. arterial CO<sub>2</sub> tension (on room air) below 6 kPa.
4. Lung function measurements, i.e. forced vital capacity (FVC), respiratory muscle strength, ventilation-perfusion mismatch.
5. Sleep studies, i.e. apnoea-hypopnoea index or mean oxygen saturation or the time spent with an arterial oxygen saturation below 90%.
6. Quality of life as assessed in individual studies.

We recorded outcomes for short-term effects (within one month) and the long-term effects (12 months or more) following implementation of mechanical ventilation.

#### Search methods for identification of studies

On 10 June 2014, we searched the Cochrane Neuromuscular Disease Group Specialized Register, CENTRAL (2014, Issue 5 in *The Cochrane Library*), MEDLINE (January 1966 to May 2014) and EMBASE (January 1980 to May 2014).

We checked all references in the identified trials and contacted authors to identify any additional published or unpublished data.

The detailed search strategies are in the appendices: Neuromuscular Disease Group Specialized Register [Appendix 1](#), CENTRAL [Appendix 2](#), MEDLINE [Appendix 3](#) and EMBASE [Appendix 4](#).

#### Data collection and analysis

##### Selection of studies

Two review authors (DA, DO) checked titles and abstracts identified from the database searches. We obtained the full text of all studies of possible relevance for independent assessment by both review authors. The review authors decided which trials fitted the inclusion criteria, and graded their risk of bias. Any disagreement was resolved by discussion between the review authors. We contacted the authors of one large trial in DMD to clarify whether the study had included people with chronic hypoventilation ([Raphaël 1994](#)).

##### Data extraction and management

Two review authors independently performed data extraction and the review authors systematically contacted authors of trials to provide missing data where possible. The review authors resolved any disagreement by discussion. One review author entered data into the Cochrane authoring software Review Manager (currently RevMan 5, [RevMan 2014](#)), and the other review authors checked this.

##### Assessment of risk of bias in included studies

We assessed the risk of bias in included studies using the Cochrane 'Risk of bias' tool ([Higgins 2011](#)).

We documented the risk of bias using the following criteria: baseline comparison of experimental groups, explicit diagnostic criteria, completeness of follow-up. The review authors resolved any disagreement by discussion.

##### Measures of treatment effect

For each outcome measure we computed 2 x 2 tables, summarising the number of people who experienced the event or outcome in each comparison group and the total number in each group. These tables were organised so that a beneficial effect of treatment was associated with a risk ratio (RR) < 1. We performed intention-to-treat analyses. We performed all statistical calculations using RevMan.

##### Assessment of reporting biases

We would have sought evidence of publication bias using the funnel plot method but there were too few studies included in any

meta-analysis (the Cochrane Handbook recommends at least 10, "because when there are fewer studies the power of the tests is too low to distinguish chance from real asymmetry" (Higgins 2011)).

### Data synthesis

We calculated a weighted treatment effect (using a fixed-effect model) across trials. We expressed the results as risk ratios (RRs) and 95% confidence intervals (CIs) for dichotomous outcomes and mean difference (MD and 95% CI) for continuous outcomes. We considered methods based on random-effects only when there was heterogeneity.

We included a 'Summary of findings' table for each comparison for which data were available and included the following outcomes:

1. the number of deaths at one year;
2. admission to hospital (other than routine visits);
3. the number of participants with improvement in symptoms of hypoventilation in the long term
4. the number of participants with improvement in daytime hypercapnia in the long term

We used the GRADE criteria (study limitations (risk of bias), consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the evidence for each outcome. We followed the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic*

*Reviews of Interventions* (Higgins 2011) and used GRADEpro software (GRADEpro 2008).

### Subgroup analysis and investigation of heterogeneity

We carried out a subgroup analysis to consider people with skeletal disorders and those with primary central nervous system or neuromuscular dysfunction separately.

When we found significant heterogeneity, we performed a graphic analysis to identify the trials and the factors responsible (related to participants' selection or treatment).

### Sensitivity analysis

We performed sensitivity analyses on the basis of risk of bias to test for heterogeneity in the results.

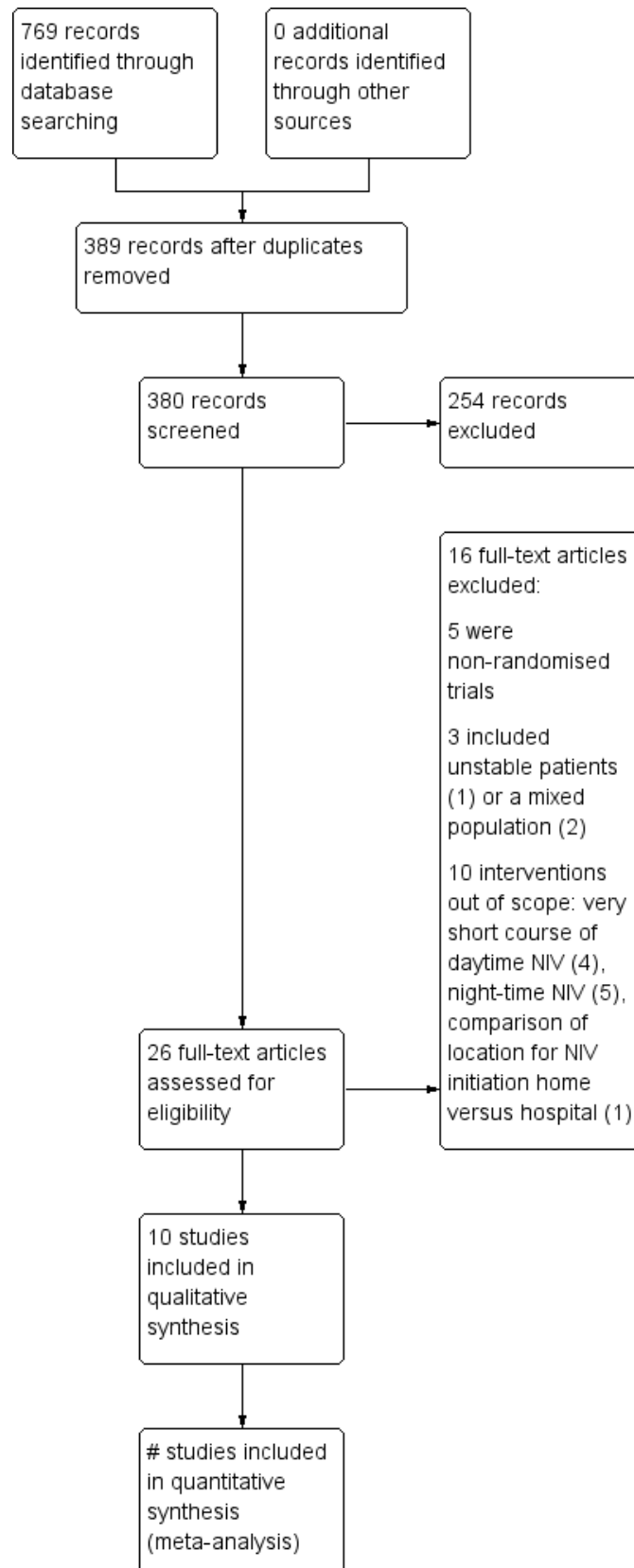
## RESULTS

### Description of studies

#### Results of the search

Our search results are detailed in [Figure 1](#). In June 2014, the updated search revealed 26 possible randomised trials. We excluded 16 trials (see [Characteristics of excluded studies](#)). There remained 10 trials that fulfilled the selection criteria (see [Characteristics of included studies](#)).

**Figure 1. Study flow diagram.**



**Figure 1. (Continued)**

(meta-analysis)

**Included studies**
**Source of information**

In addition to the extracted data from the publications, we obtained unpublished information from one trial (Raphaël 1994).

**Trial centres and design**

There was only one multicentre trial, involving 17 hospitals in France (Raphaël 1994). This trial was performed on two parallel groups. Four were small, single-centre, cross-over studies (Jaye 2009; Laserna 2003; Tuggey 2005; Willson 2004).

**Age of participants**

Two trials enrolled both children and adults (Raphaël 1994; Ward 2005). All remaining trials enrolled only adults.

**Trial populations**

Three trials included only participants with motor neuron diseases (Bourke 2006; Jackson 2001; Pinto 1995). Three trials included only participants with chest wall deformities (Laserna 2003; Struik 2011; Tuggey 2005). One trial included only participants with DMD (Raphaël 1994). All remaining trials enrolled a mixed population of congenital or acquired neuromuscular diseases or chest wall deformation. All trials included only participants with stable chronic hypoventilation. One trial included both asymptomatic and symptomatic chronic hypoventilation (Raphaël 1994). Contact with the primary trial author resulted in provision of individual data showing that 19 of the 70 participants had symptoms of nocturnal hypoventilation or daytime hypercapnia, 10 in the ventilation group and nine in the control group. Individual data from these 19 participants were available.

**Control intervention**

None of the studies used sham mechanical ventilation. The control arm was spontaneous ventilation in all except four trials (Jaye 2009; Struik 2011; Tuggey 2005; Willson 2004). In the first trial, the authors compared two different modalities for bilevel positive airway pressure (Jaye 2009). In two trials, the authors compared volume-targeted to pressure-targeted non-invasive ventilation (Struik 2011; Tuggey 2005). In the last trial, the authors compared two different interfaces (nasal versus full face mask) to deliver bilevel positive airway pressure (Willson 2004). In all trials, co-interventions included, as needed, oxygen, physiotherapy, antibiotics and other palliative care measures.

**Nocturnal mechanical ventilation**

The experimental treatments were volume-cycle positive intermittent ventilation in two studies (Laserna 2003; Raphaël 1994), and BiPAP in all remaining trials. One study had three arms (one control arm and two experimental arms) (Laserna 2003).

Three trials compared volume-cycle versus BiPAP (Laserna 2003; Struik 2011; Tuggey 2005).

**Outcomes**

Mortality at one year was reported in four trials (Bourke 2006; Pinto 1995; Raphaël 1994; Ward 2005).

Unplanned hospital admission was reported in two trials (Raphaël 1994; Ward 2005).

Four trials reported short-term effects of interventions on arterial blood gas, pulmonary function tests and sleep studies (Jackson 2001; Jaye 2009; Laserna 2003; Tuggey 2005). One study reported only arterial blood gas at hospital discharge and at three months (Struik 2011). We extrapolated short-term (within one month) values from the three-month values. One study reported only short-term effects on sleep studies (Willson 2004).

Long-term effects of intervention on clinical symptoms of nocturnal hypoventilation were reported in three studies (Jackson 2001; Pinto 1995; Raphaël 1994). Five trials reported long-term effects of interventions on arterial blood gas, pulmonary function, sleep studies and quality of life (Bourke 2006; Jackson 2001; Pinto 1995; Raphaël 1994; Ward 2005).

**Qualitative analysis of included trials**

Four were cross-over trials. A first study compared one-month effects of volume-cycle nocturnal intermittent positive ventilation to pressure-cycle ventilation (i.e. BiPAP) in people with kyphoscoliosis-related chronic hypoventilation (Laserna 2003). This study showed that, compared to baseline, both modes of nocturnal ventilation improved daytime arterial blood gas and nocturnal mean arterial oxygen saturation. Another study compared the short-term effects of nocturnal BiPAP delivered through a nasal mask or through a full face mask in people with symptomatic chronic hypoventilation (Willson 2004). This study showed that nocturnal BiPAP was equally effective on nocturnal mean oxygen saturation and nocturnal transcutaneous CO<sub>2</sub> tension. This study did not assess daytime or long-term effects of ventilation. Another study compared a one-month treatment with two different modes of pressure support ventilation with or without automatic titration in 20 participants with neuromuscular disorders (Jaye 2009). This study showed comparable effects of the two modes of ventilation on nocturnal oxygenation and sleep quality. However, there was a small but significant increase in nocturnal arterial CO<sub>2</sub> tension with automatic pressure support titration compared with standard pressure support ventilation (mean transcutaneous CO<sub>2</sub> tension: MD -0.80, 95% CI -1.18 to -0.42). The last cross-over trial compared a one-month treatment with volume-cycled or pressure-cycled nocturnal non-invasive ventilation in 13 participants with chest wall deformities (Tuggey 2005). This trial found comparable effects of the two modes of ventilation on daytime arterial gas exchange, sleep studies, pulmonary function, psychometric tests and health status.

Six studies were conducted on parallel groups, one in DMD (Raphaël 1994), three in motor neuron disease (Bourke 2006; Jackson 2001; Pinto 1995), one in people with chest wall deformities (Struik 2011), and one in people with various congenital

neuromuscular and chest wall diseases (Ward 2005). The first was a multicentre study and included 70 participants (Raphaël 1994). Contact with the primary author resulted in provision of individual data showing that 19 of the 70 participants had symptoms of nocturnal hypoventilation or daytime hypercapnia, 10 in the ventilation group and nine in the control group. Individual data from these 19 participants were available. This study compared nocturnal intermittent positive ventilation versus supportive treatment, i.e. physiotherapy and antibiotics if needed. This study showed that nocturnal mechanical ventilation improved daytime arterial blood gases in the short term. At one year, nocturnal mechanical ventilation improved symptoms related to nocturnal hypoventilation, tended to improve daytime arterial blood gases and had no significant effect on FVC. At one year, one of the 10 participants in the experimental group died, and none of the nine participants in the control group. This study provided no data on sleep studies. The second study included 20 participants in a single centre, 10 in the experimental group, who received nocturnal BiPAP, and 10 in the control group, who received oxygen, bronchodilators and other palliative measures (Pinto 1995). This study provided no data on short-term effects of nocturnal ventilation. This study showed at one year a significant difference in survival rate in favour of nocturnal ventilation and no significant difference for daytime arterial blood gases and FVC between nocturnal ventilation and supportive treatment. This study provided no data on symptoms related to nocturnal hypoventilation or on sleep studies. The third study included 13 participants with ALS, an FVC of 70% or more, and nocturnal oxygen desaturation of at least one minute or at least two clinical signs of chronic hypoventilation (Jackson 2001). Participants were followed up every three months on the basis of ALS functional rating scale-respiratory, pulmonary symptom scale, Short Form (SF) 36, pulmonary function testing and nocturnal oxymetry. In this small-sized study, nocturnal positive pressure ventilation improved the vitality subscale of SF-36, the mean pulmonary symptom score (before treatment of 72.7 versus after treatment of 80.8,  $P$  value = 0.04). The fourth study included 41 participants with ALS and either orthopnoea with maximum inspiratory pressure less than 60% of that predicted or symptomatic hypercapnia (Bourke 2006). Twenty-two participants were randomly assigned to nocturnal BiPAP and 19 to standard care, that is physiotherapy and assisted cough techniques as needed. In both groups participants received pneumococcal and annual influenza vaccines and had access to palliative care, including hospice facilities, whenever needed. This study showed that nocturnal ventilation improved survival and prolonged quality of life on several scales including the generic SF-36, and two specific scales, namely the symptoms domain of the sleep apnoea quality of life index and the chronic respiratory disease questionnaire. This study provided no data on short-term effects of nocturnal ventilation, and no data on arterial blood gas, lung function or sleep studies. The fifth study involved 16 participants with chest wall deformities and compared the effects of volume-cycled (nine participants) with pressure-cycled non-

invasive ventilation (seven participants) on the time to achieve normalisation of daytime arterial CO<sub>2</sub> tension (Struik 2011). Four participants were lost to follow-up in the volume-cycled non-invasive ventilation arm and one was lost to follow-up in the pressure-cycled non-invasive ventilation arm. Per protocol analysis showed a significant drop of PaCO<sub>2</sub> at hospital discharge in the pressure-cycled non-invasive ventilation arm ( $5.3 \pm 1.2$  versus  $7.6 \pm 1.2$  kPa) but not in the volume-cycled non-invasive ventilation arm ( $6.4 \pm 0.9$  versus  $7.2 \pm 0.7$  kPa). At three months, PaCO<sub>2</sub> dropped significantly from baseline in both arms,  $5.6 \pm 1.3$  versus  $7.6 \pm 1.2$  kPa and  $5.3 \pm 1.3$  versus  $7.2 \pm 0.7$  kPa. This study provided no information on mortality, unplanned hospitalisation, clinical symptoms, pulmonary function tests or sleep studies.

In the last study, 26 participants with chronic nocturnal hypoventilation and normal daytime CO<sub>2</sub> tension were randomly assigned to nocturnal bilevel airway positive pressure ( $n = 12$ ) or to standard care ( $n = 14$ ), that is physiotherapy and antibiotics if needed (Ward 2005). Participants were followed up for 24 months. This study showed that nocturnal BiPAP reduced time spent with nocturnal hypercapnia and improved mean nocturnal oxygen saturation. There was no significant difference between groups in daytime arterial CO<sub>2</sub> tension variations over time. There were more participants in the control group that met the criteria for mandatory ventilation than in the experimental group. Finally, compared with controls, a gain in SF-36 general health score was seen in the experimental group by 18 months. In addition, in this study, participants with daytime hypercapnia at the time of randomisation were not included but were similarly followed up. These participants had significant reductions in daytime mean arterial CO<sub>2</sub> tension with no significant changes in lung function.

### Excluded studies

Five of the 10 excluded studies were non-randomised studies (Aboussouan 1997; Bach 1998; Fanfulla 2005; Masa 1997; Padman 1998). One study included participants in an unstable condition (i.e. acute respiratory failure) (Celikel 1998). Four studies assessed the effects of a very short course of mechanical ventilation during the daytime and provided no data on nocturnal mechanical ventilation (Ambrosino 1997; Elliott 1994; Hart 2002; Meecham Jones 1993). Five trials compared a short course (one to three nights) of different modes of non-invasive ventilation with a control night on spontaneous breathing (Ellis 1987; Restruck 1993), or without such a control night (Crescimanno 2011; Highcock 2002; Orlikowski 2009). Another trial compared initiation of non-invasive nocturnal ventilation at home versus at hospital in people with neuromuscular or chest wall diseases and chronic hypoventilation (Chatwin 2008).

### Risk of bias in included studies

The detailed risk of bias in the included trials is reported in the 'Risk of bias' tables (Characteristics of included studies) and in Figure 2.

Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Bourke 2006	+	+	-	-	+	+
Jackson 2001	+	?	-	+	-	-
Jaye 2009	+	+	-	-	-	+
Laserna 2003	?	?	-	-	+	+
Pinto 1995	-	-	-	-	+	+
Raphaël 1994	+	+	-	-	+	+
Struik 2011	?	+	-	-	-	?
Tuggey 2005	?	?	-	-	+	?
Ward 2005	?	?	-	-	-	+
Willson 2004	?	?	-	-	+	+



## Allocation

In four trials, we considered allocation concealment adequate (Bourke 2006; Jaye 2009; Raphaël 1994; Struik 2011). In one trial, participants were alternately assigned to nocturnal BiPAP or supportive treatment and we considered the randomisation concealment inadequate (Pinto 1995). In the remaining trials allocation concealment was unclear.

## Blinding

Observer blinding was intended in only one study (Jackson 2001). In one trial, participants were blinded to the intervention they received, i.e. volume-cycled or pressure-cycled non-invasive ventilation (Tuggey 2005). In the remaining trials, participant blinding was felt not to be feasible and none of trials used sham mechanical ventilation.

## Incomplete outcome data

In all trials the baseline clinical features were similar in each group. In one trial, two of 12 participants in the experimental group and two of 14 in the control group were lost to follow-up (Ward 2005). In a second trial, one participant in the experimental arm was lost to follow-up (Jackson 2001). In a third trial that compared volume-cycled non-invasive ventilation to pressure-cycled non-invasive ventilation, five participants were lost to follow-up, four in the volume-cycled non-invasive ventilation arm and one in the pressure-cycled non-invasive ventilation arm (Struik 2011). Two participants did not tolerate volume-cycled non-invasive ventilation and were switched to pressure-cycled non-invasive ventilation after two days following randomisation. One participant in each arm died and one participant in the volume-cycled non-invasive ventilation arm did not want to return for measurements in hospital at three months. In all other trials, follow-up was complete and adherence to treatment was good.

## Selective reporting

We assessed the trials as at low risk of bias from selective reporting with the exception of three trials. Jackson 2001 was at high risk of bias because the investigators reported only preliminary results. Two trials did not provide information allowing us to assess reporting bias and we considered them at unclear risk (Struik 2011; Tuggey 2005).

## Explicit definition

All trials used explicit and internationally accepted diagnostic criteria for DMD, other congenital neuromuscular disease, motor neuron diseases and chest wall disease. All trials used explicit criteria to define chronic nocturnal hypoventilation.

## Effects of interventions

See: [Summary of findings for the main comparison Nocturnal ventilation versus no ventilation for chronic hypoventilation in patients with neuromuscular and chest wall disorders](#); [Summary of findings 2 Volume-cycled ventilation versus pressure-cycled ventilation for chronic hypoventilation in patients with neuromuscular and chest wall disorders](#)

## Nocturnal ventilation versus no ventilation

### Primary outcome measure: mortality at one year

Four studies reported the one-year mortality rate (Bourke 2006; Pinto 1995; Raphaël 1994; Ward 2005). In Raphaël 1994, one out of 10 participants died in the treatment group compared to none of the control group. In Pinto 1995, three out of 10 participants died in the treatment group compared to nine out of 10 in the control group. In Bourke 2006, 13 out of 22 participants died in the treatment group compared to 16 out of 19 in the control group. In Ward 2005, after 24 months of follow-up there were no reported deaths. In the pooled analysis, 17 deaths occurred among 51 participants in the nocturnal ventilation group versus 25 deaths among 48 participants in the control group, resulting in a risk ratio (RR) of dying of 0.62 (95% confidence interval (CI) 0.42 to 0.91, P value = 0.01) in favour of the experimental arm (Analysis 1.1). There was some heterogeneity across the studies ( $I^2 = 30%$ ) that may be explained by differences in the rate of disease progression, which was faster for participants with hypercapnic amyotrophic lateral sclerosis (ALS) (Bourke 2006; Pinto 1995) than in participants with Duchenne muscular dystrophy (DMD) (Raphaël 1994) or other slowly progressive diseases (Ward 2005). It was also the case that observed mortality rates were higher in the two studies conducted in ALS participants than in the two other trials.

### Secondary outcome measures

#### Admission to hospital (other than routine visits)

Two studies, accounting for 38 participants, reported this outcome in the long term (Raphaël 1994; Ward 2005). Two of 19 participants in the nocturnal ventilation group had unplanned hospital admission versus 10 of 19 in the control group, resulting in a RR of 0.25 (95% CI 0.08 to 0.82, P value = 0.02) (Analysis 1.2). There was no heterogeneity across the studies ( $I^2 = 0%$ ).

#### Reversal of daytime hypoventilation-related clinical symptoms

None of the trials provided data for this outcome in the short term.

Three trials, accounting for 51 participants, reported this outcome in the long term (Jackson 2001; Raphaël 1994; Ward 2005). In Raphaël 1994, four out of 10 participants in the treatment group did not have improved clinical symptoms at one year compared to seven out of nine participants in the control group. The estimated risk of "no improvement of hypoventilation related clinical symptoms" in this study was not significant (RR 0.51, 95% CI 0.22 to 1.19). Jackson 2001 reported failure to improve hypoventilation-related clinical symptoms at three months in three out of six participants in the experimental arm and all seven controls. In this study, the pulmonary symptom score improved from baseline in the experimental arm (80.8 versus 72.7, P value = 0.04) (RR 0.53, 95% CI 0.25 to 1.14). In Ward 2005, at 24 months there was an absence of improvement in clinical symptoms in none of the nine treated participants and nine of 10 participants in the control arm (RR 0.06, 95% CI 0.00 to 0.87).

Combining these three trials, seven of 25 participants in the nocturnal ventilation group did not experience improvement in hypoventilation-related symptoms versus 23 of 26 participants in the control group. The RR was 0.43 (95% CI 0.18 to 1.03, P value = 0.06) (Analysis 1.3).

### Reversal of daytime hypercapnia

One study provided data on this outcome in the short term ([Raphaël 1994](#)). Three out of seven participants in the treatment group did not have improved daytime hypercapnia compared to nine out of nine in the control group (RR 0.33, 95% CI 0.14 to 0.80, P value = 0.01) (see [Analysis 1.4](#)).

Three studies, accounting for 58 participants, reported the proportion of participants who did not experience an improvement in daytime hypercapnia ([Pinto 1995](#); [Raphaël 1994](#); [Ward 2005](#)). There were 14 of 29 such participants in the experimental arm versus 24 of 29 in the control arm. The pooled RR was 0.59 (95% CI 0.41 to 0.86, P value = 0.006) in favour of nocturnal ventilation ([Analysis 1.5](#)). There was significant heterogeneity across the studies ( $I^2 = 94%$ ). This heterogeneity may be explained by differences in the speed of disease progression: slow in two trials ([Raphaël 1994](#); [Ward 2005](#)) versus rapid in one trial ([Pinto 1995](#)).

However, at one year, from 60 participants in these three studies ([Pinto 1995](#); [Raphaël 1994](#); [Ward 2005](#)), the mean difference (MD) of the arterial CO<sub>2</sub> tension was -0.26 kPa (95% CI -0.61 to 0.09 kPa), which means that it was lower in the treated group but not significantly (see [Analysis 1.6](#)).

### Lung function measurements

None of the studies assessed this outcome in the short term. Two studies reported one-year values for forced vital capacity (FVC) ([Pinto 1995](#); [Raphaël 1994](#)), for 13 participants in the treated group and 15 participants in the control group. The MD of the FVC in these two trials was 159 mL (95% CI -84 to 401 mL), non-significantly more in the treated than the control group (see [Analysis 1.7](#)). At 24 months of follow-up, one study showed no significant difference in changes in sniff nasal inspiratory pressure (SNIP), which was 1.62 (6.1) in the control group versus -4.1 (14.1) cmH<sub>2</sub>O in the treated group (see [Analysis 1.8](#)), or changes in cough peak flow, which was 43.3 (52.2) L/min in the control group versus -0.9 (34.4) L/min in the treated group ([Ward 2005](#)). The other subcategory outcome, namely ventilation-perfusion mismatch, was not available.

### Sleep studies

One study assessed this outcome in the long term, at 24 months, in 14 treated and 12 control participants ([Ward 2005](#)). This study showed that mean nocturnal oxygen saturation increased from 93.5 (1.9)% to 96.6 (1.2)% in the treated group versus 95.2 (2.1)% to 93.6 (1.7)% in the control group, and the MD of nocturnal oxygen saturation in this study was 3.00% (95% CI 1.85% to 4.15%) (see [Analysis 1.9](#)). There was no significant difference between the two groups for the minimum overnight oxygen saturation.

### Quality of life

In a small-sized study, nocturnal positive pressure ventilation improved the vitality subscale of SF-36, the mean pulmonary symptom score (before treatment of 72.7 versus after treatment of 80.8, P value = 0.04) ([Jackson 2001](#)). In a second trial of 41 participants with ALS, nocturnal ventilation improved survival and prolonged quality of life on several scales including the generic SF-36, and two specific scales, namely the symptoms domain of the sleep apnoea quality of life index and the chronic respiratory disease questionnaire ([Pinto 1995](#)).

### Invasive ventilation versus non-invasive ventilation

We found no study that compared invasive to non-invasive ventilation.

### Intermittent positive pressure ventilation versus negative pressure ventilation

We found no study that compared invasive ventilation versus non-invasive ventilation.

### Volume-cycled versus pressure-cycled ventilation

#### Primary outcome: mortality at one year

We found only one study of volume-cycled versus pressure-cycled ventilation, which provided mortality data after three months following randomisation ([Struik 2011](#)). In this small (16 participants), single-centre trial only two deaths were reported, one in each group (see [Analysis 2.1](#)).

#### Secondary outcome measures

##### Admission to hospital (other than routine visits)

This outcome was not available.

##### Reversal of daytime hypoventilation-related clinical symptoms

This outcome was not available.

### Reversal of daytime hypercapnia

One study reported in the short term, i.e. at one month, that six of 10 participants in the pressure-cycled non-invasive ventilation group and six of 10 participants in the volume-cycled non-invasive ventilation group did not improve daytime hypercapnia (RR 1.00, 95% CI 0.49 to 2.05, P value = 1.00) (see [Analysis 2.2](#)) ([Laserna 2003](#)).

Three studies, accounting for 39 participants, reported daytime arterial oxygen tension after one month of intervention ([Laserna 2003](#); [Struik 2011](#); [Tuggey 2005](#)). The MD in arterial CO<sub>2</sub> tension was 0.45 kPa (95% CI -0.21 to 1.10, P value = 0.18) in favour of volume-cycled ventilation with significant heterogeneity across the studies ( $I^2 = 93%$ ) (see [Analysis 2.3](#)).

### Lung function measurements

This outcome was not available in the long term.

One trial, which was a cross-over study with 13 participants, reported in the short term (at one month) ([Tuggey 2005](#)). The trial found no significant difference between pressure- and volume-cycled non-invasive ventilation for FVC with a mean difference of 40.00% (95% CI -7.04 to 87.04, P value = 0.10) (see [Analysis 2.4](#)), maximal inspiratory pressure (mean difference -2.20 cmH<sub>2</sub>O (95% CI -4.92 to 0.52, P value = 0.11) and sniff nasal inspiratory pressure (SNIP) (mean difference -1.70 cm H<sub>2</sub>O (95% CI -4.70 to 1.30, P value = 0.06) (see [Analysis 2.5](#)).

### Sleep studies

One study, which was a cross-over study with 13 participants, provided treatment effects on mean nocturnal SaO<sub>2</sub> in the short term ([Tuggey 2005](#)). There was no difference between pressure- and volume-cycled non-invasive ventilation, with a mean difference of 1.20 (95% CI -0.70 to 3.10, P value = 0.22) (see [Analysis 2.6](#)).



Two studies, accounting for 23 participants, reported treatment effects on the time spent with nocturnal SaO<sub>2</sub> below 90%, in the short term (Laserna 2003; Tuggey 2005). The MD was 6.83 minutes (95% CI 4.68 to 8.98 minutes, P value < 0.00001) in favour of the volume-cycled non-invasive ventilation. However, there was strong heterogeneity across the studies ( $I^2 = 99%$ ) (see Analysis 2.7).

Two studies, accounting for 23 participants, reported the apnea-hypopnoea index per hour of sleep in the short term (Laserna 2003; Tuggey 2005). The MD was -0.65 (95% CI -0.84 to -0.46, P value < 0.00001) in favour of the volume-cycled non-invasive ventilation. There was no heterogeneity across the studies ( $I^2 = 0%$ ) (see Analysis 2.8).

### Quality of life

In one study, which was a cross-over study with 13 participants, there were no differences between volume-cycled and pressure-cycled ventilated patients in any of the components of the SF-36 scale.

## DISCUSSION

A huge number of reports of uncontrolled trials claim beneficial effects of nocturnal mechanical ventilation for chronic hypoventilation related to neuromuscular or chest wall disorders (Claman 1996; Make 1998). By contrast, we found a limited number of randomised studies. Only one study was a multicentre trial (Raphaël 1994). This trial enrolled 70 participants with Duchenne muscular dystrophy (DMD) during a five-year period. The study was designed to assess whether implementation of nocturnal mechanical ventilation early in the course of the disease prevents respiratory failure and prolongs survival. At randomisation, only 19 out of the 70 participants met the criteria currently proposed for long-term mechanical ventilation, namely symptoms of nocturnal hypoventilation or daytime hypercapnia (Make 1998). Three studies were based on a cross-over design and the population size was very small (Laserna 2003; Tuggey 2005; Willson 2004). The allocation concealment was adequate in only four of the 10 studies. Thus, the overall methodological quality of these trials was weak.

This systematic review suggests that, in people with chronic hypoventilation related to neuromuscular or chest wall diseases, nocturnal mechanical ventilation improves hypoventilation-related clinical symptoms, nocturnal mean oxygen saturation, daytime hypercapnia and quality of life, and reduces the risk of unplanned hospitalisation and mortality, compared to no ventilation. However, taking into account the small number of participants, the lack of observer blinding and the presence of significant heterogeneity across the studies, any conclusions must be drawn very cautiously. Data on the effects of nocturnal mechanical ventilation on lung function measurements and on sleep studies are too scarce to allow any definite conclusion. A large, Italian, single-centre, retrospective cohort study of patients with DMD showed a progressive increase in crude survival (Passamano 2012). The survival rate in DMD at the age of 20 years was 23.3% in the 1960s, 54% in patients born in the 1970s and 59.8% in those born in the 1980s (P value < 0.001). In this observational study, the crude mean age for respiratory-related death was 17.7 years in patients who did not receive mechanical ventilation and 27.9 years in mechanically ventilated patients (P value < 0.001). Similar findings in patients with DMD were found in other, single-centre, retrospective observational studies from the United

Kingdom (Eagle 2002), the United States of America (Bach 2011), Canada (McKim 2013), Belgium (Toussaint 2006), and Germany (Wollinsky 2012). An observational study of 144 children (47% with neuromuscular disorders, including DMD, spinal muscular atrophy (SMA) type 1 and type 2, and congenital myopathy) showed 94% and 91% survival rates at 5 and 10 years, respectively, with long-term mechanical ventilation (McDougall 2013).

It seems likely that hypoventilation-related symptoms may reflect different degrees of respiratory failure more in rapidly progressive diseases than in less rapidly progressive neuromuscular disorders. Subsequently, the effects of nocturnal mechanical ventilation should be different. So, it seems likely that the criteria for nocturnal mechanical ventilation should differ in rapidly progressive and less rapidly progressive neuromuscular disorders (Raphaël 1999). Similarly, correcting nocturnal hypoventilation in people with diurnal hypercapnia may yield a more rapid, clinically evident benefit than in people with normal daytime hypercapnia.

Data from two small cross-over studies showed that volume-cycled and pressure-cycled ventilation improved symptoms related to chronic hypoventilation and daytime hypercapnia significantly and similarly, at least in the short term (Laserna 2003; Tuggey 2005). Volume-cycled non-invasive ventilation may be associated with less nocturnal desaturation and apneas. However, taking into account the small number of participants, any conclusion should be drawn very cautiously.

There were no available data from randomised trials to decide on comparisons between invasive ventilation and non-invasive ventilation, or between intermittent positive ventilation and negative pressure ventilation. Observational studies have suggested that, in DMD with nocturnal mechanical ventilation and diurnal hypercapnia, daytime non-invasive ventilation may prolong survival and may be safe even when patients required 24-hour continuous respiratory support, thus preventing tracheostomy (Bach 2011; McKim 2013; Toussaint 2006). Likewise, an observational study of 144 children requiring long-term respiratory support, including patients with DMD (n = 18), SMA type 1 (n = 6) and type 2 (n = 14), and other congenital myopathies (n = 18), showed that five-year survival was 94% overall and was significantly higher for patients on non-invasive ventilation (97%) than invasively ventilated patients (84%) (McDougall 2013). Another study of 194 infants with SMA type 1, found that in comparison with invasive mechanical ventilation, non-invasive ventilation with mechanical cough assist was associated with lower survival rates at 24 months of life (68% versus 95%, P value < 0.001) and at 48 months of life (45% versus 89%, P value < 0.001) (Gregoret 2013).

The lack of assessment of adverse events associated with long-term mechanical ventilation is a limitation of the current review. Unpublished information was available for only one trial. Subsequently, there were missing data for several outcomes of interest.

## AUTHORS' CONCLUSIONS

### Implications for practice

Current evidence about the therapeutic benefit of mechanical ventilation is of very low quality, but directionally consistent, suggesting alleviation of the symptoms of chronic hypoventilation,

improvement in survival and reduced risk of unplanned hospitalisation.

### Implications for research

Large randomised trials are needed to confirm the possible long-term beneficial effects of nocturnal mechanical ventilation on hypoventilation-related symptoms, quality of life, unplanned hospital admission rate and mortality, and to evaluate its cost-effectiveness in people with chest wall disorders and in people with neuromuscular diseases other than motor neuron disease or Duchenne muscular dystrophy, because natural history studies have shown substantial improvements in survival. Future trials should be stratified according to the type of disease and whether the course is rapidly progressive or not. The comparisons between invasive and non-invasive ventilation, and between volume-cycled and pressure-cycled ventilation, also require well-designed, multicentre, randomised trials. Finally, particular attention may be

given to new modes of ventilation, such as auto-titrating pressure support devices, which are increasingly used.

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**CHARACTERISTICS OF STUDIES**
**Characteristics of included studies [ordered by study ID]**
**Bourke 2006**

Methods	Single-centre, open, parallel-group study with a follow-up period of at least 1 year
Participants	41 participants with ALS with or without bulbar features, meeting definite diagnostic criteria, who had orthopnoea with inspiratory maximal pressure less than 60% of predicted or symptomatic daytime hypercapnia
Interventions	Control: standard care Experimental: non-invasive nasal nocturnal ventilation with bilevel airway pressure  At least 1 year follow-up period
Outcomes	Survival time  Quality of life SF-36 mental component summary  Sleep apnoea quality of life index symptoms domain
Notes	—

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list
Allocation concealment (selection bias)	Low risk	Computer-generated list; centralised randomisation
Blinding of participants and personnel (performance bias) All outcomes	High risk	No party was blinded to the intervention
Blinding of outcome assessment (detection bias) All outcomes	High risk	The outcome assessor was not blinded to the intervention

**Bourke 2006** (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	Outcomes presented in the results section matched those reported in the methods

**Jackson 2001**

Methods	Single-centre, single-blind study, randomisation stratified according to bulbar versus limb onset	
Participants	13 adults with ALS of less than 3 years duration, with an FVC $\geq$ 70% and nocturnal oxygen desaturation for $\geq$ 1 minute or at least 2 clinical symptoms of chronic hypoventilation	
Interventions	Control: no respiratory support until FVC fell below 50% Experimental: nocturnal positive pressure ventilation	
Outcomes	No clear primary outcome <ul style="list-style-type: none"> <li>• ALS functional rating scale-respiratory version (ALSFRS-R)</li> <li>• Short Form 36</li> <li>• Modified Calgary Sleep Apnea Quality of Life Index (SAQLI)</li> <li>• FVC% (sitting and supine, maximal inspiratory force (MIP), maximal expiratory force (MEP))</li> <li>• Daytime and nocturnal oximetry, and peak cough expiratory flow (PCEF)</li> <li>• Symptoms of hypoventilation, assessed using a pulmonary symptom scale consisting of 14 questions, which were answered on a scale from 1 to 7</li> </ul>	
Notes	—	

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list
Allocation concealment (selection bias)	Unclear risk	No information was provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel were not blinded to the intervention
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcomes were assessed by a blinded clinical evaluator
Incomplete outcome data (attrition bias) All outcomes	High risk	One participant out of 7 in the experimental arm was lost to follow-up at 3 months
Selective reporting (reporting bias)	High risk	Only preliminary data were published

**Jaye 2009**

Methods	Single-centre, randomised, cross-over trial
Participants	25 adults meeting the following criteria: <ol style="list-style-type: none"> <li>1. with neuromuscular disease or chest wall deformation related chronic hypoventilation</li> <li>2. on nocturnal non-invasive mechanical ventilation for <math>\geq 6</math> months</li> <li>3. stable respiratory condition for <math>\geq 3</math> months</li> </ol>
Interventions	Control: 1-month treatment with conventional nocturnal positive pressure support ventilation Experimental: 1-month treatment with auto-titrated nocturnal positive pressure ventilation
Outcomes	Primary outcome: mean overnight oxygen saturation Secondary outcomes: <ul style="list-style-type: none"> <li>• sleep studies: overnight mean and maximum transcutaneous CO<sub>2</sub>, minimum SaO<sub>2</sub>, SaO<sub>2</sub> desaturation index, total sleep time, sleep latency, sleep efficiency, percentage of sleep stages, arousals, arousal index and heart rate variability</li> <li>• pulmonary function</li> <li>• non-invasive assessment of respiratory muscles strength</li> <li>• subjective assessment of tolerance to the ventilator on a visual analogical scale</li> </ul>
Notes	—

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Low risk	Centralised
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel were not blinded to the intervention
Blinding of outcome assessment (detection bias) All outcomes	High risk	The outcome assessor was not blinded to the intervention
Incomplete outcome data (attrition bias) All outcomes	High risk	5 out of 25 randomised participants were dropped from the analysis for incomplete data
Selective reporting (reporting bias)	Low risk	Outcomes presented in the results section matched those reported in the methods



**Laserna 2003**

Methods	Single-centre, open, cross-over study
Participants	10 participants with kyphoscoliosis and chronic hypercapnic respiratory failure
Interventions	Control: spontaneous ventilation Experimental 1: nocturnal ventilation with bilevel airway pressure Experimental 2: nocturnal volume-cycle ventilation
Outcomes	1-month improvement in sleep parameters, clinical symptoms and arterial blood gas
Notes	—

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information was not provided
Allocation concealment (selection bias)	Unclear risk	Information was not provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No party was blinded to the intervention
Blinding of outcome assessment (detection bias) All outcomes	High risk	The outcome assessor was not blinded to the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	Outcomes presented in the results section matched those reported in the methods

**Pinto 1995**

Methods	Single-centre, open, parallel-group study with a 3-year follow-up period
Participants	20 participants having ALS with bulbar features (definite diagnostic criteria) and with chronic hypercapnic respiratory failure
Interventions	Control: oxygen, bronchodilators and other palliative measures Experimental group: non-invasive nasal nocturnal ventilation with bilevel airway pressure
Outcomes	Mortality at 1 and 3 years  Survival time  Bulbar and spinal Norris scores  Quality of life  Modified Barthel score

**Nocturnal mechanical ventilation for chronic hypoventilation in patients with neuromuscular and chest wall disorders (Review)**

**Pinto 1995** (Continued)

 Arterial blood gases  
 Respiratory function tests

Notes —

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Participants were alternately assigned to experimental or control arms
Allocation concealment (selection bias)	High risk	Participants were alternately assigned to experimental or control arms
Blinding of participants and personnel (performance bias) All outcomes	High risk	No party was blinded to the intervention
Blinding of outcome assessment (detection bias) All outcomes	High risk	The outcome assessor was not blinded to the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	Outcomes presented in the results section matched those reported in the methods

**Raphaël 1994**

Methods	Multicentre (17 centres in France), open, parallel-group study
Participants	Children and adults with Duchenne muscular dystrophy 19 of the 70 included participants presenting with symptoms of nocturnal hypoventilation or daytime PaCO <sub>2</sub> ≥ 6 kPa and were evaluable
Interventions	Control group: combination of antibiotic and physiotherapy, if needed Experimental group: nocturnal intermittent positive ventilation through a nose mask or a mouthpiece
Outcomes	Short-term (24 hours): arterial blood gases  Long-term (6 months to 1 year): <ul style="list-style-type: none"> <li>• Symptoms of nocturnal hypoventilation</li> <li>• Death</li> <li>• Number of unplanned hospitalisations</li> <li>• Arterial blood gases</li> <li>• Forced vital capacity</li> </ul>
Notes	Individual data were available from the co-ordinating centre. 5-year inclusion period

**Risk of bias**
**Nocturnal mechanical ventilation for chronic hypoventilation in patients with neuromuscular and chest wall disorders (Review)**

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**Raphaël 1994** (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list
Allocation concealment (selection bias)	Low risk	Computer-generated list, centralised randomisation, stratified for centre
Blinding of participants and personnel (performance bias) All outcomes	High risk	No party was blinded to the intervention
Blinding of outcome assessment (detection bias) All outcomes	High risk	The outcome assessor was not blinded to the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up  Only a subgroup of participants had symptoms of chronic hypoventilation
Selective reporting (reporting bias)	Low risk	Outcomes presented in the results section matched those reported in the methods

**Struik 2011**

Methods	Single-centre, open-label trial with 2 parallel groups
Participants	16 adults with chest wall deformities and daytime PaCO <sub>2</sub> > 45 mm Hg, and one of the following symptoms of nocturnal hypoventilation: daytime sleepiness, fatigue, morning headaches and/or dyspnea, or weight loss. All the participants were NIV-naïve
Interventions	Control treatment: volume-targeted NIV during the night-time  Experimental treatment: pressure-targeted NIV during the night-time  In both arms NIV was titrated to decrease PaCO <sub>2</sub> to 45 mmHg, maintain SaO <sub>2</sub> above 90%, and improve symptoms while maintaining patient comfort
Outcomes	The number of days needed to successfully establish the patient on NIV, defined as adequate patient adjustment to NIV and effective ventilation (PaCO <sub>2</sub> < 45 mm Hg). NIV adjustment was considered adequate when the patient could sleep with the NIV for at least 6 hours per night
Notes	—

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method for generating the sequence of randomisation was not available
Allocation concealment (selection bias)	Low risk	Sealed envelope

**Struik 2011** (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Neither the participants nor the personnel were blinded to the intervention
Blinding of outcome assessment (detection bias) All outcomes	High risk	The outcome assessors were not blinded to the intervention
Incomplete outcome data (attrition bias) All outcomes	High risk	2 participants did not tolerate volume NIV and switched to pressure NIV after 2 days. 3 participants dropped out: 2 died (1 from cancer, the other from pneumothorax), and 1 did not want to return for measurements in hospital at 3 months
Selective reporting (reporting bias)	Unclear risk	No information available

**Tuggey 2005**

Methods	Single-centre, single-blinded, cross-over study	
Participants	13 adults with chronic respiratory failure related to chest wall deformities and with stable clinical status on long-term night-time mechanical ventilation	
Interventions	Control treatment: 4-week course of night-time ventilation with volume-targeted NIV Experimental treatment: 1-week course of night-time ventilation with pressure-targeted NIV	
Outcomes	Primary outcome: daytime arterial blood gas tensions during spontaneous breathing  Secondary outcomes: <ol style="list-style-type: none"> <li>1. Resting minute ventilation and occlusion pressure at 100 ms (P0.1), hypercapnic ventilatory responses</li> <li>2. Spirometry, maximal (plateau) inspiratory and expiratory mouth pressures, and sniff nasal inspiratory pressures</li> <li>3. Psychometric measures included a battery of tests sensitive to changes due to chronic hypoxia and sleep deprivation</li> <li>4. Health status assessed by validated disease specific (MRF-28) and generic (SF-36v2) questionnaires together with the Hospital Anxiety and Depression Scale</li> <li>5. Physical activity at home measured using a pedometer</li> </ol>	
Notes	—	

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method for generating the random sequence generation was not available
Allocation concealment (selection bias)	Unclear risk	Method for allocation concealment was not available
Blinding of participants and personnel (performance bias)	High risk	Participants were blinded to treatment received in an appropriate manner, i.e. use of same ventilator and ventilator setting masked to the participant. Personnel were not blinded to experimental treatments

**Tuggey 2005** (Continued)

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	High risk	The outcome assessor was not blinded to the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed treatments sessions and none was lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No information available

**Ward 2005**

Methods	Single-centre, open, parallel-group study with a 2-year follow-up period	
Participants	n = 26 adults and children with congenital neuromuscular and chest wall disease Chronic respiratory failure with diurnal normocapnia	
Interventions	Control: spontaneous ventilation Experimental: nocturnal ventilation with bilevel airway pressure	
Outcomes	Peak transcutaneous arterial CO <sub>2</sub> tension Number of participants who developed criteria for mandatory mechanical ventilation Changes in pulmonary function and respiratory muscles strength  SF-36 quality of life domain	
Notes	—	

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information was not provided
Allocation concealment (selection bias)	Unclear risk	Information was not provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No party was blinded to the intervention
Blinding of outcome assessment (detection bias) All outcomes	High risk	The outcome assessor was not blinded to the intervention
Incomplete outcome data (attrition bias) All outcomes	High risk	There were 2/12 and 2/14 participants lost to follow-up in the control and experimental arms, respectively  Half way through the follow-up period (12 months), 70% of control participants received the experimental treatment NIV, as they worsened to meet criteria for mechanical ventilation

**Ward 2005** (Continued)

Selective reporting (reporting bias)	Low risk	Outcomes presented in the results section matched those reported in the methods
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**Willson 2004**

Methods	Single-centre, cross-over, open study
Participants	16 participants with neuromuscular diseases (n = 3), chest wall diseases (n = 5) or non-neuromuscular and non-chest wall diseases (n = 8)
Interventions	Control: nocturnal ventilation with bilevel airway pressure using nasal mask Experimental: nocturnal ventilation with bilevel airway pressure using full face mask
Outcomes	Short-term (1-night treatment) effects on sleep parameters
Notes	—

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information was not provided
Allocation concealment (selection bias)	Unclear risk	Information was not provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No party was blinded to the intervention
Blinding of outcome assessment (detection bias) All outcomes	High risk	The outcome assessor was not blinded to the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	Outcomes presented in the results section matched those reported in the methods

ALS: amyotrophic lateral sclerosis

CO<sub>2</sub>: carbon dioxide

FVC: forced vital capacity

NIV: non-invasive ventilation

PaCO<sub>2</sub>: carbon dioxide tension

SaO<sub>2</sub>: oxygen saturation

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

Study	Reason for exclusion
<a href="#">Aboussouan 1997</a>	Non-randomised, open study
<a href="#">Ambrosino 1997</a>	Mechanical ventilation was implemented for 1-hour run during the daytime. No data are available for the effects of nocturnal ventilation
<a href="#">Bach 1998</a>	Non-randomised, open study
<a href="#">Celikel 1998</a>	Participants in an unstable condition, i.e. acute respiratory failure
<a href="#">Chatwin 2008</a>	This trial compared initiation of NIV at home versus in hospital
<a href="#">Crescimanno 2011</a>	This trial compared the very short-term (over 3 nights) effect on gas exchange, sleep and respiratory function of 3 different modes of ventilation
<a href="#">Elliott 1994</a>	Mixed population, i.e. COPD and only 4 participants with chest wall disorders. Mechanical ventilation was implemented for 5-minute courses during daytime. No data were available for night-time ventilation effects
<a href="#">Ellis 1987</a>	This trial compared short-term (24-hour) effects of 1 night on positive- or negative-pressure ventilation or spontaneous breathing
<a href="#">Fanfulla 2005</a>	Non-randomised, open study
<a href="#">Hart 2002</a>	This trial compared a very short course (i.e. 40 minutes) of proportional assisted ventilation and pressure support ventilation
<a href="#">Highcock 2002</a>	This trial compared the short-term (overnight) effects on sleep and gas exchange of 2 different ventilators for pressure support ventilation in participants with chronic respiratory failure due to chest wall deformities
<a href="#">Masa 1997</a>	Non-randomised, open study
<a href="#">Meecham Jones 1993</a>	Mixed population, i.e. COPD and only 3 participants with neuromuscular or chest wall disorders. Mechanical ventilation was implemented for a 2-hour course during daytime. No data were available for the effects of nocturnal ventilation
<a href="#">Orlikowski 2009</a>	This trial compared overnight effects on air leaks of 2 modes of ventilation with or without automatic air leak compensation
<a href="#">Padman 1998</a>	Non-randomised, open study. Participants were in an unstable condition, i.e. acute respiratory failure
<a href="#">Restrck 1993</a>	This trial compared the short-term effects (24-hour) of 1 overnight session of volume-cycled or pressure-cycled NIV or spontaneous breathing

COPD: chronic obstructive pulmonary disease

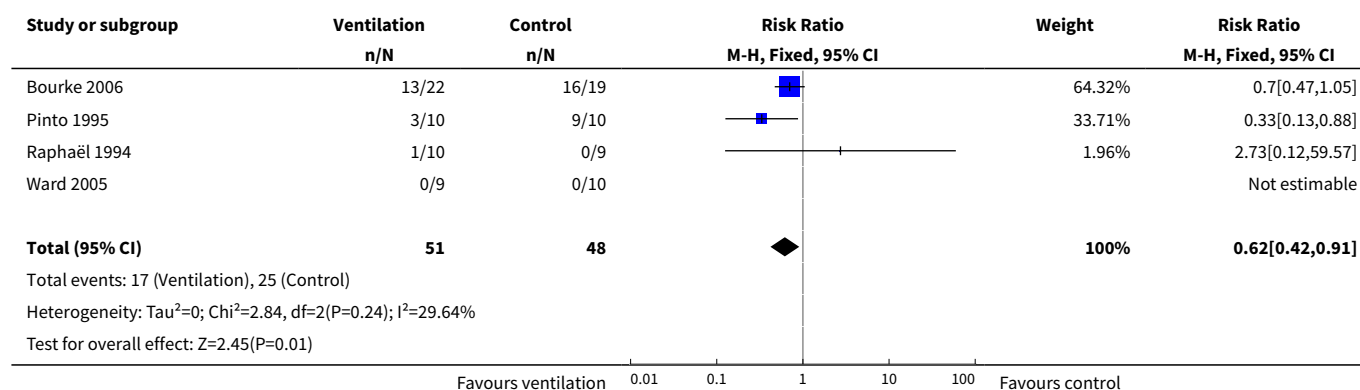
NIV: non-invasive ventilation

## DATA AND ANALYSES

**Comparison 1. Nocturnal ventilation versus no ventilation**

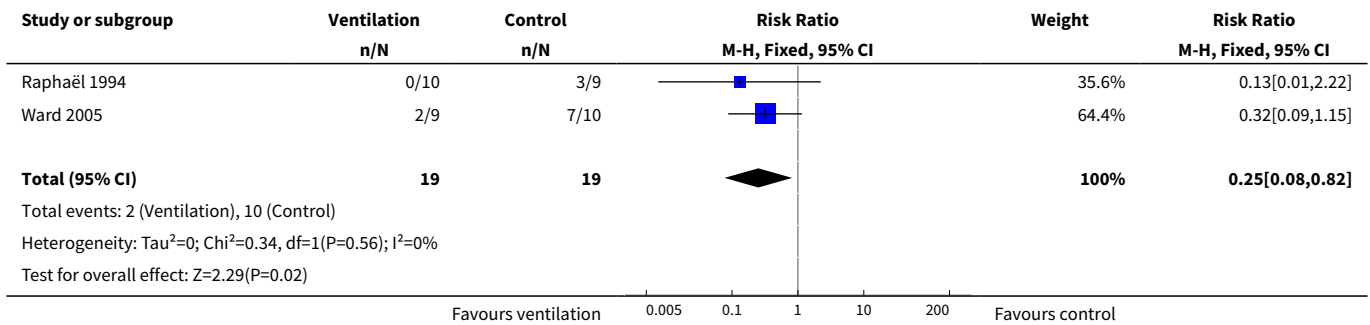
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality at one year	4	99	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.42, 0.91]
2 Unplanned admission to hospital	2	38	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.08, 0.82]
3 No improvement of hypoventilation symptoms: long-term	3	51	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.18, 1.03]
4 No improvement of daytime hypercapnia: short-term	1	19	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.14, 0.80]
5 No improvement of daytime hypercapnia: long-term	3	58	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.41, 0.86]
6 Daytime PaCO <sub>2</sub> : long-term	3	60	Mean Difference (IV, Fixed, 95% CI)	-0.26 [-0.61, 0.09]
7 Forced vital capacity: long-term	2	28	Mean Difference (IV, Fixed, 95% CI)	158.50 [-84.43, 401.43]
8 Respiratory muscle strength: long-term	1	28	Mean Difference (IV, Fixed, 95% CI)	-5.72 [-13.87, 2.43]
8.1 Mean improvement in maximal inspiratory pressure	1	2	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Mean improvement in SNIP	1	26	Mean Difference (IV, Fixed, 95% CI)	-5.72 [-13.87, 2.43]
9 Mean nocturnal SaO <sub>2</sub> : long-term	1	26	Mean Difference (IV, Fixed, 95% CI)	3.00 [1.85, 4.15]

**Analysis 1.1. Comparison 1 Nocturnal ventilation versus no ventilation, Outcome 1 Mortality at one year.**

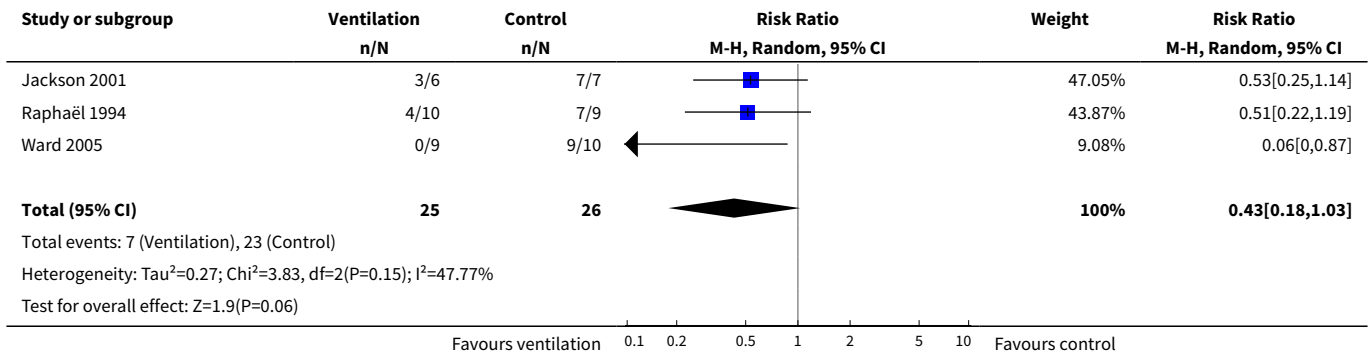




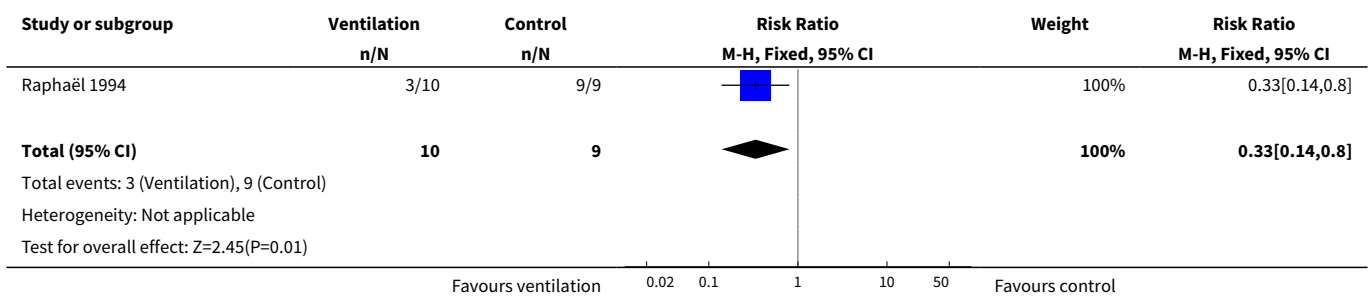
**Analysis 1.2. Comparison 1 Nocturnal ventilation versus no ventilation, Outcome 2 Unplanned admission to hospital.**



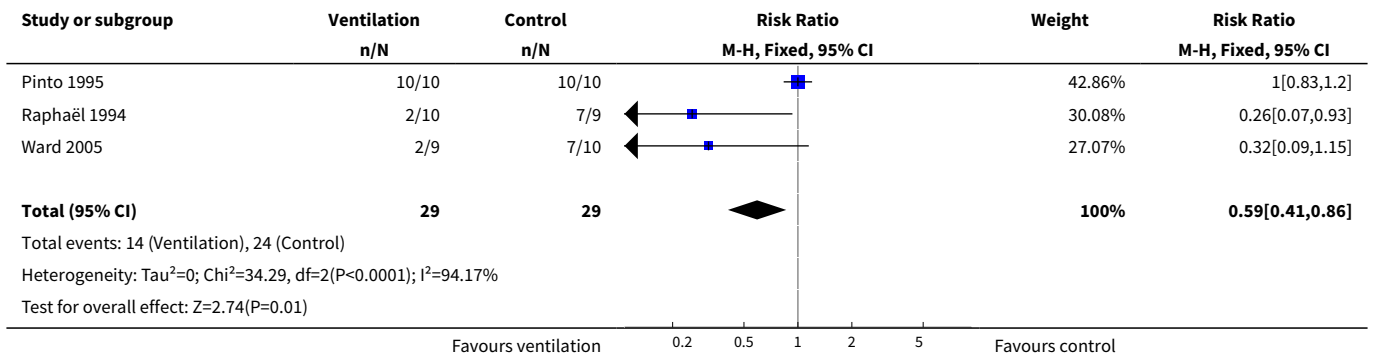
**Analysis 1.3. Comparison 1 Nocturnal ventilation versus no ventilation, Outcome 3 No improvement of hypoventilation symptoms: long-term.**



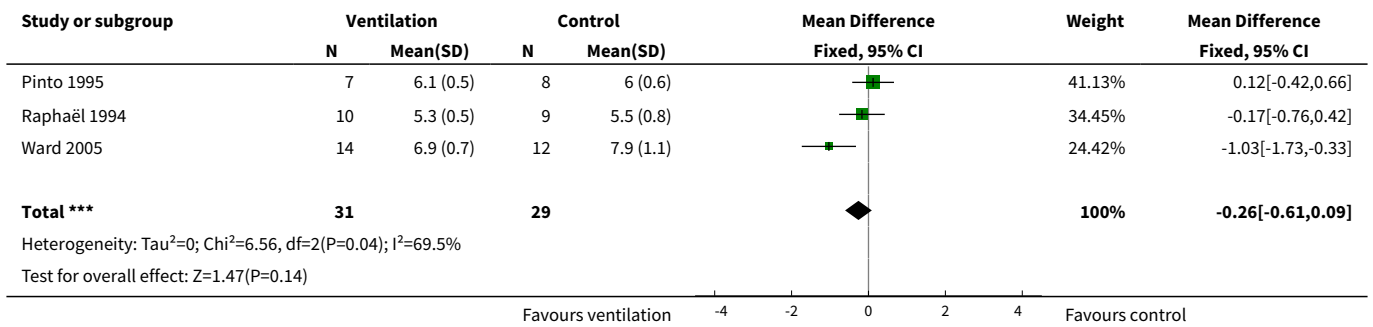
**Analysis 1.4. Comparison 1 Nocturnal ventilation versus no ventilation, Outcome 4 No improvement of daytime hypercapnia: short-term.**



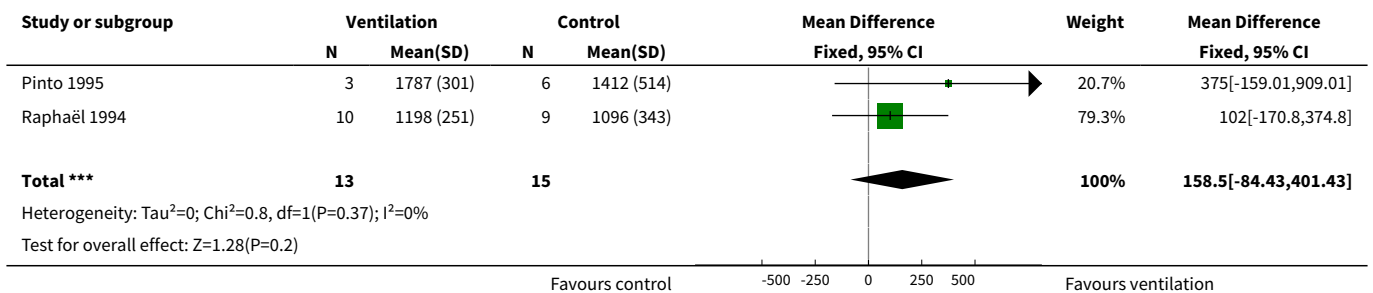
**Analysis 1.5. Comparison 1 Nocturnal ventilation versus no ventilation, Outcome 5 No improvement of daytime hypercapnia: long-term.**



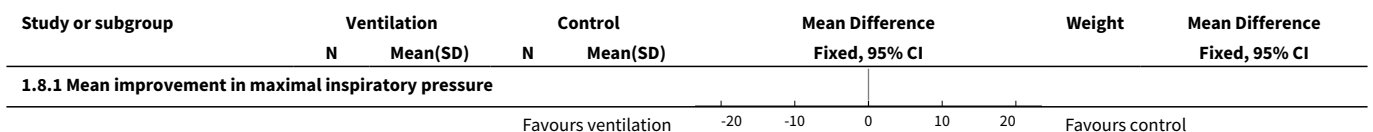
**Analysis 1.6. Comparison 1 Nocturnal ventilation versus no ventilation, Outcome 6 Daytime PaCO<sub>2</sub>: long-term.**

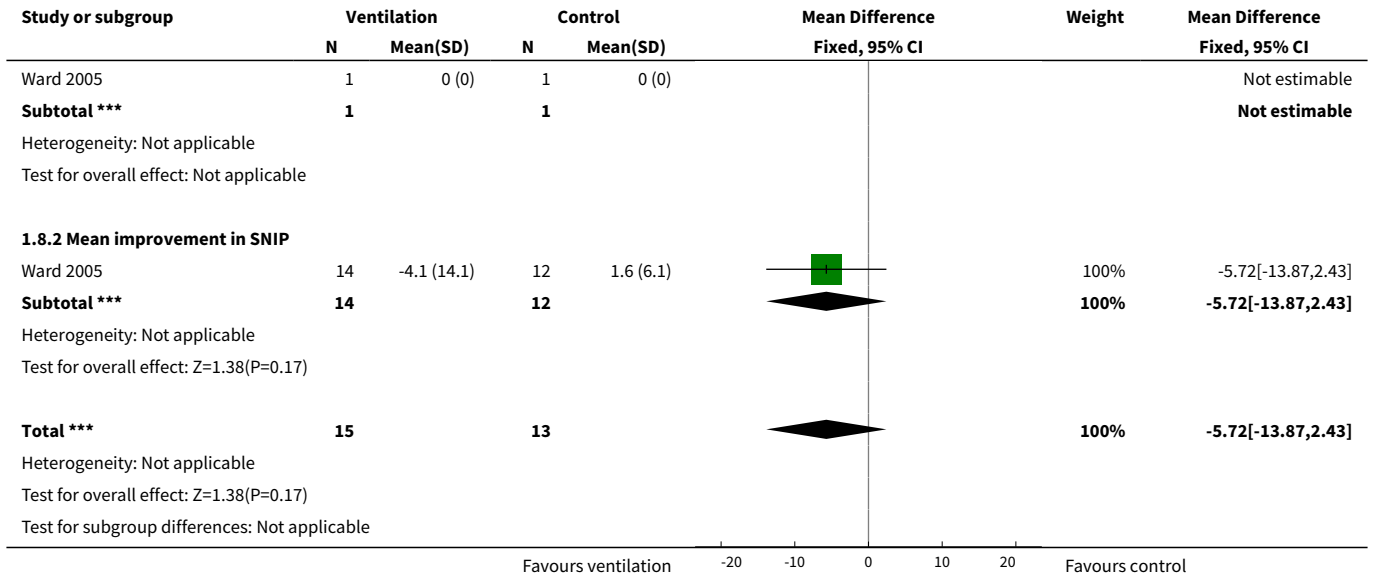


**Analysis 1.7. Comparison 1 Nocturnal ventilation versus no ventilation, Outcome 7 Forced vital capacity: long-term.**

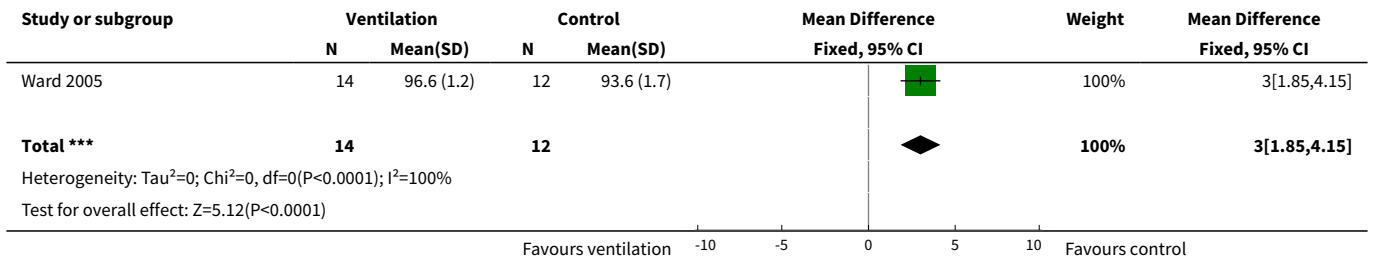


**Analysis 1.8. Comparison 1 Nocturnal ventilation versus no ventilation, Outcome 8 Respiratory muscle strength: long-term.**





**Analysis 1.9. Comparison 1 Nocturnal ventilation versus no ventilation, Outcome 9 Mean nocturnal SaO<sub>2</sub>: long-term.**

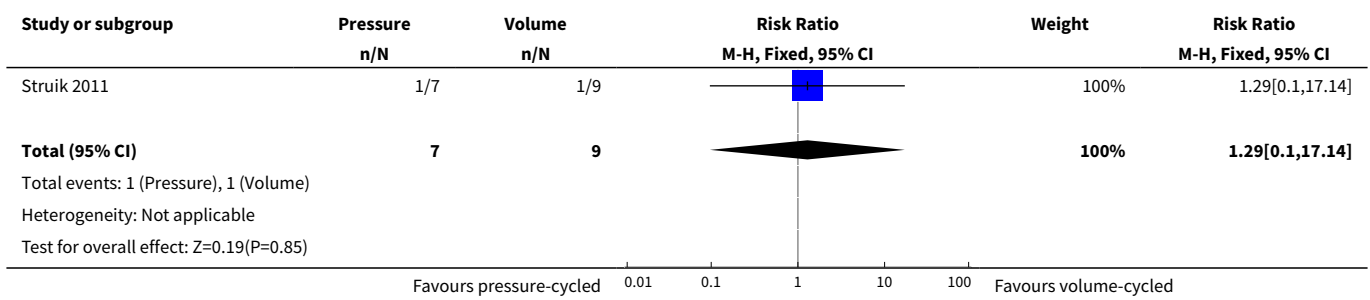


**Comparison 2. Volume-cycled ventilation versus pressure-cycled ventilation**

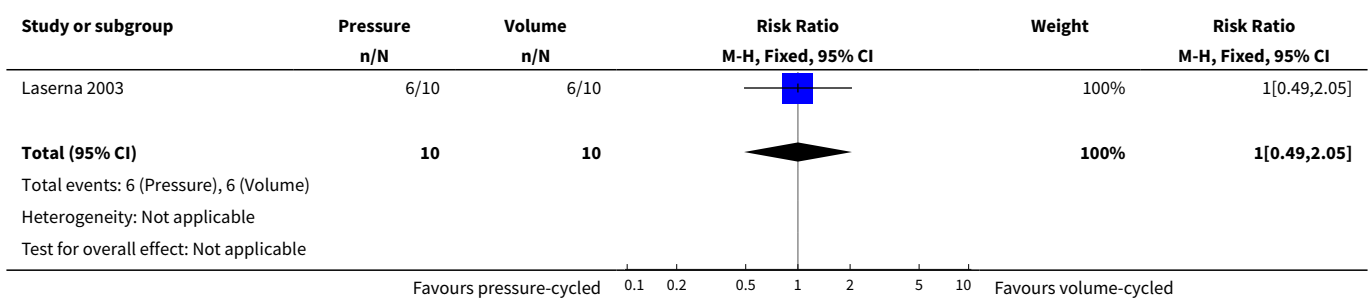
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality at one year (here 3-month data)	1	16	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.10, 17.14]
2 No improvement of daytime hypercapnia: short-term	1	20	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.49, 2.05]
3 Daytime PaCO <sub>2</sub> : short-term	3		Mean Difference (Fixed, 95% CI)	0.45 [-0.21, 1.10]
4 Forced vital capacity: short-term	1		Mean Difference (Fixed, 95% CI)	40.00 [-7.04, 87.04]
5 Respiratory muscles strength	1		Mean Difference (Fixed, 95% CI)	-1.97 [-3.99, 0.04]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Maximal inspiratory pressure	1		Mean Difference (Fixed, 95% CI)	-2.2 [-4.92, 0.52]
5.2 Sniff nasal inspiratory pressure	1		Mean Difference (Fixed, 95% CI)	-1.7 [-4.70, 1.30]
6 Mean nocturnal SaO <sub>2</sub> : short-term	1		Mean Difference (Fixed, 95% CI)	1.2 [-0.70, 3.10]
7 Time spent with nocturnal SaO <sub>2</sub> below 90%: short-term	2		Mean Difference (Fixed, 95% CI)	6.83 [4.68, 8.98]
8 Apnoea-hypopnoea index (/hour): short-term	2		Mean Difference (Fixed, 95% CI)	-0.65 [-0.84, -0.46]

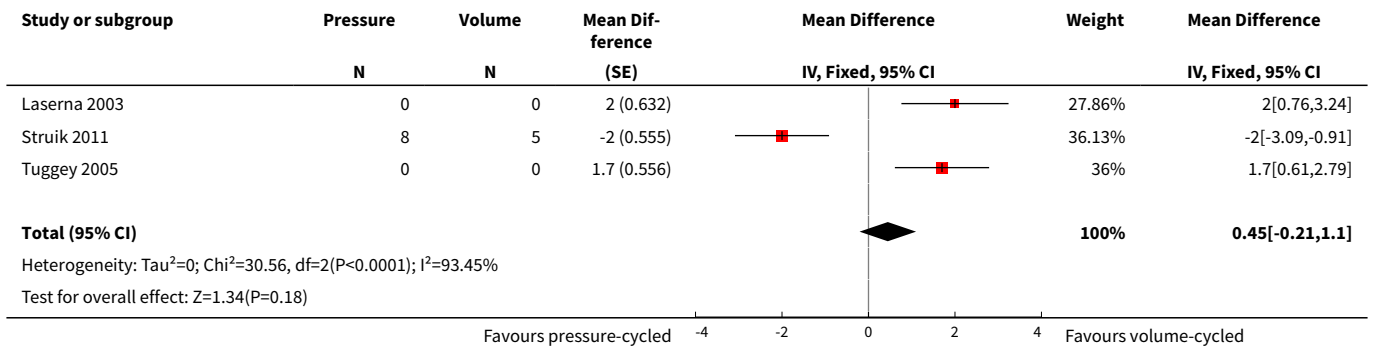
**Analysis 2.1. Comparison 2 Volume-cycled ventilation versus pressure-cycled ventilation, Outcome 1 Mortality at one year (here 3-month data).**



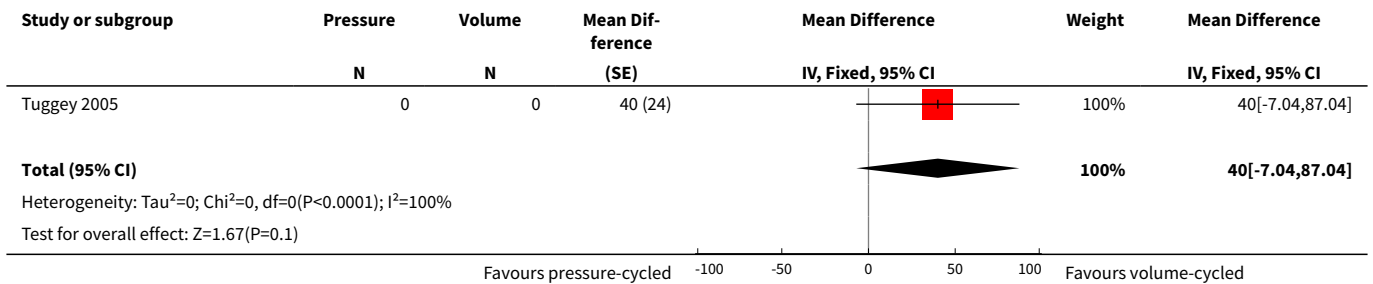
**Analysis 2.2. Comparison 2 Volume-cycled ventilation versus pressure-cycled ventilation, Outcome 2 No improvement of daytime hypercapnia: short-term.**



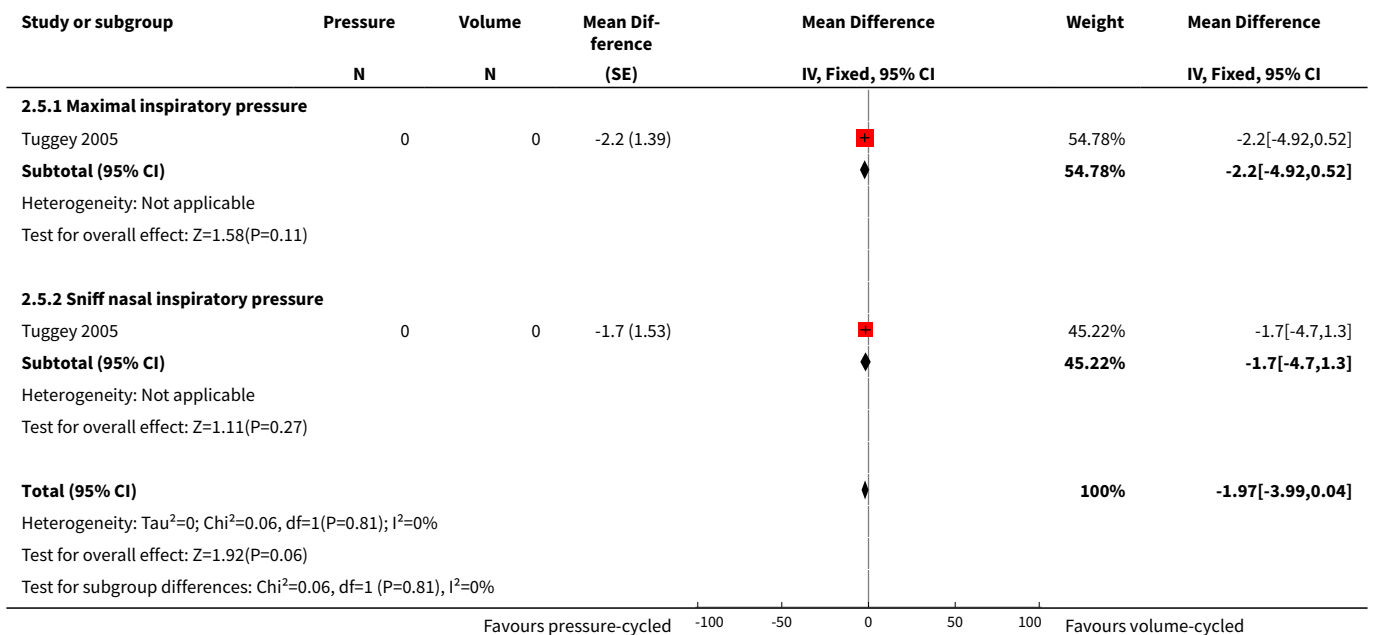
**Analysis 2.3. Comparison 2 Volume-cycled ventilation versus pressure-cycled ventilation, Outcome 3 Daytime PaCO<sub>2</sub>: short-term.**



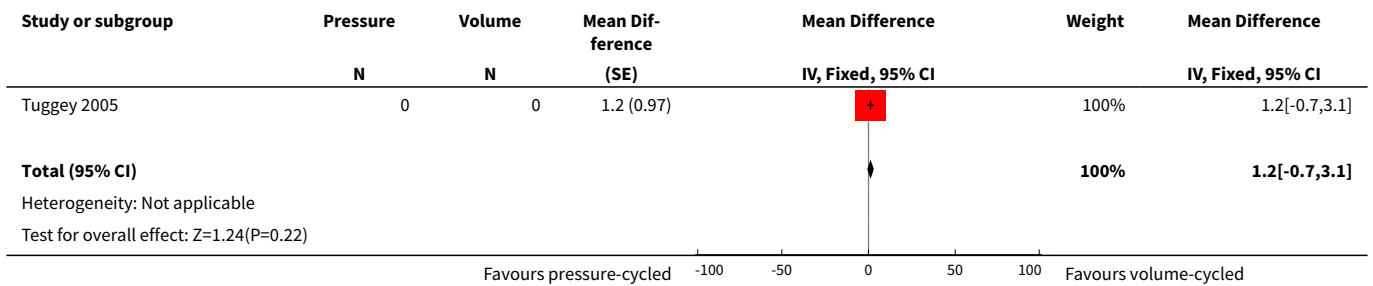
**Analysis 2.4. Comparison 2 Volume-cycled ventilation versus pressure-cycled ventilation, Outcome 4 Forced vital capacity: short-term.**



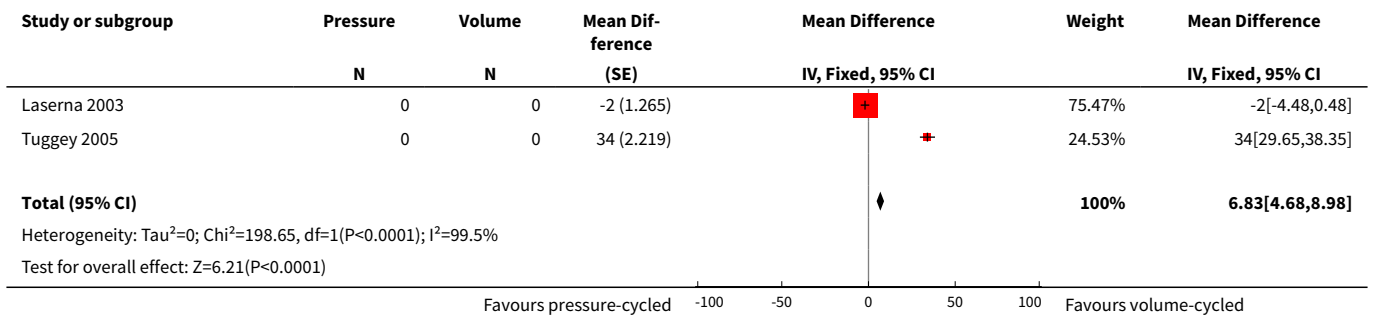
**Analysis 2.5. Comparison 2 Volume-cycled ventilation versus pressure-cycled ventilation, Outcome 5 Respiratory muscles strength.**



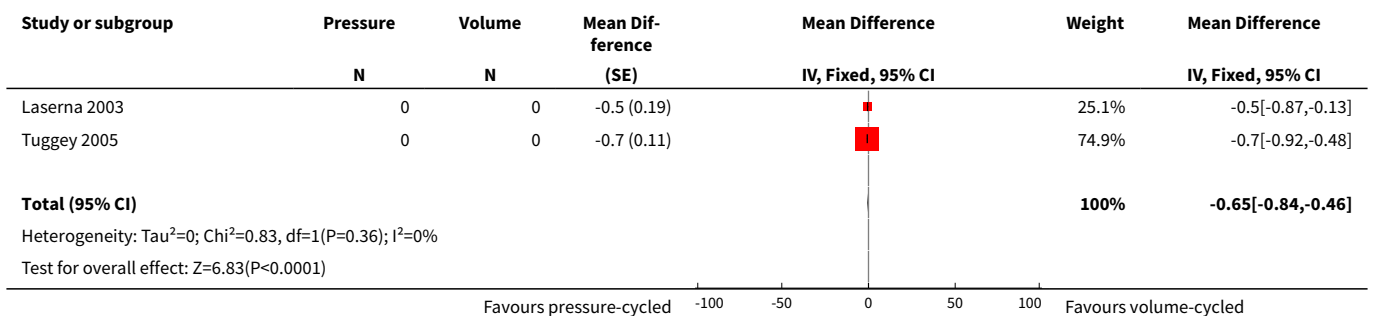
**Analysis 2.6. Comparison 2 Volume-cycled ventilation versus pressure-cycled ventilation, Outcome 6 Mean nocturnal SaO<sub>2</sub>: short-term.**



**Analysis 2.7. Comparison 2 Volume-cycled ventilation versus pressure-cycled ventilation, Outcome 7 Time spent with nocturnal SaO<sub>2</sub> below 90%: short-term.**



**Analysis 2.8. Comparison 2 Volume-cycled ventilation versus pressure-cycled ventilation, Outcome 8 Apnoea-hypopnoea index (/hour): short-term.**



**APPENDICES**

**Appendix 1. NMD Register (CRS) search strategy**

- #1 MeSH DESCRIPTOR Musculoskeletal Diseases Explode All [REFERENCE] [STANDARD]
- #2 MeSH DESCRIPTOR Nervous System Diseases Explode All [REFERENCE] [STANDARD]

#3 "central nervous" or neuromuscular or muscular or motor or musculo\* or musculoskeletal\* or bone\* or "chest wall" [REFERENCE] [STANDARD]  
 #4 #1 or #2 or #3 [REFERENCE] [STANDARD]  
 #5 Hypoventilat\* or ((gas or oxygen\* or "carbon dioxide") and tension\*) [REFERENCE] [STANDARD]  
 #6 (respirat\* or breath\* or ventilat\*) NEAR10 (insufficienc\* or failur\* or deficienc\* or disorder\* or difficult\* or depress\*) [REFERENCE] [STANDARD]  
 #7 #5 or #6 [REFERENCE] [STANDARD]  
 #8 MeSH DESCRIPTOR Ventilators, Mechanical Explode All [REFERENCE] [STANDARD]  
 #9 MeSH DESCRIPTOR Respiration, Artificial Explode All [REFERENCE] [STANDARD]  
 #10 ventilat\* or NIPPV or ((positiv\* or negativ\* or inspirator\*) NEAR10 pressur\*) [REFERENCE] [STANDARD]  
 #11 #8 or #9 or #10 [REFERENCE] [STANDARD]  
 #12 #4 and #7 and #11 [REFERENCE] [STANDARD]  
 #13 (#4 and #7 and #11) AND (INREGISTER) [REFERENCE] [STANDARD]

## Appendix 2. CENTRAL search strategy

#1 MeSH descriptor: [Musculoskeletal Diseases] explode all trees  
 #2 MeSH descriptor: [Nervous System Diseases] explode all trees  
 #3 "central nervous system" or neuromuscular\* or muscul\* or motor or musculoskeletal or bone\* or chest wall  
 #4 #1 or #2 or #3  
 #5 (Hypoventilat\* or ((oxygen\* or carbon dioxid\*) and tensio\*))  
 #6 ((respirat\* or breath\* or ventilat\*) near/10 (insufficienc\* or failur\* or deficienc\* or disorder\* or difficult\* or depress\*))  
 #7 #5 or #6  
 #8 MeSH descriptor: [Ventilators, Mechanical] explode all trees  
 #9 MeSH descriptor: [Respiration, Artificial] this term only  
 #10 ventilat\* or NIPPV or ((positiv\* or negativ\* or inspirator\*) and pressur\*)  
 #11 #8 or #9 or #10  
 #12 #4 and #7 and #11

## Appendix 3. MEDLINE (OvidSP) Search Strategy

Database: Ovid MEDLINE(R) <1946 to May Week 4 2014>

Search strategy:

-----  
 1 randomized controlled trial.pt. (374960)  
 2 controlled clinical trial.pt. (88427)  
 3 randomized.ab. (273382)  
 4 placebo.ab. (146420)  
 5 drug therapy.fs. (1704068)  
 6 randomly.ab. (193925)  
 7 trial.ab. (283482)  
 8 groups.ab. (1246094)  
 9 or/1-8 (3198880)  
 10 exp animals/ not humans.sh. (3947165)

- 11 9 not 10 (2722297)
- 12 exp musculoskeletal diseases/ or exp nervous system diseases/ (2679148)
- 13 (central nervous\$ or neuromuscular\$ or muscul\$ or motor or skelet\$ or musculoskeletal\$ or bone\$ or chest wall\$).mp. (1487938)
- 14 12 or 13 (3617875)
- 15 (Hypoventilat\$ or ((gas\$2 or oxygen\$ or carbon dioxid\$) adj10 tension\$)).mp. (19652)
- 16 ((respirat\$ or breath\$ or ventilat\$) adj10 (insufficienc\$ or failur\$ or deficienc\$ or disorder\$ or difficult\$ or depress\$)).mp. (79973)
- 17 15 or 16 (97242)
- 18 exp Ventilators, Mechanical/ or Respiration, Artificial/ (44530)
- 19 (ventilat\$ or ((positiv\$ or negativ\$ or inspirator\$) and pressur\$) or NIPPV).mp. (213803)
- 20 18 or 19 (225419)
- 21 11 and 14 and 17 and 20 (1592)
- 22 remove duplicates from 21 (1568)

#### Appendix 4. EMBASE (OvidSP) search strategy

Database: EMBASE <1980 to 2014 Week 23>

Search strategy:

- 
- 1 crossover-procedure.sh. (39104)
- 2 double-blind procedure.sh. (113517)
- 3 single-blind procedure.sh. (18341)
- 4 randomized controlled trial.sh. (343012)
- 5 (random\$ or crossover\$ or cross over\$ or placebo\$ or (doubl\$ adj blind\$) or allocat\$).tw,ot. (1030618)
- 6 trial.ti. (157233)
- 7 or/1-6 (1161845)
- 8 (animal/ or nonhuman/ or animal experiment/) and human/ (1263730)
- 9 animal/ or nonanimal/ or animal experiment/ (3217383)
- 10 9 not 8 (2697085)
- 11 7 not 10 (1066806)
- 12 limit 11 to embase (882304)
- 13 exp Motor Dysfunction/ (495826)
- 14 exp musculoskeletal disease/ or exp central nervous system disease/ or exp neuromuscular disease/ or exp neuropathy/ or exp radiculopathy/ (3197454)
- 15 (central nervous\$ or neuromuscular\$ or motor or muscular or muscul\$ skelet\$ or musculoskeletal\$ or bone\$ or chest wall\$ or nocturnal hypoventilation).mp. (1921421)
- 16 or/13-15 (4373364)
- 17 exp Hypoventilation/ (5545)
- 18 ((gas\$2 or oxygen\$ or carbon dioxid\$) adj10 tension\$).mp. (49894)



19 ((respirat\$ or breath\$) adj10 (insufficienc\$ or failur\$ or deficienc\$ or disorder\$ or difficult\$)).mp. (106507)

20 sleep apnoea.mp. (6018)

21 or/17-20 (159898)

22 exp artificial ventilation/ (118120)

23 (ventilat\$ or NIPPV or ((positiv\$ or negativ\$ or inspirator\$) adj10 pressur\$)).mp. (243294)

24 22 or 23 (248409)

25 16 and 21 and 24 (12441)

26 12 and 25 (700)

27 remove duplicates from 26 (698)

## WHAT'S NEW

Date	Event	Description
31 May 2014	New search has been performed	<p>The review has been updated, with inclusion of new trials</p> <p>We have re-arranged the outcomes to move up mortality at one year (or more) to be the primary outcome</p> <p>We have excluded trials that have investigated short-course and short-term effects (from a few minutes to a few nights) as this review aims to summarise the effects of long-term mechanical ventilation</p>
8 August 2013	New citation required but conclusions have not changed	We have included two new trials

## HISTORY

Protocol first published: Issue 1, 1999

Review first published: Issue 1, 2000

Date	Event	Description
20 June 2008	Amended	Converted to new review format.
21 August 2007	New citation required and conclusions have changed	The searches for MEDLINE, EMBASE and the Cochrane Neuro-muscular Disease Group Trials Register were updated in June 2006. Four new trials were identified.

## CONTRIBUTIONS OF AUTHORS

All authors contributed to the design of the protocol for this review. All authors contributed to the search for published and unpublished trials. D Annane and S Chevret were responsible for data extraction and entry onto the computer, and for data analyses. All authors contributed to the interpretation of data and D Annane and S Chevret wrote the final review.

## DECLARATIONS OF INTEREST

D Annane: my group was the co-ordinating centre of a publicly funded multicentre trial of non-invasive ventilation in DMD that has been included in this review (Raphaël 1994), and we are co-ordinating an ongoing, publicly funded, multicentre trial of non-invasive ventilation in adults with myotonic dystrophy type 1.

S Chevret: none known.

D Orlikowski declares the following:

- grants from AFM for a randomised study of non-invasive ventilation in myotonic dystrophy type 1 and from Phillips for a study of Average Volume Assured Pressure Support (AVAPS) in myotonic dystrophy type 1;
- fees from IP Santé à domicile;
- he has acted as a medical referee for Foyer ADEP Evry.

All the activities mentioned are in the field of care and research conducted in neuromuscular diseases and home ventilation.

Outside this work, he received funding from Covidien and from Genzyme to attend the AAN conference 2012.

## SOURCES OF SUPPORT

### Internal sources

- Assistance Publique Hôpitaux de Paris, France.
- University of Versailles SQY, France.

### External sources

- Association Française de lutte contre la Myopathie, France.

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Change in authorship: JC Raphael (deceased) and JC Chevrolet are no longer authors of the review for this update.

We included 'Summary of findings' tables.

We have re-arranged the outcomes to move up mortality at one year (or more) to be the primary outcome.

## INDEX TERMS

### Medical Subject Headings (MeSH)

\*Respiration, Artificial [mortality]; Chronic Disease; Hypoventilation [etiology] [mortality] [\*therapy]; Motor Neuron Disease [complications]; Muscular Dystrophy, Duchenne [complications]; Neuromuscular Diseases [\*complications]; Randomized Controlled Trials as Topic; Sleep; Thoracic Wall [abnormalities]; Time Factors

### MeSH check words

Humans