National Institute for Health and Care Excellence

Final

# Obstructive sleep apnoea/hypopnoea syndrome and obesity hypoventilation syndrome in over 16s

## Evidence review F: Positive airway pressure therapy variants for OSAHS, OHS and COPD–OSAHS overlap syndrome

*NICE guideline NG202*

*Intervention evidence review*

*August 2021*

*Final*

*Developed by the National Guideline Centre, hosted by the Royal College of Physicians*

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# Contents

# 1 Positive airway pressure therapy variants

## 1.1 Review question: What is the comparative clinical and cost effectiveness of different types of positive airway pressure devices (for example, fixed-pressure CPAP, variable-pressure CPAP, bi-level positive airway pressure or other modes of non-invasive ventilation) for managing obstructive sleep apnoea/hypopnoea syndrome (OSAHS), obesity hypoventilation syndrome (OHS) and COPD-OSAHS overlap syndrome?

## 1.2 Introduction

People with significant sleep disordered breathing who suffer from repeated partial or full airway obstruction are often treated with devices that deliver positive airway pressure. This pressure is sufficient to force the relaxed soft tissues and muscles apart, and in doing so splint open the airway. There are a number of benefits, not least that breathing can resume as normal and can greatly improve the quality of sleep. The impact of this is the reduction of excessive sleepiness during waking hours, as well as other health benefits for example, reduced risk of cardiovascular disease and stroke. Some people with disorders such as obesity hypoventilation syndrome or Chronic Obstructive Pulmonary Disease (COPD) alongside Obstructive sleep Apnoea/Hypopnea (COPD-OSAHS overlap syndrome) may also benefit from a device that delivers positive pressure.

Positive airway pressure treatment can be delivered via a number of devices and through the use of fixed, auto or bi-level pressure. The clinical and cost effectiveness of these different forms of positive pressure treatment are compared in this review.

## 1.3 PICO table

For full details see the review protocol in appendix A.

**Table 1: PICO characteristics of review question**

| | |
|---|---|
| **Population** | People (16 and older) with OSAHS, OHS or COPD-OSAHS overlap syndrome<br><br>Population will be stratified by:<br>• OSAHS vs OHS vs COPD-OSAHS overlap syndrome<br>• Mild vs moderate vs severe (based on AHI/ODI) (AHI >5 but <15 = mild,>/= 15 but <30 moderate and AHI >/= 30 severe) |
| **Interventions** | • Fixed pressure (default) CPAP with humidification<br>• Variable pressure CPAP with humidification<br>• Fixed pressure CPAP without humidification<br>• Variable pressure CPAP without humidification<br>• Bi-level positive airway pressure*/ Non-invasive ventilation (NIV) with humidification<br>• Bi-level positive airway pressure*/Non-invasive ventilation (NIV) without humidification |

| | |
|---|---|
| | *Non-invasive ventilation is the preferred terminology |
| **Comparisons** | Compare variable pressure CPAP (with or without humidification) and bilevel positive airway pressure/ Non-invasive ventilation (with or without humidification) with fixed CPAP<br>No positive airway pressure device (for OHS and mild OSAHS only)<br>[Positive pressure airway devices are mandated for use for moderate/severe OSAHS in NICE technology appraisal TA 139. Evidence for CPAP vs no device in mild OSAHS is presented in evidence report E] |
| **Outcomes** | **Critical**<br>• generic or disease specific quality of life measures (continuous)<br>• mortality (dichotomous)<br><br>**Important**<br>• sleepiness scores (continuous, e.g. Epworth)<br>• apnoea-Hypopnoea index (continuous)<br>• oxygen desaturation index (continuous)<br>• $CO_2$ control (continuous)<br>• hours of use (adherence measure, continuous)<br>• minor adverse effects of treatment (rates or dichotomous)<br>• driving outcomes (continuous)<br>• neurocognitive outcomes (continuous)<br>• impact on co-existing conditions:<br>○ HbA1c for diabetes (continuous)<br>○ cardiovascular events for cardiovascular disease (dichotomous)<br>○ systolic blood pressure for hypertension (continuous) |
| **Study design** | • RCTs only<br>• Minimum duration of follow-up 1 months<br>Parallel or crossover to be included |

# 1.4 Clinical evidence

## 1.4.1 Included studies

### OSAHS population

One Cochrane review[110] including 48 RCTs was included in the review. The review included randomised parallel group and crossover trials in people with OSAHS. Studies that compared auto-titrating CPAP (auto-CPAP), or non-invasive ventilation, or the addition of heated humidification to CPAP with fixed level CPAP alone were included. We have not included all studies from the Cochrane review, as the committee agreed that some of the interventions/comparisons were not relevant.

Thirty six studies compared auto-CPAP with fixed level CPAP: [18, 23, 34, 36, 50, 51, 62, 66, 70, 98, 102, 105, 107, 113, 132, 147, 150, 153, 185, 188, 189, 193, 199, 214, 221, 224, 225, 228, 237-239, 253, 254, 257, 260, 265]

Six studies compared bi-level PAP machines with fixed pressure CPAP.[74, 77, 81, 137, 161, 219]

Six studies assessed the addition of humidification to fixed pressure CPAP.[84, 180, 230, 231, 246, 267]

Studies mainly recruited men who were recently diagnosed with OSAHS. The majority of study participants had not used CPAP previously. They had excessive daytime sleepiness

(average ESS at baseline was 13), majority of the studies had people with severe sleep disturbance (AHI range 14.7 to 59.7) and average Body Mass Index of about 35kg/$m^{2.}$ .

The duration of included studies ranged from 2 weeks to 2 years. All evidence was in people with moderate to severe sleep apnoea (AHI >/= 15 but <30 moderate and AHI >/= 30 severe); however the majority of the studies were in people with severe sleep apnoea.

The use of standard CPAP titration protocols was common across the studies. Most were conducted over one or two nights. Extended adaptation protocols which increased the exposure of participants to CPAP devices were undertaken in two studies in order to establish optimal CPAP pressure and comfort prior to formal initiation of treatment (e.g. Bloch 2018; Senn 2003).

Two instruments validated in sleep apnoea research were used for measuring quality of life (SAQLI and FOSQ) either in combination with the Short-form 36 (SF-36) or on their own. For some studies only the SF-36 was used.

There was considerable variation in the methods used to measure tolerability or adverse events. Studies used diary records and interviews to capture effects, and both dichotomous data (did or did not experience the event) or scales to rate problems with mask leak, pressure tolerance, dry mouth and nasal symptoms.

The data reported in the summary of studies, evidence tables, forest plots and exclusion list in this review is from the Cochrane review. The GRADE quality assessments were done by the NGC.

**OHS population**

Nine studies were included in the review;[25, 95, 135, 137, 139, 142, 168, 206, 249] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 4).

Three studies compared non-invasive ventilation (NIV) with lifestyle advice only, 3 studies compared non-invasive ventilation with CPAP, 1 study compared non-invasive ventilation, CPAP and lifestyle advice and 2 studies compared volume assured non-invasive ventilation with fixed non-invasive ventilation.

The data reported in the summary of studies and forest plots is from an unpublished Cochrane review.[40] The GRADE quality assessments, evidence tables and exclusion list were done by the NGC. See also the study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E and GRADE tables in appendix H.

**COPD-OSAHS overlap syndrome**

There was no evidence available people with COPD-OSAHS overlap syndrome.

### 1.4.2 Excluded studies

See the excluded studies list in appendix I.

### 1.4.3 Summary of clinical studies included in the evidence review -OSAHS

**Table 2: Summary of Cochrane review in the evidence review**

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| Kennedy 2019[110]<br>Cochrane review<br><br>48 studies<br><br>Studies conducted in Europe, USA, Hong Kong, New Zealand, Thailand, and Australia | Participants had to be randomised in trials assessing one of the following comparisons:<br>1. Automatically adjusted-CPAP (auto-CPAP including forced oscillation technique) versus fixed CPAP (fixed pressure setting);<br>2. Bi-level PAP/non-invasive ventilation (NIV) versus fixed CPAP;<br>3. Humidification plus CPAP versus fixed CPAP; | N= 2819 (48 studies)<br>Participants were adults of either sex with a diagnosis of OSA, based on history and results of sleep studies.<br><br>The sleep studies were either oximetry studies showing desaturation index (DI) of at least 5 per hour or of respiratory movements and airflow to give an apnoea hypopnoea index (AHI) of at least 5 per hour.<br><br>The populations had similar characteristics across the seven comparisons considered by this review. Average age of the study populations ranged between 49 and 55 and average body mass index was between 32 and 35 kg/m$^2$. Baseline sleep disruption as measured by AHI was severe and ESS scores indicated that the study populations had excessive daytime sleepiness (11 to 16). One study recruited people with co-existing sleep apnoea | **Primary outcomes**<br>Usage of CPAP, measured as initial acceptance, where data were available, and subsequent usage as measured by:<br>• counter output that records the cumulative time that power is turned on to a CPAP machine (this does not provide information on actual time of day and duration of CPAP used each 24-hour period);<br>• microprocessor and monitor that measures the pressure at the mask;<br>• subjective patient reports of the duration of CPAP use.<br>Data for this outcome could be measured as mean differences in hourly use per participant per night or as the number of participants who used machines for more than 4 hours per night.<br><br>**Secondary outcomes**<br>• Withdrawals | Studies that were conducted as short-term laboratory based interventions, since they did not intend to capture the effects of interventions administered on a nightly basis at home. We excluded studies that were less than two weeks in duration because we were primarily interested in the effects of pressure modification in the context of ongoing use of CPAP were excluded from the review.<br><br>Average study duration was between 12 and 16 weeks in studies comparing auto-CPAP, Bi-level PAP/non-invasive ventilation with fixed pressure CPAP. Studies comparing additional humidification with fixed pressure CPAP had shorter average durations (8 and 6 weeks respectively).<br><br>Note:<br><br>We have not included all studies from the Cochrane review as the GC felt that some of the interventions/comparisons were |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | and obesity hypoventilation syndrome (Masa 2015).<br><br>Trials assessing interventions in people with central sleep apnoea and where sleep apnoea was related to sleeping position were excluded from the review. | • Symptom scores, such as the Epworth Sleepiness Scale (ESS), Stanford Sleepiness Score and nasal symptoms.<br>• Quality of life or Health Status, such as the Functional Outcomes of Sleep Questionnaire (FOSQ) and Sleep Association Quality of Life Index (SAQLI) scores. We analysed data from the Short Form 36 but we did not use it as the basis for the Summary of Findings tables<br>• Apnoea hypopnoea index (AHI).<br>• Blood pressure outcomes.<br>• Treatment pressure (for auto-CPAP).<br>• Adverse events.<br>For the comparison of humidification and CPAP versus CPAP alone, nasal symptoms were considered as an additional outcome. This was intended to capture the effects of humidity directly where the mechanism of action is targeted | not relevant. Comparisons not included: CPAP with expiratory pressure relief versus fixed CPAP; Auto bi-level PAP versus fixed CPAP; Auto-flex versus fixed CPAP; Bi-level PAP with pressure relief (ABRP-PAP) versus fixed CPAP;CPAP with expiratory pressure relief triggered on wakefulness versus fixed CPAP.<br><br>Majority of the studies for each comparison was in people with severe OSAHS (based on mean AHI) hence they have been categorised as severe OSAHS. When moderate OSAHS studies were included in this strata we have downgraded the evidence for indirectness. |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| **Auto-CPAP with fixed CPAP –** 36 studies | | | | |
| Berry 2014[18]<br><br>Randomised, open label, parallel group, singe centre trial | Auto-CPAP versus Home PSG CPAP titration over followed by fixed pressure CPAP treatment.<br>Study duration: 6 weeks | N = 156 participants. Age: 59 years; BMI: 36kg/m$^2$; AHI: 28.5 ESS: 14.8.<br><br>Inclusion criteria: AHI ≥ 10/hour; ESS ≥ 8; Living within 200 miles of treatment centre; Age > 18 years<br><br>Exclusion criteria: Previous CPAP therapy; shift work; unstable depression/psychosis; non-adherence with medication; COPD; uncontrolled hypertension or restless legs syndrome; narcolepsy; supplemental oxygen use; congestive heart failure; nightly narcotic use; hypoventilation; neuromuscular weakness; regular sleep of < 4 hours per night; low baseline SaO2; central apnea index > 5/hour. | • Machine usage (average hours used)<br>• Withdrawals<br>• Symptoms (ESS)<br>• Quality of life (FOSQ)<br>• AHI | This study was supported by a research grant from the Res Med Foundation and an unrestricted research grant from Philips Respironics. Both grants were made to the North Florida Foundation for Research and Education.<br><br>Study included in the Cochrane review<br><br>Moderate OSAHS based on mean AHI |
| Bloch 2018[23]<br><br>Randomised, double-blind, parallel group trial | Auto-CPAP v fixed CPAP<br>Study duration: 2 years | N= 208 participants (177 M/31 F). Age 55.5; BMI 32.7kg/m$^2$; AHI 48.4; ESS 13.<br>Inclusion Criteria: Epworth Sleepiness Score > or = 8; | • Machine usage (average hours used)<br>• Symptoms (ESS)<br>• Quality of life (SF-36, FOSQ)<br>• AHI | The study was supported by the Swiss National Science Foundation, the lung leagues of Zurich, St. Gallen and Thurgau and by unconditional grants from the respironics Foundation and resMed Switzerland. This was an |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | AHI > or = 10/hour; Age 18-75.<br>Exclusion Criteria: Psychophysiological incapacity to perform questionnaires, other sleep disorders, psychiatric disease, previous CPAP therapy, previous uvulopalatopharyngoplasty, chronic nasal obstruction, cancer, COPD, with FEV1 < 50% predicted, symptomatic cardiovascular disease, previous stroke, cheyne-Stokes respiration, chronic pain syndromes, fibromyalgia, drug or alcohol addiction | • Blood pressure<br>• Adverse events | investigator initiated trial, and the commercial companies were not involved in study design, data acquisition and analysis or writing the manuscript.<br><br>Study included in the Cochrane review.<br><br>Severe OSAHS based on mean AHI |
| Castronovo 2006[34]<br><br>Randomised, cross-over study. | Auto-CPAP versus fixed CPAP (RemStar machines set in 2 different modes)<br><br>Study duration: 2 x 4 weeks | N = 50 participants. 40 completed and analysed. Age: 53 years. No other baseline details reported. Inclusion criteria: Severe OSA (RDI > 30) | • Machine usage (average hours used)<br>• Symptoms (ESS) | No details available on funding<br><br>Study included in the Cochrane review<br><br>No mean AHI available from Cochrane review |
| Chang 2015[36]<br><br>Prospective, randomised, crossover study. | AutoCPAP versus Fixed CPAP<br>Study duration: 12 weeks | N = 19 participants. M/F 18/1. Age 46.2; BMI 30.2 kg/m$^2$; AHI 59.7; ESS 9.6<br>Inclusion criteria: Age > 20, AHI > 15, consent to wear CPAP.<br>Exclusion criteria: not consenting to positive pressure device, treatment | Machine usage (average hours used & average days used)<br><br>Quality of life (SF36)AHI<br>Treatment pressure | Study included in the Cochrane review<br><br>Severe OSAHS based on mean AHI.<br><br>Funding not declared. |

| Study | Intervention and comparison | Population | Outcomes | Comments |
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| | | for mood disorders such as anxiety and depression. | | |
| Damjanovic 2009[51]<br>Controlled, parallel group trial | 4 groups. Auto adjusting CPAP ± intensive support versus fixed CPAP ± intensive support.<br>Study duration: 9 months | N = 100 participants. Newly diagnosed OSA patients. 78 male and 22 female; mean ±SD age 57±12 yrs; BMI 31±5 kg/m2.<br>Inclusion criteria: AHI>15, with or without corresponding daytime symptoms.<br>Exclusion criteria 1. global respiratory failure 2. central sleep apnoea syndrome 3. severe mental or psychological impairment. | • Machine usage (hours of use & % days used)<br>• AHI<br>• Oxygen desaturation index<br>• Symptoms (ESS) | No information on funding<br>Study included in the Cochrane review.<br><br>Study included in the Cochrane review<br><br>No mean AHI available from Cochrane review. |
| d'Ortho 2000[50]<br><br>Randomised, single-blind, crossover study | Auto-CPAP versus fixed CPAP. No washout period<br>Study duration: 2 x 4 week treatment arms | N (assumed) = 25; 22 M:3 F; mean age 57 (11); mean AHI 57.8 (5.8)<br>Inclusion criteria: OSA confirmed by PSG; AHI > 10/hr; ATS recommended indication for CPAP treatment | • Machine usage (average hours used)<br>• AHI<br>• Symptoms (ESS) | Funded by Institut National de la sante et de la Recherche Medicale & by Nellcor-Puritan Bennett.<br>Study included in the Cochrane review<br>Severe OSAHS based on mean AHI |
| Ficker 2003[62]<br><br>Randomised, parallel group study. | Auto-CPAP (forced oscillation technique) versus fixed CPAP<br>Conference abstract reported 8 weeks duration (Published paper reported 2 nights data from laboratory studies). | N = 100 participants. Mean age: 54.3; BMI: 31.8 kg/m$^2$; AHI: 47.9; ESS: 12.6<br>Inclusion criteria: Diurnal somnolence (>/= 8 on ESS); AHI > 10; written consent<br>Exclusion criteria: Prior CPAP therapy; central sleep apnoea or Cheyne-Stokes | • Machine usage (average hours used)<br>• AHI<br>• Symptoms (ESS)<br>• Quality of life (SF-36) | Funding information not available (conference abstract).<br><br>Study included in the Cochrane review.<br><br>Severe OSAHS based on mean AHI |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | respiration; severe nasal obstruction or other conditions contraindicating CPAP treatment; COPD (FEV1 < 70% predicted); congestive heart failure (NYHA III or IV) | | |
| Fietze 2007[66]<br><br>Randomised, double blind, parallel group study. Participants randomised for 2 night crossover and retained device assigned on second night for subsequent 6 week period. | Auto-CPAP versus fixed pressure CPAP (established by manual titration after 2 night crossover study)<br>Study duration: 6 weeks | N = 21 (20 men and 1 woman) participants. Mean age 54.2; BMI: 30.9 kg/m$^2$. AHI: 41.8. ESS: 12.9<br>Inclusion criteria: AHI >10 or excessive sleepiness (if AHI <10). Participants who did not have excessive sleepiness at baseline also eligible if AHI >20<br>Exclusion criteria: Other sleep disorders (e.g. restless leg syndrome or periodic leg movement syndrome; cardiac, pulmonary or other medical disorders; psychiatric/neurological disorders; abuse of sleep-inducing agents or other drugs; suspected or confirmed central sleep apnea syndrome; prior OSA treatment (e.g. CPAP, oral devices or surgery). | • Machine usage (average hours used)<br>• Symptoms (ESS)<br>• Quality of life (SF 36)<br>• AHI | Funding: 'This study was supported by an unrestricted grant from Respironics Inc.'. No declarations reported from authors.<br><br>Study included in the Cochrane review.<br><br>Severe OSAHS based on mean AHI |
| Galetke 2008[73]<br><br>Randomised, single-blind, | Auto-CPAP versus fixed pressure CPAP | N = 20 participants completed & analysed. Mean | • Machine usage (average hours used)<br>• AHI | Study included in the Cochrane review<br><br>Funding information not provided |

| Study | Intervention and comparison | Population | Outcomes | Comments |
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| crossover study (participants not informed of order/setting) | Same machine delivered the different treatment pressure settings<br>Study duration: 2 x 8 weeks | age: 56 years. AHI: 33; ESS: 10.3<br>Inclusion criteria: New diagnosis of OSA (diagnosis established through polysomnography, AHI > 10)<br>Exclusion criteria: COPD, congestive heart failure and other serious medical disorders | • Symptoms (ESS) | Study included in the Cochrane review<br><br>Severe OSAHS based on mean AHI |
| Hudgel 2000[98]<br><br>Randomised, single-blind, cross-over study. | Auto-CPAP versus fixed CPAP. No washout.<br>Study duration: 2 x 12 week treatment periods | N = 60 (53 with OSA and 7 with Upper Airway Resistance Syndrome (UARS)). 21 withdrawals 2 stopped due to medical complications (not stated) and the rest did not complete the study. Further 6 did not have machine usage data. (21 M/18 F). Total number of OSA patients completing trial is 29. Data analysed for 33 patients which included 4 patients with UARS<br>Mean age: 46 years; AHI 30; BMI: 42 kg/m$^2$<br>Inclusion criteria: Diagnosed OSA or UARS (confirmation by polysomnography)<br>Exclusion criteria: Prior CPAP treatment, facial/pharyngeal abnormalities requiring surgery, chronic airways disease necessitating | • Machine usage (hours of usage, % nights used effectively & % days used)<br>• Symptoms (ESS)<br>• AHI | Funding information not provided<br><br>Included in Cochrane review<br>Severe OSAHS based on mean AHI |

| Study | Intervention and comparison | Population | Outcomes | Comments |
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| | | bronchodilator usage, obesity hypoventilation syndrome, shift workers, congestive heart failure, seizure disorder, mental retardation, sedative/antidepressant/hypnotic treatment | | |
| Hukins 2004[102]<br>Randomised, single-blind, cross-over study. | Auto-CPAP (Autoset T) versus fixed pressure CPAP<br>Study duration: 2 x 8-week treatment periods | N = 55 adults (48M/7F) randomised (46 completed).<br>Age: 50 years; BMI: 35 kg/m$^2$; AHI: 54; ESS: 12.5<br>Inclusion criteria: AHI >/= 5; optimal treatment PSG determined optimal treatment pressure; no previous home use of CPAP<br>Exclusion criteria: Significant comorbidity; complication (e.g. hypercapnic respiratory failure); non-obstructive sleep apnoea; patients unable to use masks with Autoset T machines | • Machine usage (average hours used)<br>• Quality of life (SF-36)<br>• Symptoms (ESS) | This was an industry supported study by ResMed Australia.<br><br>Study included in the Cochrane review<br><br>Severe OSAHS based on mean AHI |
| Hussain 2004[105]<br><br>Randomised, single-blind, crossover study | Auto-CPAP versus fixed CPAP<br>Study duration: 2 x 4-week treatment periods (washout 2 weeks) | N = 10 (10 completed the study). Mean age: 44.98 (SD 9.7); 9M; AHI: 47.2 (SD35.6); BMI: 35.9 kg/m$^2$ (SD 12.9); ESS: 11.1 (SD 6.4)<br>Inclusion criteria: CPAP-naive at baseline; symptomatic OSA (AHI > 15/h) | • Machine usage (average hours used)<br>• Symptoms (ESS)<br>• AHI | This study was funded by Respironics Inc., Murrysville, PA.<br><br>Study included in the Cochrane review<br><br>Severe OSAHS based on mean AHI |

| Study | Intervention and comparison | Population | Outcomes | Comments |
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| | | Exclusion criteria: not described | | |
| Jarvis 2006[107]<br>Randomised, crossover study. | Modified APAP (bi-level pressure mode) versus fixed CPAP<br>Study duration: 2 x 2 weeks | N = 20<br>Inclusion criteria: Diagnosed with obstructive sleep apnoea (OSA); established on CPAP therapy | • Machine usage (average hours used)<br>• AHI | Resmed sponsored the study but no other details were available.<br><br>Study included in the Cochrane review<br><br>mean AHI not available from cochrane review. |
| Kendrick 2001[265]<br><br>Randomised, double-blind, cross-over study | Auto-CPAP versus fixed CPAP<br>Study duration: 2 x 2-week treatment periods | N = 41 (38M/3F). 27 completed the stud. Mean age: 52.4 years; BMI: 32.3 kg/m$^2$; ESS 13.9<br>Eligibility criteria not provided | • Machine usage<br>• Symptoms (ESS)<br>• AHI<br>• Quality of life (SF-36) | Funding information not available (conference abstract).<br><br>Study included in the Cochrane review<br><br>Mean AHI not available from Cochrane review |
| Konermann 1998[113]<br><br>Randomised, single-blind, parallel group study. | Auto-CPAP versus fixed CPAP<br>Study duration: 3 to 6 weeks | N = 50 participants (assumed) (44 M/6F); Age 53.5. No other baseline details available. | • Machine usage (average hours used & week with CPAP use > 4 hours)<br>• AHI | Funding information not provided<br>Sleep study following treatment done between 3 to 6 months<br><br>Study included in the Cochrane review<br><br>Mean AHI not available from Cochrane review |
| Marrone 2004[132]<br><br>Randomised, single-blind, cross-over study. | Auto-CPAP versus fixed CPAP<br>Study duration: 2 x 4 weeks. No washout described | N = 22 participants (21M); mean age 53.45; BMI: 32.9 kg/m$^2$; ESS: 16.3<br>Inclusion criteria: Newly diagnosed OSA; AHI >/= 30<br>Exclusion criteria: Not described | • Machine usage (average hours used, nights used effectively & frequency of use as % days))<br>• Symptoms (ESS) | Funding: 'This study was supported by Air Products Medical GmbH<br><br>Study included in the Cochrane review<br><br>Severe OSAHS based on AHI |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | | | |
| Massie 2003[145]<br><br>Randomised, single-blind, cross-over study. | Auto-CPAP versus fixed CPAP. No washout period.<br>Study duration: 2 x 6-week treatment periods | N = 46 participants (36 M/10 F) 1 drop-out and 1 data unavailable from machine.<br>Mean age: 49; BMI: 32kg/m$^2$<br>Inclusion criteria: 18 to 65 years; symptomatic OSA; AHI > 15; > 10 cm H2O to correct AHI<br>Exclusion criteria: Pre-existing lung disease; awake resting SaO2 < 90%; 10 or more central apneas/hr; patients taking medication considered to interfere with sleep respiration. | • Machine usage (average hours used & % days used)<br>• AHI<br>• Quality of life (SF-36 score reported by domain)<br>• Symptoms (ESS & sleep diary score) | Supported by a grant from ResMed Corporation. One of the authors (Neil Douglas) declared a role as medical advisor to ResMed.<br><br>Study included in the Cochrane review<br><br>Mean AHI not available from Cochrane review |
| Meurice 1996[153]<br><br>Randomised, parallel group study. | Auto-CPAP versus fixed CPAP<br>Study duration: 2 x 3-week treatment periods | N = 16 participants. Mean age: 54; BMI: 34.2 kg/m$^2$; AHI: 43.6; ESS: 14.8<br>Inclusion criteria: Diagnosis of OSA (confirmed by polysomnography; untreated OSA)<br>Exclusion criteria: Not reported | • Machine usage (average hours used)<br>• AHI<br>• Symptoms (ESS) | Funding information not provided.<br><br>Study included in the Cochrane review<br><br>Severe OSAHS based on mean AHI |
| Meurice 2007[150]<br><br>Randomised, multicentre, parallel group trial | Four Auto-CPAP machines assessed:<br>1. GK 418 P, 3.1 version<br>2. AutoSet Spirit, 302 version<br>3. PV 10I, firmware 0.92 version<br>4. Somnosmart 1, 2.02 version | N = 83. Mean age: 56 years; AHI: 52; ESS: 11.5<br>Inclusion criteria: New diagnosis of OSA; CPAP-naive; AHI > 30 | • Machine usage (average hours used)<br>• AHI<br>• Symptoms (ESS)<br>• Quality of life (SF-36) | Study included in the Cochrane review<br><br>Funding information not provided.<br>Study included in the Cochrane review<br><br>Severe OSAHS based on mean AHI |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | All 4 compared against fixed pressure CPAP<br>Study duration: 24 weeks | | | |
| Nolan 2007[185]<br><br>Randomised, single-blind, crossover study | Auto-CPAP versus fixed pressure CPAP<br>Study duration: 2 x 8-week treatment periods | Randomised: 34; Completed: 29. Mean age: 53 years; BMI: 29.9kg/m$^2$; AHI: 14.7; ESS: 12.3<br>Inclusion criteria: Mild to moderate OSA (AHI 5-30)<br>Exclusion criteria: Not reported | • Machine usage (average hours used & % days used)<br>• Symptoms (ESS)<br>• AHI | This was not an industry supported study.<br><br>Study included in the Cochrane review<br><br>Mild OSAHS based on mean AHI |
| Noseda 2004[188]<br>Randomised, single-blind, cross-over study. | Auto-CPAP versus fixed CPAP. Need for pressure assessed over a 14-night run-in period with auto-CPAP.<br>No washout period described<br>Study duration: 2 x 8-week treatment periods | N = 27 participants (23M/4F). Withdrawals: 3. Total completed and analysed N = 24. Mean age: 49 years; BMI: 32.3kg/m$^2$; AHI: 50.9; ESS 10.7<br>Inclusion criteria: AHI > 20/h; MAI: > 30/h; high variability of within night pressure to correct AHI<br>Exclusion criteria: Prior treatment with CPAP; central OSA/Cheyne Stokes; major facial abnormality; night/shift work; severe chronic heart failure/COPD; seizure disorder; mental retardation; sedative, hypnotic or antidepressant therapy; previous UPPP; prolonged hypoventilation during REM | • Machine usage (nights used effectively)<br>• Symptoms (ESS) | Study included in the Cochrane review<br><br>Funding information not provided. Study included in the Cochrane review<br><br>Severe OSAHS based on mean AHI |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| Nussbaumer 2006[189]<br><br>Randomised, crossover study. | Auto-CPAP versus fixed CPAP<br>No washout period described<br>Study duration: 2 x 4-week treatment periods | N = 38 (30 completed the study & contributed to the analysis). 27 M/3F. Mean age: 49 years; BMI: 31kg/m$^2$; ESS: 12.7; AHI: 41.1<br>Inclusion criteria: AHI >10 events/hr<br>Exclusion criteria: CHF; chronic rhinitis; other sleep disorders | • Machine usage (average hours used & % nights used > 4 hours)<br>• Symptoms (ESS)<br>• AHI<br>• Quality of life (SF-36) | Study supported by MADELA AG, distributors of Respironics products in Switzerland'.<br>Study included in the Cochrane review<br><br>Severe OSAHS based on mean AHI |
| Patruno 2007[193]<br><br>Randomised, parallel group trial | Auto-CPAP versus fixed CPAP<br>Study duration: 12 weeks | N = 31 participants (Auto-CPAP: 15; fixed CPAP: 16). Mean age: 48 years; BMI: 36.5kg/m$^2$; AHI: 47; ESS: 15<br>Inclusion criteria: AHI > 20; ESS > 12<br>Exclusion criteria: Not specified | • Machine usage (average hours used)<br>• AHI<br>• Symptoms (ESS)<br>• Blood pressure | This work was supported by a University of Milan Fondo Interuniversitario per la Ricerca Scienfifica e Technologia Grant and a Minister for Instruction, University and Research Progetto di Ricerca di Interesse Nazionale 2003 grant to Dr. Montano.<br><br>Study included in the Cochrane review.<br><br>Severe OSAHS based on mean AHI |
| Pépin 2016[199]<br><br>Single-centre, randomised controlled, double-blind, parallel group trial | Fixed versus auto-adjusting CPAP<br>Study duration: 4 months | N = 322 participants (70% male). Age: 58; BMI: 30kg/m$^2$ AHI: 38.8<br>Inclusion criteria: age: 18 to 80 years, capable of providing written informed consent, patients claiming social insurance and patients with OSA needing CPAP treatment. | • Machine usage (average hours used & N using > 4 hours per night)<br>• Blood pressure<br>• Quality of life (SF-36) | The study was funded by the 'Fondation Agir pour les maladies chroniques'. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.'<br><br>Study included in the Cochrane review. |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | Exclusion criteria: cardiac failure known and treated, central Apnea syndrome, patients who stopped CPAP treatment in the previous year, pregnancy, patients under guardianship, imprisoned patients, patients in hospital, patients included in another clinical study. | | Severe OSAHS based on mean AHI. |
| Randerath 2001[214]<br><br>Randomised, cross-over study. | Auto-CPAP versus fixed CPAP. No washout.<br>Study duration: 2 x 6-week treatment periods<br>24- hour telephone helpline was at the disposal of the participants. | N = 52. (45 M/7 F). Mean age: 54.7 years; BMI: 32.4 kg/m$^2$; AHI 35.1<br>Inclusion criteria: Confirmed OSA by polysomnography<br>Exclusion criteria: Prior treatment with CPAP | • Machine usage (average hours used)<br>• AHI | 'The devices were supplied by the Weinmann Company, Hamburg, Germany.'<br><br>Study included in the Cochrane review<br>Severe OSAHS based on mean AHI |
| Resta 2004[221]<br><br>Randomised, parallel group trial. Single-blinded study | Auto-CPAP versus fixed pressure CPAP. CPAP titration undertaken manually in sleep laboratory<br>Study duration: 4 weeks | N = 20 participants (18 M/2 F). Mean age: 47 years; BMI: 37 kg/m$^2$; ESS: 14<br>Inclusion criteria: Untreated OSA; PSG-confirmed diagnosis of OSA (ASDA criteria)<br>Exclusion criteria: Not reported | • Machine usage<br>• ESS<br>• AHI | Funding information not provided<br><br>Study included in the Cochrane review<br><br>Mean AHI not available from Cochrane review |
| Rochford 2006[224]<br><br>Randomised, cross-over study<br>Statistical analysis: information not available | Auto-CPAP (Autoset Spirit, ResMed) versus fixed CPAP<br>Auto-CPAP (APAP, Compumedics) versus fixed CPAP<br>Study duration: 3 x 4-week duration. 2-week washout | N = 13 participants. Mean age: 48.2 years; AHI: 22.5; ESS: 11.2<br>Inclusion criteria: Newly diagnosed OSA patients<br>Exclusion criteria: Not reported | • Machine usage (average hours used)<br>• Symptoms (ESS)<br>• AHI<br>• Quality of life (FOSQ) | Funding information not available (conference abstract).<br><br>Study included in the Cochrane review |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | | | Moderate OSAHS based on mean AHI |
| Rohling 2011[225]<br>Single-blind, randomised, cross-over trial | Pressure restricted auto-adapting CPAP versus fixed CPAP.<br>Study duration 2 x 12 weeks | N = 33 participants. Mean age: 52; BMI: 30.6 kg/m$^2$; AHI: 35; ESS: 7.5<br>Inclusion Criteria: Age > 18 years, CPAP naive with diagnosis of OSA, understand Dutch language, AHI > 15 events per hour with mild sleepiness or AHI > 5 events/hour with moderate/severe sleepiness.<br>Exclusion Criteria: Central Sleep Apnoea, Cheyne-Stoke Respiration, severe nasal obstruction, facial/pharyngeal abnormalities, shift work, psychiatric disorder, heart failure, COPD, seizure disorder, pregnancy, learning disability. | • Symptoms (ESS)<br>• AHI | Funding information not available (conference abstract)<br><br>Study included in the Cochrane review.<br><br>Severe OSAHS based on mean AHI |
| Rostig 2003[228]<br><br>Randomised, cross-over study. | Auto-CPAP (AutoSet T) versus fixed pressure CPAP<br>Study duration: 2 x 4-week treatment periods | N = 30. No baseline details provided.<br>Participants were on long-term CPAP for OSA, but were using it for less than 4 hours per night. | • Machine usage (average hours used)<br>• AHI | Funding information not available (conference abstract).<br><br>Study included in the Cochrane review<br><br>Mean AHI not available from Cochran review |
| Senn 2003[237] | AutoCPAP (DeVilbiss - response to apnoeas and snoring) & AutoSet T - response to apnoea and | N = 31. Withdrawals: N = 2. 23 M/6 F. Mean age: 53 years; BMI: 33.3 kg/m$^2$; AHI: 45.8; ESS: 14.2 | • Machine usage (average hours used) | 'Supported by the Lung League of Zurich, Lung League of Schaffhausen, Lamprecht AG & Labhardt AG'. |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| Randomised, cross-over study. Method of randomisation not reported.<br><br>. | snoring + flow limitation) versus fixed pressure CPAP<br>Study duration: 2-week run-in with either auto-CPAP device. 3 x 4 week treatment periods. | Inclusion criteria: AHI > 10 per/hour; CPAP-naive | • Quality of life (SF-36: Vitality subdomain)<br>• Symptoms (ESS)<br>• AHI | Study included in the Cochrane review<br><br>Severe OSAHS based on mean AHI |
| Sériès 1997[238]<br><br>Randomised, single-blind, parallel group study | Auto-CPAP 1 (measured effective pressure based upon polysomnography) versus Auto-CPAP 2 (effective pressure estimated by pre-specified formula) versus fixed CPAP.<br>Data entered from Auto-CPAP 1.<br>Study duration: 3 weeks | N = 36. 12 in each group. No drop-outs. Age range 36 to 65; AHI: 43.6; ESS: 15.5<br>Inclusion criteria: OSA confirmed by polysomnography and by clinical features; participants chosen to be treated by CPAP<br>Exclusion criteria: Life threatening OSA (severe hypersomnolence); OSA associated with non-obstructive breathing disorders (narcolepsy); estimated pressure < 15 cm2 H2O. All participants were recruited from the Hôpital Laval sleep clinic | • Machine usage (average hours used & N participants using machine for > 4 hours)<br>• Sleep architecture<br>• AHI<br>• Symptoms (ESS)<br>• Withdrawals | Funded in part by Pierre Medical France.<br>Study included in the Cochrane review<br><br>Severe OSAHS based on mean AHI |
| Sériès 2001[239]<br><br>Randomised, parallel group trial | Auto-CPAP (Morphée) versus fixed CPAP<br>Study duration: 3 weeks | N = 48. 40 had previously participated in other trials of auto and fixed CPAP. Mean age: 48; BMI: 39.5kg/$m^2$<br>Inclusion criteria: PSG-diagnosed OSA<br>Exclusion criteria: Corrective surgery for OSA | • Machine use (average hours used)<br>• Symptoms (ESS)<br>• AHI<br>• Withdrawals | Funding information not provided.<br><br>Study included in the Cochrane review<br><br>Mean AHI not available from Cochrane review |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| Teschler 2000[253]<br>Randomised, double-blind, crossover study | Auto-CPAP versus fixed CPAP.<br>No washout period.<br>Study duration: 2 x 8-week treatment periods | N = 10 participants (10 M).<br>Mean age 52 years; AHI 52.9<br>Inclusion criteria: > 20 AHI, residence < 50 km from clinic and newly diagnosed with OSA<br>Exclusion criteria: Co-existing airways disease (asthma/COPD), rhinitis or cardiac failure | • Machine usage (average hours used & % days CPAP used)<br>• AHI | Funding information not provided.<br><br>Study included in the Cochrane review<br><br>Severe OSAHS based on mean AHI |
| To 2008[254]<br><br>Randomised, crossover study. | Auto-CPAP versus fixed CPAP<br>Study duration: 2 x 8 weeks (washout: 1 week) | N = 43 (2 lost to follow up).<br>BMI: 28.7 kg/m$^2$; AHI: 54.3; ESS: 13.4<br>Inclusion criteria: 18 to 65 years; newly diagnosed OSA (AHI > 30)<br>Exclusion criteria: prior treatment for OSA | • Machine usage (average hours used)<br>• Symptoms (ESS)<br>• AHI<br>• Quality of life (SAQLI) | The authors declared no conflict of interest between ResMed Company and the participating institutions, which received no external funding support for this study.'<br><br>Study included in the Cochrane review.<br><br>Severe OSAHS based on mean AHI |
| Vennelle 2010[257]<br>Randomised, blinded, cross-over trial. | Fixed pressure versus variable pressure CPAP<br>Study duration: 2 x 6 weeks | N=200. (46 F). Mean age 50; BMI 34.5 kg/m$^2$; AHI: 33; ESS 14<br>Inclusion criteria: ESS > 10 or sleepiness while driving; AHI > 15 on PSG or > 25 apnoeas / hypopneas per hour on limited sleep study; age 18 to 75; CPAP naive.<br>Exclusion criteria: neurological deficit compromising CPAP use; significant co-morbidity; co- | • Machine usage (average hours used)<br>• Symptoms (ESS)<br>• QoL (SF-36)<br>• Withdrawals | This study was supported by a grant from ResMed, Poway, CA. Dr. Douglas is a shareholder in ResMed.<br><br>Study included in the Cochrane review<br><br>Severe OSAHS based on mean AHI |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | existing narcolepsy / periodic limb movements; contraindication to CPAP | | |
| West 2006[261]<br>Randomised, parallel group trial. | Auto-CPAP versus algorithm established fixed CPAP<br>Additional treatment group not considered for this review: 1 week auto-titration followed by fixed pressure at the level of 95th centile pressure from the auto-CPAP week data.<br>Study duration: 24 weeks | N = 98. (N considered for this review: 65). Mean age: 47; ESS: 16;<br>Inclusion criteria: 18 to 75 years of age; ESS > 9; proven OSA (PSG); 10 dips/hr in arterial O2 saturation; CPAP-naive<br>Exclusion criteria: Respiratory failure requiring urgent treatment; unable to give written consent<br>Participants were not excluded on the basis of co-morbidities | • Machine usage (average hours used)<br>• Symptoms (ESS)<br>• Quality of life (SF-36 & SAQLI)<br>• AHI<br>• Withdrawals | ResMed UK provided part financial support for the purchase of CPAP machines for the study but was not involved in its design or analysis.<br><br>Study included in the Cochrane review<br><br>Mean AHI not available from Cochrane review. |
| **Bi-level PAP/Non-invasive ventilation machines with fixed pressure CPAP – 6 studies** | | | | |
| Gay 2003[74]<br><br>Randomised, double-blind, parallel group trial. | Bi-level PAP (non-invasive ventilation) versus CPAP. Participants also given instruction via educational video on CPAP and OSA.<br>Study duration: 30 days | N = 27 participants. Age: 44 years; BMI: 35kg/m$^2$; AHI: 43; ESS: 13.8<br>Inclusion criteria: > 18 years; AHI > 10 and < 100; ability to follow instructions and provide informed consent; willingness to return for follow-up visit 30 days after random allocation to CPAP/BiPAP (non-invasive ventilation); residence within 200 miles of clinic<br>Exclusion criteria: inability to wear a mask; prior surgical treatment for OSA; prior | • Machine usage (average hours used)<br>• Symptoms (ESS)<br>• AHI<br>• Quality of life (FOSQ) | Dr. Peter Gay received grant support for this study by Respironics Inc. (noted in manuscript).'<br><br>Study included in the Cochrane review<br><br>Severe OSAHS based on mean AHI |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | CPAP usage; other significant co-morbidities | | |
| Gonzalez-Moro 2005[77]<br><br>Randomised parallel group study. | BiPAP (non-invasive ventilation) versus fixed pressure CPAP<br>Study duration: 12 weeks | N = 20; ESS: 12. No other baseline details provided<br>Inclusion criteria: OSA and obstructive hyperventilation syndrome<br>Exclusion criteria: Not reported | • Symptoms (ESS)<br>• Blood gases (PaO2 & PaCO2) | Funding information not available (conference abstract)<br>Unpublished conference abstract.<br><br>Study included in the Cochrane review<br><br>Mean AHI not available from Cochrane review |
| Gulati 2015[81]<br><br>Prospective, randomized, crossover study in patients who were sub optimally compliant with CPAP despite appropriate interventions | BiPAP (non-invasive ventilation) vs new CPAP (brand of fixed CPAP different from the one used prior to study entry)<br>Study duration: 2 x 4 weeks with 2 weeks washout in-between | N = 28 participants (24M/4F). Mean Age 56.7 years; BMI 35 kg/$m^2$; ESS 13.2; AHI 35<br>Inclusion criteria: OSA with AHI > 5, CPAP compliance < 4 hours per night for 6 weeks after CPAP prescription despite technical and educational interventions, symptoms of pressure intolerance.<br>Exclusion criteria: Significant airflow obstruction (FEV1/FVC < 60%), pre-treatment study showing central sleep apnoea, clinical evidence of congestive heart failure, daytime hypercapnia ($PaCO_2$ > 6.5kPa) or previous prescription of BiPAP. | • Machine usage (average hours used)<br>• Symptoms (ESS)<br>• Quality of life (SAQLI)<br>• AHI | Funding source: not declared.<br><br>Study included in the Cochrane review<br><br>Severe OSAHS based on mean AHI |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| Masa 2015[137]<br><br>Randomised, three-arm, parallel group | Fixed CPAP versus Non-invasive ventilation treatment set at bilevel pressure with assured volume. Study assigned to Bi-level PAP comparison. Supplemental oxygen offered if participants met additional criteria (daytime PaO2 < 55 mm Hg, with the necessary flow to maintain waking arterial oxygen saturation between 88 and 92% or PaO2 greater than or equal to 55 mm Hg for at least 17 h/d).<br>Third treatment arm consisting of a usual care control was not of interest to this review.<br>Study duration: 3 years (for hospitalisation & withdrawal outcomes). Other outcome data reported at 8 weeks unless stated. | N = 151 participants (entered in to treatment groups relevant to this review question). 66m/ 85f Age: 60 years; BMI: 44 kg/m$^2$; AHI: 69; ESS: 11.<br>Inclusion criteria: 15-80 years; AHI: >30; no other significant sleep disorders (e.g. narcolepsy or restless leg syndrome); correctly executed 30-minute CPAP/NIV test<br>Exclusion criteria: Significant comorbidity | • Machine usage (average hours used)<br>• Blood gas (PaCO2 at 3 months)<br>• Quality of life (FOSQ)<br>• Symptoms (ESS)<br>• AHI<br>• Adverse events | Supported by the Instituto de Salud Carlos III (Fondo de Investigaciones Sanitarias, Ministerio de Sanidad y Consumo) grant PI050402, the Spanish Respiratory Foundation 2005 (FEPAR), and Air Liquide Spain'. Funders did not participate in the design or conduct of the study, analysis or interpretation of data, or manuscript preparation.<br><br>Study included in the Cochrane review<br><br>Severe OSAHS based on mean AHI |
| Muir 1998[161]<br><br>Randomised, double-blind, crossover study. | Bi-level PAP (non-invasive ventilation) versus fixed CPAP<br>Study duration: 2 x 8-week treatment periods<br>Pressure levels for inspiratory pressure were: 12.3 cm H2O (SD 1.8), and expiratory pressure: 7.6 cm H2O (SD 2.2) for bilevel PAP treatment, and for fixed CPAP: 9.4 cm H2O (SD 2.3) (no P value reported) | N = 16 participants. Mean age: 59 years; BMI: 31kg/m$^2$; AHI: 69<br>Inclusion criteria: previously documented OSA and poor compliance with CPAP (< 3 hours per night) | • Machine usage<br>• Adverse events | Funding information not available (conference abstract)<br><br>Study published as conference abstract.<br><br>Study included in the Cochrane review<br><br>Severe OSAHS based on mean AHI |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| Reeves-Hoché 1995[219]<br><br>Randomised, parallel group trial | Bi-level Positive Airways Pressure (non-invasive ventilation) versus Continuous Positive Airways Pressure administered at home<br>Study duration: 52 weeks<br>Prescribed inspiratory pressure was 11 mmHg ± 0.3 and expiratory pressure was 7 mmHg ± 0.3 in the BiPAP group versus 10 mm Hg ± 0.2 in the fixed CPAP group at baseline | N = 83, 17 Females (out of 62 completers). Mean age: 47; BMI: 40kg/m$^{2;}$ AHI: 51<br>Inclusion criteria: OSA diagnosed according to American Sleep Disorders Association AHI >10; "heavy snoring"; excessive daytime sleepiness<br>Exclusion criteria: Concomitant illness requiring hospitalisation 6 months previously; psychiatric illness; pregnancy. | • Machine usage<br>• Withdrawals | Supported in part by Respironics'.<br><br>Study included in the Cochrane review<br><br>Severe OSAHS based on mean AHI |
| **humidification to fixed level CPAP** | | | | |
| Heiser 2010[84]<br>Randomised, parallel group study | CPAP with warm air humidifier versus CPAP without warm air humidifier<br>Study duration: 12 weeks | N = 74 participants (M/F 60/14). Mean age 58 years; BMI 31 kg/m$^2$; AHI 35; ESS 9<br>Inclusion criteria: Newly diagnosed OSA patients (AHI > 15 on polysomnography). | • Machine Usage (average hours used)<br>• Symptoms (ESS)<br>• Withdrawals | Funding source: Study was funded by manufacturers ('Diese Studie wurde finanziell unterstützt durch die Firmen Fisher & Paykel Healthcare und Air Products Medical GmbH.)<br><br>Study included in the Cochrane review<br><br>Severe OSAHS based on mean AHI |
| Neill 2003[180]<br>Randomised, double-blind, crossover study. | Humidification in addition to nasal CPAP versus sham humidifier in addition to nasal CPAP<br>Study duration: 2 x 3-week treatment periods (3 day washout) | N = 42 randomised (37 completed study protocol and were analysed). Mean age: 49 years. BMI: 35kg/m$^2$; RDI: 50; ESS: 12.1<br>Inclusion criteria: Newly diagnosed OSA requiring treatment with CPAP | • Machine usage (average hours used)<br>• ESS | This study was funded by an Otago University Research Grant.'<br><br>Study included in the Cochrane review<br><br>Severe OSAHS based on mean AHI |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | Exclusion criteria: Significant nasal obstruction; requirement for supplemental oxygen | | |
| Worsnop 2010[267]<br><br>Randomised, parallel group study | Fixed pressure CPAP + humidification versus fixed pressure CPAP alone<br>Study duration: 12 weeks | N = 54 participants. Mean age 55 years; AHI 46. ESS 14<br>Consecutive OSA patients referred for CPAP, under a program paid for by the Victorian State government, were enrolled. | • Machine usage (average hours used)<br>• Quality of life (SF-36)<br>• Symptoms ESS | Fisher and Paykel Healthcare, Auckland, New Zealand funded this study.<br><br>Study included in the Cochrane review.<br><br>Severe OSAHS based on mean AHI |
| Ruhle 2011[230]<br><br>Randomised, cross-over study | CPAP with heated humidification versus CPAP without heated humidification<br>Study duration: 2 x 4 weeks | N = 51 participants. Age 51.5; BMI: 30.9 kg/m$^2$; AHI: 43; ESS 10.3<br>Inclusion criteria: all patients referred with OSA, aged between 30 and 80 and without nasal or throat complaints<br>Exclusion criteria: >5 central apneas per hour of sleep, acute infection, NYHA III or IV heart failure, acute pulmonary embolism or acute coronary syndrome. Previous use of CPAP | • Machine usage (average hours used) | K-H. Ruhle and G. Nilius received research funding from Fisher & Paykel Healthcare, Heinen und Löwenstein, ResMed and Weinmann. The author's study was supported by a grant from Fisher & Paykel Healthcare Germany GmbH & Co. KG, 73636 Welzheim, Germany. with this investigation.'<br><br>Study included in the Cochrane review.<br><br>Severe OSAHS based on mean AHI. |
| Ryan 2009[231]<br><br>Randomised, parallel group trial | Standard (dry) CPAP versus CPAP with heated humidification versus CPAP with nasal steroid spray<br>Study duration: 4 weeks | N = 125 participants consecutively recruited from Respiratory Sleep Disorders Unit. Age: 48; BMI: 35 kg/m$^2$; AHI: 36; ESS: 12.5 | • Machine usage (average hours used & % nights used)<br>• Quality of life (SF-36)<br>• Symptoms (ESS) | 'This was not an industry supported study.<br><br>Study included in the Cochrane review |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | Inclusion criteria: AHI ≥ 10, CPAP naive, successful nasal CPAP titration study, adequate nasal breathing. Exclusion criteria: BiPAP or supplemental oxygen; malignant disease; psychiatric disease; regular use of narcotics; sedatives or psychoactive substances. | | Severe OSAHS based on mean AHI |
| Soudorn 2016[246] Prospective, single blinded, randomised, crossover study in climate with a high humidity level | CPAP with heated humidification versus conventional CPAP alone Study duration: 2 x 4 weeks | N = 20. (M/F 14/6). Mean age 48.9 years; BMI 28.1 kg/m$^2$; AHI 53.7; ESS 11.5 Inclusion criteria: Age > 18 years; AHI > 15 on split-night polysomnogarphy; nasopharyngeal symptoms according to modified XERO questionnaire. Exclusion Criteria: > 5 central apnoeas per hour; acute infection; heart failure with NYHA class 3 or 4; acute pulmonary embolus; acute coronary syndrome; travel outside of Thailand within 2 months of study baseline pattern of split-night PSG < 2 hours, less than optimal CPAP titration, use of humidification during split-night study | • Machine usage (average hours used)<br>• AHI<br>• Symptoms (ESS)<br>• Quality of life (FOSQ) | 'This work was supported by the Ratchadaphiseksomphot Endowment Fund of Chulalongkorn University. All CPAP machines and related equipment were sponsored by Fisher and Paykel Healthcare Limited.<br><br>Study included in the Cochrane review<br><br>Severe OSAHS based on mean AHI |

### 1.4.4 Summary of clinical studies included in the evidence review –OHS population

**Table 3: Summary of studies included in the evidence review**

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| Borel 2012[25]<br>France<br>RCT | Non-invasive Ventilation (NIV)<br>n = 19<br>Initiated over 3-4 nights in respiratory ward<br><br>Lifestyle advice<br>n = 18<br>1 hour education session, focused on general health risks of OSA and obesity, given dietary and lifestyle counselling by specialist nurse including recommendations for a healthier diet and more exercise | People with OHS and baseline AHI mean in severe OSAHS category (~48)<br><br>Mean age, (SD): 56 (7)<br><br>Entry criteria – $CO_2$ > 5.7kPa. Mean $PaCO_2$ in the NIV group 6.4±0.6kPa. Lifestyle group 6.0±0.4kPa. Recruited from newspaper ads or patients visiting clinic.<br><br>All-comers -OSA and non-OSA<br>Stable patients<br>Very modest hypercapnia<br>NIV patients were more hypercapnic at baseline. | • Epworth<br>• AHI<br>• PaCO2<br>• Pa02<br>• AHI<br>• SBP<br>• HbA1c<br><br>1 month follow-up | High risk of bias due to lack of blinding, allocation concealment |
| Howard 2017[95]<br>Australia<br>RCT | Non-invasive ventilation (NIV)<br>n = 29<br>Bi-level PAP with spontaneous timed mode of ventilatory support | People with newly diagnosed severe OHS | • QoL (SF-36)<br>• Disease specific QoL (SRI) -Severe Respiratory | Low risk of bias |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | CPAP<br>n = 31<br>Fixed pressure | Participants with a primary diagnosis of OHS (body mass index<br>(BMI) over 30 kg/m$^2$ and daytime PaCO2 >45 mm Hg) were<br>recruited<br><br>Mean age, (SD): 53 (10)<br><br>Mean age was<br>53 years (SD 10), BMI 54.9 kg/m$^2$ (SD 11.9) and PaCO2<br>59.6 mm Hg (SD 13.8)<br><br>On diagnostic polysomnography (n=47, 22 in Bi-level PAP and<br>25 in CPAP groups), mean apnoea hypopnoea index was 82<br>events per hour (SD 45.1) with oxygen saturation <90% for<br>67% (SD 31.4%) of sleep (no difference between groups). | Insufficiency Questionnaire:<br>• Epworth<br>• Adherence (h/night)<br>• Systolic BP<br><br>3 month follow-up | |
| Masa 2015[137]<br>Spain<br>RCT | Non-invasive ventilation (NIV)<br>n = 71<br>Lifestyle and oxygen as below plus NIV at bilevel pressure with assured volume | People with OHS and severe OSAHS<br><br>Mean age, (SD): 60 (13) | • QoL<br>• Disease specific QoL (FOSQ)<br>• Epworth<br>• AHI<br>• ODI | High risk of bias for subjective items due to lack of blinding, low risk of bias for objective outcomes |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | CPAP<br>n = 80<br>Lifestyle and oxygen as below plus at home fixed CPAP during entire period<br><br>Lifestyle<br>n = 70<br>1,000 calorie diet, maintenance of sleep hygiene and habits, oxygen therapy if required | 221 patients recruited over 4-years from 19 hospitals. All stable with pH≥7.35 and no clinical worsening during the preceding 2 months. Obesity hypoventilation and severe OSA (AHI≥30/hr).<br>BMI 44±7 kg/m$^2$. PaCO2 6.8±0.6 kPa.<br><br>All stable with pH≥7.35 and no clinical worsening during the preceding 2 months. Obesity hypoventilation and severe OSA (AHI≥30/hr).<br>BMI 44±7 kg/m$^2$. PaCO2 6.8±0.6 kPa | • $PaCO_2$<br>• Adherence (h/night)<br><br>2 month follow-up | |
| Masa 2019[142]<br><br>multicentre, open-label, randomised controlled trial at 16 clinical sites in Spain | Non-invasive ventilation (NIV)<br><br>N=100<br><br>Vs<br><br>CPAP<br>N=115 | N= 215<br>Patients<br>aged 15–80 years with untreated obesity hypoventilation syndrome and an apnoea-hypopnoea index of 30 or more events per h.<br><br>Baseline :<br>BMI 42.8 kg/m$^2$<br>PaCO2 6.7 kPa<br>AHI 68 | • Mean hospitalisation days per patient-year<br>• CV events<br>• Death<br>• improvement in BP<br>• $PaCO_2$,<br>• ESS<br>• HRQL | The median follow-up was 5·44 years for all patients, 5·37 years in the continuous positive airway pressure group, and 5·55 years in the non-invasive ventilation group.<br><br>Long-term follow-up of the Masa 2015 publication patients. |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| Masa 2016[139]<br>Spain<br>RCT | Non-invasive ventilation (NIV)<br>n = 40<br>Lifestyle and oxygen as below plus NIV at bilevel pressure with assured volume<br><br>Lifestyle<br>n = 46<br>1,000 calorie diet, maintenance of sleep hygiene and habits, oxygen therapy if required | People with OHS and without severe OSAHS (could have OSAHS but not with baseline AHI >30)<br><br>AHI <30/hr.<br>BMI 40±5.9 kg/$m^2$<br>Neck 42±5.8 cm<br>PaCO2 6.5 0.5 kPa<br>Mean AHI = 14/ hr | • QoL<br>• Disease specific QoL (FOSQ)<br>• Epworth<br>• AHI<br>• ODI<br>• $PaCO_2$<br><br>2 month follow-up | High risk of bias for subjective items due to lack of blinding, low risk of bias for objective outcomes |
| [135]Masa 2020[135]<br>RCT<br>Spain | Non-invasive ventilation (NIV)<br>n = 49<br>Patients randomised to NIV were also instructed on lifestyle modification. Supplemental oxygen therapy was added if baseline daytime or nocturnal hypoxemia was detected during baseline polysomnography (control group) or titration polysomnography (NIV arm)<br><br>Lifestyle<br>n = 49<br>The lifestyle modification consisted of a 1,000-calorie diet and the maintenance of correct sleep hygiene and habits. | Stable ambulatory patients with untreated OHS and apnea-hypopnea index < 30 events/h (ie, no severe OSA)<br><br>Age, yrs: NIV- 68.5 (58.8-74.0); control- 67.0 (61.5-72.0)<br>ESS: NIV- 8.00 (5.00-12.0);control- 7.00 (4.00-12.5).<br>AHI: NIV -14.4 (9.99-21.9); control-16.4 (6.37-22.2)<br>BMI, kg/m2:NIV- 39.1 (35.6-43.1); control- 40.9 (35.0-44.5) | • hospitalisation days per year<br>• Mortality<br>• PaCO2<br>• SF 36<br>• FOSQ<br>• ESS<br>• Systolic blood pressure for hypertension<br>• Diastolic blood pressure for hypertension<br>• Cardiovascular events<br><br>Median follow-up of 4.98 years<br><br>The study is the second phase of the “Pickwick” study- the randomised | High risk of bias for subjective items due to lack of blinding, low risk of bias for objective outcomes |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | | clinical trial of patients with OHS without severe OSA. | |
| Murphy 2012[168]<br>UK<br>RCT | Volume assured Non-invasive ventilation (NIV)<br>n = 25<br>AVAPS (average volume-assured pressure support) mode, mean Vte 657ml, 2/25 required supplemental oxygen<br><br>Fixed Non-invasive ventilation (NIV)<br>n = 25<br>Fixed bi-level PS, mean IPAP 25cm $H_2O$, 4/25 required supplemental oxygen<br><br>Ventilator set-up done over ~2 days in both groups | People with OHS<br><br>Mean age, (SD): 55 (10)<br><br>Patients. BMI 50± 7 kg/$m^2$. PaCO2 6.9±0.8 kPa. SRI 53±17. | • Disease specific QoL Severe Respiratory Insufficiency Questionnaire: (SRI)<br>• Epworth<br>• Adherence (h/night)<br>• PaCO2<br>• Pa02<br><br>3 month follow-up | Low risk of bias |
| Piper 2008[206]<br>Australia<br>RCT | Non-invasive ventilation (NIV)<br>n = 18<br><br>CPAP<br>n = 18 | People with OHS and no severe nocturnal desaturation<br><br>Mean age, (SD): 50 (15)<br><br>Patients recruited from Sleep Disorders Clinic. Excluded patients with acute respiratory failure (n=17) or who showed an inadequate response to CPAP during an initial trial (n=11, defined as nocturnal $SaO_2$ <80% for > 10 min, or $CO_2$ > 1.3 kPa). | • Epworth<br>• $PaCO_2$<br>• Adherence (h/night) | High risk of bias for subjective items due to lack of blinding, low risk of bias for objective outcomes |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | BMI 53±15 kg/$m^2$. $CO_2$ 6.7 kPa. Did not screen for OSA.<br><br>All-comers not screened for OSA<br>Stable patients<br>Pressure support in the NIV group is only 6 $cmH_2O$. | | |
| Storre 2006[249]<br>Germany<br>cross-over trial | n=10<br><br>Voume assured Non-invasive ventilation (NIV)<br>Bilevel pressure ventilation device with AVAPS (average volume-assured pressure support) enabled<br><br>Fixed Non-invasive ventilation (NIV)<br>Bilevel pressure ventilation device without AVAPS (average volume-assured pressure support) enabled | People with OHS who did not respond to CPAP therapy (failed to achieve $PCO_2$ <45mmHg and RDI <10/hr)<br>Excluded if unwell (RR>30; pH < 7.35) or had any previous ventilatory support.<br>Mean $P_{tc}CO_2$ 7.7±12kPa.<br><br>Mean age, (SD): 53.5 (11.7) | • Disease specific QoL Severe Respiratory Insufficiency Questionnaire: (SRI)<br>• AHI<br>• ODI<br>• $PaCO_2$<br><br>6 week follow-up | High risk of bias for subjective items due to lack of blinding, low risk of bias for objective outcomes |

See appendix D for full evidence tables.

### 1.4.5 Quality assessment of clinical studies included in the evidence review –OSAHS population

**Table 4: Clinical evidence summary: Auto-CPAP versus fixed level CPAP for improving usage of continuous positive airway pressure machines in adults with OSAHS –severe OSAHS**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GNRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Control | Risk difference with Auto-CPAP versus fixed CPAP (95% CI) |
| Machine usage (hours/night)<br>Median follow-up 6 weeks | 1452<br>(31 studies) | ⨁⨁⊖⊖<br>LOW[1,5]<br><br>due to risk of bias, indirectness | | control group risk not available[6] | The mean machine usage (hours/night) in the intervention groups was<br>0.21 higher<br>(0.11 to 0.31 higher) |
| Number of participants who used CPAP therapy > 4 hours per night<br>Follow-up range 3 to 16 weeks | 346<br>(2 studies) | ⨁⨁⊖⊖<br>LOW[1,5]<br>due to risk of bias, indirectness | RR 1.06<br>(0.9 to 1.24) | Moderate | |
| | | | | 448 per 1000 | 27 more per 1000<br>(from 45 fewer to 108 more) |
| Symptoms (Epworth Sleepiness Scale)<br>Scale 0 to 24<br>Higher is worse<br>Median follow-up 6 weeks | 1285<br>(25 studies) | ⨁⨁⊖⊖<br>LOW[1,5]<br><br>due to risk of bias, indirectness | | control group risk not available[6] | The mean symptoms (epworth sleepiness scale) in the intervention groups was<br>0.44 lower<br>(0.72 to 0.16 lower) |
| Withdrawals (parallel group trials/first arm crossover trials)<br>Median follow-up 6 weeks | 1275<br>(13 studies) | ⨁⊖⊖⊖<br>VERY LOW[1,2,5]<br>due to risk of bias, imprecision, indirectness | RR 0.91<br>(0.67 to 1.24) | Moderate | |
| | | | | 80 per 1000 | 7 fewer per 1000<br>(from 26 fewer to 19 more) |
| Quality of life (Functional Outcome of Sleep Questionnaire) | 352<br>(3 studies) | ⨁⊖⊖⊖ | | control group risk | The mean quality of life (functional outcome of sleep questionnaire) in the intervention groups was |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GNRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Control | Risk difference with Auto-CPAP versus fixed CPAP (95% CI) |
| Scale from 5-20<br>Higher is better<br>follow-up range 4 to 104 weeks | | VERY LOW[1,,5]due to risk of bias, indirectness | | not available[6] | 0.12 higher<br>(0.21 lower to 0.46 higher) |
| Quality of life (Sleep Association Quality of Life Index)<br>Scale from 1-7<br>Higher is better | 97<br>(2 studies) | ⊕⊖⊖⊖<br>VERY LOW[1, 5]<br>due to risk of bias, , indirectness | | control group risk not available[6] | The mean quality of life (sleep association quality of life index) in the intervention groups was<br>0.14 lower<br>(0.54 lower to 0.27 higher) |
| Quality of life (SF-36 questionnaire) - Physical functioning<br>Scale from 0-100<br>Higher is better | 60<br>(3 studies) | ⊕⊕⊖⊖<br>LOW[1,2]<br>due to risk of bias, imprecision | | control group risk not available[6] | The mean quality of life (sf-36 questionnaire) - physical functioning in the intervention groups was<br>0.76 higher<br>(3.5 lower to 5.01 higher) |
| Quality of life (SF-36 questionnaire) - Role physical<br>Scale from 0-100<br>Higher is better | 60<br>(2 studies) | ⊕⊕⊖⊖<br>LOW[1,2]<br>due to risk of bias, imprecision | | control group risk not available[6] | The mean quality of life (sf-36 questionnaire) - role physical in the intervention groups was<br>3.73 lower<br>(13.46 lower to 6.01 higher) |
| Quality of life (SF-36 questionnaire) - Bodily pain<br>Scale from 0-100<br>Higher is better | 60<br>(2 studies) | ⊕⊕⊖⊖<br>LOW[1,2]<br>due to risk of bias, imprecision | | control group risk not available[6] | The mean quality of life (sf-36 questionnaire) - bodily pain in the intervention groups was<br>4.21 higher<br>(4.23 lower to 12.64 higher) |
| Quality of life (SF-36 questionnaire) - General health<br>Scale from 0-100 | 60<br>(2 studies) | ⊕⊕⊖⊖<br>LOW[1,2] | | control group risk not | The mean quality of life (sf-36 questionnaire) - general health in the intervention groups was |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GNRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Control | Risk difference with Auto-CPAP versus fixed CPAP (95% CI) |
| Higher is better | | due to risk of bias, imprecision | | available[6] | 2.49 higher<br>(4.99 lower to 9.97 higher) |
| Quality of life (SF-36 questionnaire) – Vitality<br>Scale from 0-100<br>Higher is better | 298<br>(6 studies) | ⊕⊖⊖⊖<br>VERY LOW[1,2,5]<br>due to risk of bias, imprecision, indirectness | | control group risk not available[6] | The mean quality of life (sf-36 questionnaire) - vitality in the intervention groups was<br>1.32 higher<br>(1.25 lower to 3.88 higher) |
| Quality of life (SF-36 questionnaire) - Social functioning<br>Scale from 0-100<br>Higher is better | 60<br>(2 studies) | ⊕⊕⊖⊖<br>LOW[1,2]<br>due to risk of bias, imprecision | | control group risk not available[6] | The mean quality of life (sf-36 questionnaire) - social functioning in the intervention groups was<br>3.31 higher<br>(4.29 lower to 10.92 higher) |
| Quality of life (SF-36 questionnaire) - Role emotional<br>Scale from 0-100<br>Higher is better | 60<br>(3 studies) | ⊕⊕⊖⊖<br>LOW[1,2]<br>due to risk of bias, imprecision | | control group risk not available[6] | The mean quality of life (sf-36 questionnaire) - role emotional in the intervention groups was<br>0.7 higher<br>(4.19 lower to 5.59 higher) |
| Quality of life (SF-36 questionnaire) - Mental health<br>Scale from 0-100<br>Higher is better | 60<br>(3 studies) | ⊕⊕⊖⊖<br>LOW[1,]<br>due to risk of bias, | | control group risk not available[6] | The mean quality of life (sf-36 questionnaire) - mental health in the intervention groups was<br>0.2 higher<br>(1.88 lower to 2.27 higher) |
| Apnoea Hypopnoea Index (events/hr)<br>Lower is better<br>Median follow-up 6 weeks | 1256<br>(26 studies) | ⊕⊕⊖⊖<br>LOW[1,5]<br>due to risk of bias, indirectness | | control group risk not | The mean apnoea hypopnoea index (events/hr) in the intervention groups was<br>0.48 higher<br>(0.16 to 0.8 higher) |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GNRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Control | Risk difference with Auto-CPAP versus fixed CPAP (95% CI) |
| | | | | available[6] | |
| Arousals (events/hr) | 136 (4 studies) | ⊕⊕⊖⊖ LOW[1,3,5] due to risk of bias, indirectness | | control group risk not available[6] | The mean arousals (events/hr) in the intervention groups was 0.66 lower (2.9 lower to 1.58 higher) |
| Pressure of CPAP treatment (cm H2O) Median follow-up 6 weeks | 1171 (24 studies) | ⊕⊖⊖⊖ VERY LOW[1,4,5] due to risk of bias, inconsistency, indirectness | | control group risk not available[6] | The mean pressure of CPAP treatment (cm h2o) in the intervention groups was 1.49 lower (2.12 to 0.85 lower) |
| Systolic blood pressure Follow-up 12 and 16 weeks | 353 (2 studies) | ⊕⊕⊖⊖ LOW[1,] due to risk of bias, | | Mean in control group was 132.8 | The mean systolic blood pressure in the intervention groups was 1.87 higher (1.08 lower to 4.82 higher) |
| Diastolic blood pressure Follow-up 12 and 16 weeks | 353 (2 studies) | ⊕⊖⊖⊖ VERY LOW[1,2,4] due to risk of bias, inconsistency, imprecision | | Mean in control group was 77.9 | The mean diastolic blood pressure in the intervention groups was 4.01 higher (1.46 lower to 9.49 higher) |
| 24 hour mean BP | 530 (2 studies) | ⊕⊕⊕⊕ HIGH | | Mean in control group | The mean 24 hour mean bp in the intervention groups was 0.59 higher (1.05 lower to 2.22 higher) |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GNRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Control | Risk difference with Auto-CPAP versus fixed CPAP (95% CI) |
| | | | | was 92.8 | |
| 24 hour systolic BP | 530 (2 studies) | ⊕⊕⊕⊕ HIGH | | Mean in control group was 127.1 | The mean 24 hour systolic bp in the intervention groups was 0.15 lower (2.21 lower to 1.91 higher) |
| 24 hour diastolic BP | 530 (2 studies) | ⊕⊕⊕⊕⊖ HIGH | | Mean in control group was 75.9 | The mean 24 hour diastolic bp in the intervention groups was 0.9 higher (0.65 lower to 2.44 higher) |
| Tolerability outcomes - Intolerable treatment pressure<br>Follow-up 4 to 36 weeks | 171 (1 study) | ⊕⊕⊕⊖ MODERATE[2] due to imprecision | RR 0.9 (0.66 to 1.23) | Moderate | |
| | | | | 513 per 1000 | 51 fewer per 1000 (from 174 fewer to 118 more) |
| Tolerability outcomes - Mask Leak<br>Follow-up 4 to 36 weeks | 171 (1 study) | ⊕⊕⊖⊖ LOW[2] due to imprecision | RR 1.11 (0.74 to 1.66) | Moderate | |
| | | | | 338 per 1000 | 37 more per 1000 (from 88 fewer to 223 more) |
| Tolerability outcomes - Dry mouth<br>Follow-up 4 to 36 weeks | 171 (1 study) | ⊕⊕⊕⊖ MODERATE[2] due to imprecision | RR 0.82 (0.61 to 1.1) | Moderate | |
| | | | | 563 per 1000 | 101 fewer per 1000 (from 220 fewer to 56 more) |
| Tolerability outcomes - Stuffy nose | | | | Moderate | |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GNRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Control | Risk difference with Auto-CPAP versus fixed CPAP (95% CI) |
| Follow-up 4 to 36 weeks | 171 (1 study) | ⊕⊕⊖⊖ LOW[2] due to imprecision | RR 0.98 (0.63 to 1.54) | 313 per 1000 | 6 fewer per 1000 (from 116 fewer to 169 more) |
| Patient preference (auto-CPAP/not auto-CPAP) | 1082 (14 studies) | ⊕⊖⊖⊖ VERY LOW[1,2,4,5] due to risk of bias, inconsistency, imprecision, indirectness | RR 0.99 (0.64 to 1.56) | Moderate | |
| | | | | 475 per 1000 | 5 fewer per 1000 (from 171 fewer to 266 more) |
| Mortality | No outcome reported | | | | |

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

2 Downgraded by one increment if the confidence interval crossed one MID and downgraded by two increments if the confidence interval crossed both MIDs. MID for machine usage (adherence)- 1 hour ; Established MIDs for SF-36 physical/mental- 2/3 ; FOSQ- 2 ; ESS –2.5; SAQLI – 2. GRADE default MID (0.5XSD) used for all other continuous outcomes.

3 Imprecision could not be assessed as control group SD not available

4 Downgraded by 1 or 2 increments for heterogeneity. Random effect analysis used. Subgroup analysis not conducted in Cochrane review.

5 Downgraded by 1 or 2 increments because the majority of the evidence included an indirect population (downgrade by one increment) or a very indirect population (downgrade by two increments). The population was deemed to be indirect when the outcome included evidence from studies with different severity OSAHS populations or when the study did not report the AHI of the population included.

6 Cochrane review used mean difference (SE) in the analysis, control group risk data not available.

**Table 5: Clinical evidence summary:**

**Non-invasive ventilation versus fixed level CPAP for improving usage of continuous positive airway pressure machines in adults with OSAHS-severe OSAHS**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Control | Risk difference with NIV versus fixed CPAP (95% CI) |
| Machine usage (hours/night)<br>Follow-up 4 to 52 weeks | 268<br>(4 studies) | ⊕⊕⊖⊖<br>LOW1[1,]<br>due to risk of bias, | | control group risk not available[4] | The mean machine usage (hours/night) in the intervention groups was<br>0.14 higher<br>(0.17 lower to 0.45 higher) |
| Symptoms (Epworth Sleepiness Scale)<br>Scale from 0-24<br>Higher is worse<br>Follow-up 4 to 12 weeks | 226<br>(4 studies) | ⊕⊖⊖⊖<br>LOW1[1,]<br>due to risk of bias, | | control group risk not available[4] | The mean symptoms (epworth sleepiness scale) in the intervention groups was<br>0.49 lower<br>(1.46 lower to 0.48 higher) |
| Withdrawals (parallel group trials/first arm cross-over trials)<br>Follow-up 4 to 52 weeks | 261<br>(3 studies) | ⊕⊖⊖⊖<br>VERY LOW1[1,2]<br>due to risk of bias, imprecision | RR 0.61 (0.33 to 1.15) | Moderate | |
| | | | | 138 per 1000 | 54 fewer per 1000<br>(from 92 fewer to 21 more) |
| Quality of life (Functional Outcome of Sleep Questionnaire)<br>Scale from 5-20<br>higher is better<br>Follow-up 8 weeks | 151<br>(1 study) | ⊕⊕⊖⊖<br>LOW1[1,2]<br>due to risk of bias, imprecision | | Mean in control group was 5.1 | The mean quality of life (functional outcome of sleep questionnaire) in the intervention groups was<br>0.8 lower<br>(6.08 lower to 4.48 higher) |
| Quality of life (Sleep Association Quality of Life Index)<br>Scale 1-7<br>Higher is better | 28<br>(1 study) | ⊕⊕⊕⊖<br>MODERATE[1]<br>due to risk of bias | | control group risk not available[4] | The mean quality of life (sleep association quality of life index) in the intervention groups was<br>0.4 higher<br>(0.34 lower to 1.14 higher) |
| Quality of life (SF-36 questionnaire) - Physical health<br>Scale from 0-100<br>Higher is better | 151<br>(1 study) | ⊕⊖⊖⊖<br>VERY LOW[1,2]<br>due to risk of bias, imprecision | | Mean in control group | The mean quality of life (sf-36 questionnaire) - physical health in the intervention groups was<br>0.6 higher<br>(2.21 lower to 3.41 higher) |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Control | Risk difference with NIV versus fixed CPAP (95% CI) |
| | | | | was 1.2 | |
| Quality of life (SF-36 questionnaire) - Mental heath<br>Scale from 0-100<br>Higher is better | 151<br>(1 study) | ⨁⨁⊖⊖<br>LOW[1,2]<br>due to risk of bias, imprecision | | Mean in control group was 4.6 | The mean quality of life (sf-36 questionnaire) - mental health in the intervention groups was 2.9 lower<br>(7.09 lower to 1.29 higher) |
| Apnoea Hypopnoea Index (events/hr)<br>Lower is better<br>Follow-up 4 to 8weeks | 179<br>(2 studies) | ⨁⊖⊖⊖<br>VERY LOW[1,2]<br>due to risk of bias, imprecision | | The mean AHI was 6.6 events/ hour | The mean apnoea hypopnoea index (events/hr) in the intervention groups was 1.36 higher<br>(6.92 lower to 9.63 higher) |
| Patient preference - BiPAP/no preference or CPAP | 88<br>(2 studies) | ⨁⊖⊖⊖<br>VERY LOW[1,2,3]<br>due to risk of bias, inconsistency, imprecision | RR 0.88 (0.47 to 1.65) | Moderate | |
| | | | | 545 per 1000 | 65 fewer per 1000<br>(from 289 fewer to 354 more) |
| Tolerability outcomes - Dry mouth<br>Follow-up 4 to 52 weeks | 151<br>(1 study) | ⨁⊖⊖⊖<br>VERY LOW[1,2]<br>due to risk of bias, imprecision | RR 0.56 (0.15 to 2.17) | Moderate | |
| | | | | 75 per 1000 | 33 fewer per 1000<br>(from 64 fewer to 88 more) |
| Tolerability outcomes - Mask intolerance<br>Follow-up 4 to 52 weeks | 151<br>(1 study) | ⨁⊖⊖⊖<br>VERY LOW[1,2]<br>due to risk of bias, imprecision | RR 1.13 (0.45 to 2.85) | Moderate | |
| | | | | 100 per 1000 | 13 more per 1000<br>(from 55 fewer to 185 more) |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Control | Risk difference with NIV versus fixed CPAP (95% CI) |
| Treatment comfort score<br>0-100 VAS<br>Follow-up 4 to 52 weeks | 28<br>(1 study) | ⨁⨁⊖⊖<br>LOW[1,2]<br>due to risk of bias | | control group risk not available[4] | The mean treatment comfort score in the intervention groups was<br>9 higher<br>(3.54 lower to 21.54 higher) |

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by one increment if the confidence interval crossed one MID and downgraded by two increments if the confidence interval crossed both MIDs . MID for machine usage (adherence)- 1 hour ; Established MIDs for SF-36 physical/mental- 2/3 ; FOSQ- 2 ; ESS –2.5; SAQLI – 2
3 SAQLI- established MID 2.. GRADE default MID (0.5XSD) used for all other continuous outcomes.
3 Downgraded by 1 or 2 increments for heterogeneity. Random effect analysis used.

4Cochrane review used mean difference (SE) in the analysis, control group risk data not available.

**Table 5: Clinical evidence summary: Heated humidification + fixed level CPAP versus fixed level CPAP alone for improving usage of continuous positive airway pressure machines in adults with obstructive sleep apnoea- severe OSAHS**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Control | Risk difference with Heated humidification + fixed pressure CPAP versus fixed pressure CPAP alone (95% CI) |
| Machine usage (hours/night)<br>Follow-up range 3 weeks to 12 weeks | 277<br>(6 studies) | ⨁⨁⊖⊖<br>LOW[1,] | | The mean | The mean machine usage (hours/night) in the intervention groups was |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Control | Risk difference with Heated humidification + fixed pressure CPAP versus fixed pressure CPAP alone (95% CI) |
| | | due to risk of bias, | | machine usage was 5 hours | 0.37 higher (0.1 to 0.64 higher) |
| Symptoms (Epworth Sleepiness Scale)<br>Follow-up range 3 weeks to 12 weeks<br>Scale from 0-24<br>Higher is worse | 184 (4 studies) | ⨁⨁⊖⊖ LOW[1], due to risk of bias | | The mean symptoms ranged from 4 to 9 ESS | The mean symptoms (epworth sleepiness scale) in the intervention groups was 0.34 lower (0.93 lower to 0.26 higher) |
| Withdrawals (parallel group trials/first arm cross-over trials)<br>Follow-up median 12 weeks | 209 (3 studies) | ⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision | RR 1 (0.56 to 1.79) | Moderate | |
| | | | | 128 per 1000 | 0 fewer per 1000 (from 56 fewer to 101 more) |
| Apnoea Hypopnoea Index (events/hr)<br>Lower is better<br>Follow-up 4 weeks | 44 (1 study) | ⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision | | The mean AHI (events/hr) was 4.2 events/hr | The mean apnoea hypopnoea index (events/hr) in the intervention groups was 0.3 higher (0.95 lower to 1.55 higher) |
| Quality of life (SF-36 questionnaire)<br>Scale from 0-100<br>Higher is better | 124 (2 studies) | ⨁⊖⊖⊖ VERY LOW[1,2] due to risk of | | Mean in control | The mean quality of life (sf-36 questionnaire) in the intervention groups was |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Control | Risk difference with Heated humidification + fixed pressure CPAP versus fixed pressure CPAP alone (95% CI) |
| | | bias, imprecision | | group was 70.48 | 0.11 higher (6.97 lower to 7.18 higher) |
| Nasal symptoms (parallel group trials) - Runny nose | 73 (1 study) | ⊕⊕⊕⊖ MODERATE[2] due to imprecision | RR 0.39 (0.13 to 1.15) | Moderate | |
| | | | | 265 per 1000 | 162 fewer per 1000 (from 231 fewer to 40 more) |
| Nasal symptoms (parallel group trials) - Congested or blocked nose<br>Follow-up mean 4 weeks | 73 (1 study) | ⊕⊕⊕⊕ HIGH | RR 0.37 (0.2 to 0.7) | Moderate | |
| | | | | 618 per 1000 | 389 fewer per 1000 (from 185 fewer to 494 fewer) |
| Nasal symptoms (parallel group trials) - Dry nose<br>Follow-up 4 weeks | 103 (2 studies) | ⊕⊕⊕⊖ MODERATE[1] due to risk of bias | | Mean in control group was 13.2 | The mean nasal symptoms (parallel group trials) - dry nose in the intervention groups was 0.38 standard deviations lower (0.78 lower to 0.01 higher) |
| Nasal symptoms (parallel group trials) - Runny nose<br>Follow-up 4 weeks | 103 (2 studies) | ⊕⊕⊕⊖ MODERATE[1] due to risk of bias | | Mean in control group was 13.5 | The mean nasal symptoms (parallel group trials) - runny nose in the intervention groups was 0.3 standard deviations lower (0.69 lower to 0.09 higher) |
| Nasal symptoms (parallel group trials) - Blocked nose<br>Follow-up 4 weeks | 103 (2 studies) | ⊕⊕⊕⊖ MODERATE[1] due to risk of bias | | Mean in control group was 15.9 | The mean nasal symptoms (parallel group trials) - blocked nose in the intervention groups was 0.38 standard deviations lower (0.78 lower to 0.01 higher) |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Control | Risk difference with Heated humidification + fixed pressure CPAP versus fixed pressure CPAP alone (95% CI) |
| Nasal symptoms (parallel group trials) - Bleeding nose<br>Follow-up 4 weeks | 103<br>(2 studies) | ⨁⨁⨁⊖<br>MODERATE[1]<br>due to risk of bias | | Mean in control group was 10.5 | The mean nasal symptoms (parallel group trials) - bleeding nose in the intervention groups was 0.45 standard deviations lower<br>(0.99 lower to 0.1 higher) |
| Preference | 74<br>(1 study) | ⨁⊖⊖⊖<br>VERY LOW[1,2]<br>due to risk of bias, imprecision | RR 1.06<br>(0.67 to 1.67) | Moderate | |
| | | | | 487 per 1000 | 29 more per 1000<br>(from 161 fewer to 326 more) |
| Mortality | No outcome reported | | | | |

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by one increment if the confidence interval crossed one MID and downgraded by two increments if the confidence interval crossed both MIDs. MID for machine usage (adherence)- 1 hour ; Established MIDs for SF-36 physical/mental- 2/3 ; FOSQ- 2 ; ESS –2.5; SAQLI – 2.. GRADE default MID (0.5XSD) used for all other continuous outcomes.

### 1.4.6 Quality assessment of clinical studies included in the evidence review – OHS population

**Table 6: Clinical evidence summary: Fixed non-invasive ventilation (NIV) vs Volume assured non-invasive ventilation (NIV)**

| Outcomes | | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|---|
| | | | | | Risk with Fixed NIV | Risk difference with Volume assured NIV (95% CI) |
| Change in disease specific QoL<br>Severe Respiratory Insufficiency Questionnaire (SRI-SS) (parallel trial). Scale from: 0 to 100.<br>Higher is better | | 46<br>(1 study)<br>3 months | ⨁⨁⨁⊖<br>MODERATE[1]<br>due to imprecision | | The mean change in disease specific qol in the control groups was<br>7 | The mean change in disease specific qol in the intervention groups was<br>4 higher<br>(3.23 lower to 11.23 higher) |
| Disease specific QoL<br>Severe Respiratory Insufficiency Questionnaire (SRI-SS) (crossover trial). Scale from: 0 to 100.<br>Higher is better | | 10<br>(1 study)<br>1.5 months | ⨁⊖⊖⊖<br>VERY LOW[1,2]<br>due to risk of bias, imprecision | | The mean disease specific qol in the control groups was<br>78 | The mean disease specific qol in the intervention groups was<br>3 lower<br>(16.18 lower to 10.18 higher) |
| Change in ESS<br>Scale from: 0 to 24.<br>Higher is worse | | 46<br>(1 study)<br>3 months | ⨁⨁⨁⊖<br>MODERATE[1]<br>due to imprecision | | The mean change in ESS in the control groups was<br>-6 | The mean change in ESS in the intervention groups was<br>1 higher<br>(2.47 lower to 4.47 higher) |
| PaCO2<br>kPa | | 56<br>(2 studies)<br>1.5-3 months | ⨁⊖⊖⊖<br>VERY LOW[1,3]<br>due to inconsistency, imprecision | | The mean paco2 in the control groups was<br>6.2 | The mean paco2 in the intervention groups was<br>0.14 lower<br>(0.82 lower to 0.55 higher) |
| Adherence (hours per night) | | 46<br>(1 study)<br>3 months | ⨁⨁⨁⊖<br>MODERATE[1]<br>due to imprecision | | The mean adherence (hours per night) in the control groups was<br>5.1 | The mean adherence (hours per night) in the intervention groups was<br>0.9 lower<br>(2.44 lower to 0.64 higher) |

| Outcomes | | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|---|
| | | | | | Risk with Fixed NIV | Risk difference with Volume assured NIV (95% CI) |
| AHI (events/hr)<br>Lower is better | | 10<br>(1 study)<br>1.5 months | ⨁⨁⊖⊖<br>LOW[2,4]<br>due to risk of bias, imprecision | Not estimable | See comment | See comment |
| ODI<br>Lower is better | | 10<br>(1 study)<br>1.5 months | ⨁⊖⊖⊖<br>VERY LOW[1,2]<br>due to risk of bias, imprecision | | The mean ODI in the control groups was<br>27 | The mean ODI in the intervention groups was<br>6 higher<br>(8.05 lower to 20.05 higher) |
| PaO2 | | 46<br>(1 study) | ⨁⨁⨁⊖<br>MODERATE[1]<br>due to imprecision | | | The mean pao2 in the intervention groups was<br>0.2 higher<br>(0.89 lower to 0.49 higher) |
| Mortality | | No outcome reported | | | | |

1 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs . MID for machine usage (adherence)- 1 hour ; Established MIDs for SF-36 physical/mental- 2/3 ; SR-SS 6, FOSQ- 2 ; ESS –2.5; SAQLI – 2; SR- 2. GRADE default MID (0.5XSD) used for all other continuous outcomes.
2 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
3. Downgraded by 1 or 2 increments for heterogenity, unexplained by subgroup analysis. Random effect analysis used. 4 The mean and SD in both arms was 0.

**Table 7: Clinical evidence summary: Non-invasive ventilation (NIV) vs lifestyle**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Lifestyle | Risk difference with NIV (95% CI) |
| Change in PaCO2 at 1-2 months | 262<br>(3 studies) | ⨁⨁⨁⊖<br>MODERATE[1]<br>due to imprecision | | The mean change in paco2 in the control groups was<br>-2.8 | The mean change in paco2 in the intervention groups was<br>2.93 lower<br>(4.26 to 1.59 lower) |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Lifestyle | Risk difference with NIV (95% CI) |
| PaCO2 at 3 years (without severe OSA) | 96 (1 study) | ⨁⨁⨁⨀ MODERATE[1] due to imprecision | | The mean paco2 in the control groups was 47.54 | The mean paco2 at 3 years (without severe osa) in the intervention groups was 3.28 lower (5.63 to 0.93 lower) |
| Change in AHI at 1-2 months (people with severe OSAHS) | 176 (2 studies) | ⨁⨁⨁⨁ HIGH | | The mean change in ahi (people with severe OSAHS) in the control groups was -0.2 | The mean change in AHI (people with severe OSAHS) in the intervention groups was 48.41 lower (57.37 to 39.46 lower) |
| Change in AHI at 2 months (people without severe OSAHS) | 86 (1 study) | ⨁⨁⨁⨁ HIGH | | The mean change in ahi (people without severe OSAHS) in the control groups was 0.1 | The mean change in ahi (people without severe OSAHS) in the intervention groups was 11.10 lower (15.84 to 6.36 lower) |
| Change in ESS at 1-2 months Scale from: 0 to 24. | 262 (3 studies) | ⨁⨀⨀⨀ VERY LOW[1,2,3] due to risk of bias, imprecision, inconsistency | | The mean change in ESS in the control groups was -1.2 | The mean change in ESS in the intervention groups was 2.48 lower (4.11 to 0.86 lower) |
| ESS at 3 years (without severe OSA) | 96 (1 study) | ⨁⨁⨀⨀ LOW[1,2] due to risk of bias, imprecision | | The mean ESS in the control groups was 7.13 | The mean ess at 3 years (without severe osa) in the intervention groups was 2.97 lower (5.57 to 0.37 lower) |
| Change in HbA1c at 1 months | 35 (1 study) | ⨁⨁⨁⨀ MODERATE[1] due to imprecision | | The mean change in HbA1c in the control groups was-0.12 | The mean change in hba1c in the intervention groups was 0.16 higher (0.08 lower to 0.4 higher) |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Lifestyle | Risk difference with NIV (95% CI) |
| Change in SBP at 1-2 months | 121 (2 studies) | ⨁⨁⨁⨀ MODERATE[1] due to imprecision | | The mean change in SBP in the control groups was -4.9 | The mean change in SBP in the intervention groups was 1.57 higher (5.28 lower to 8.42 higher) |
| Systolic blood pressure at 3 years (without severe OSA) | 96 (1 study) | ⨁⨁⨁⨀ MODERATE[1] due to imprecision | | The mean change in SBP in the control groups was | The mean systolic blood pressure at 3 years (without severe osa) in the intervention groups was 3.33 higher (4.19 lower to 10.85 higher) |
| Diastolic blood pressure at 3 years (without severe OSA) | 96 (1 study) | ⨁⨁⨁⨀ MODERATE[1] due to imprecision | | The mean change in DBP in the control groups was -4.9 | The mean diastolic blood pressure at 3 years (without severe osa) in the intervention groups was 3.47 higher (1.81 lower to 8.75 higher) |
| Change in ODI at 2 months (people with severe OSAHS) | 141 (1 study) | ⨁⨁⨁⨁ HIGH | | The mean change in ODI (people with severe OSAHS) in the control groups was -4.7 | The mean change in ODI (people with severe OSAHS) in the intervention groups was 41.30 lower (50.56 to 32.04 lower) |
| Change in ODI at 2 months (people without severe OSAHS) | 86 (1 study) | ⨁⨁⨁⨁ HIGH | | The mean change in ODI (people without severe OSAHS) in the control groups was -0.4 | The mean change in ODI (people without severe OSAHS) in the intervention groups was 18.60 lower (25.71 to 11.49 lower) |
| Change in SF-36 physical summary at 2 months Scale from: 0 to 100. | 227 (2 studies) | ⨁⨁⨀⨀ LOW[1,2] due to risk of bias, imprecision | | The mean change in sf-36 physical summary in the control groups was 0.6 | The mean change in sf-36 physical summary in the intervention groups was 1.78 higher (0.39 lower to 3.94 higher) |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Lifestyle | Risk difference with NIV (95% CI) |
| SF-36 physical at 3 years (without severe OSA) | 96 (1 study) | ⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision | | The mean sf-36 physical in the control groups was 34.96 | The mean sf-36 physical at 3 years (without severe osa) in the intervention groups was 2.35 higher (3.35 lower to 8.05 higher) |
| Change in SF-36 mental summary at 2 months Scale from: 0 to 100. | 227 (2 studies) | ⨁⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, imprecision, inconsistency | | The mean change in sf-36 mental summary in the control groups was 0.2 | The mean change in sf-36 mental summary in the intervention groups was 2.26 higher (0.75 lower to 5.27 higher) |
| SF 36 mental at 3 years (without severe OSA) | 96 (1 study) | ⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision | | The mean sf-36 mental in the control groups was 44.29 | The mean sf 36 mental at 3 years (without severe osa) in the intervention groups was 1.47 lower (8.99 lower to 6.05 higher) |
| Change in FOSQ at 2 months Scale from: 5 to 30. Higher is better | 227 (2 studies) | ⨁⨁⊖⊖ LOW[1,2] due to risk of bias, imprecision | | The mean change in FOSQ in the control groups was 0.2 | The mean change in FOSQ in the intervention groups was 6.35 higher (1.87 to 10.84 higher) |
| FOSQ at 3 years (without severe OSA) Higher is better | 96 (1 study) | ⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision | | The mean FOSQ in the control groups was 72.16 | The mean fosq at 3 years (without severe osa) in the intervention groups was 5.05 higher (5.96 lower to 16.06 higher) |
| Change in Pa02 at 2 months | 35 (1 study) | ⨁⨁⊖⊖ LOW[1] due to imprecision | | The mean change in pao2 in the control groups was 0.15 | The mean pa02 in the intervention groups was 2.25 higher (5.89 lower to 10.39higher) |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Lifestyle | Risk difference with NIV (95% CI) |
| Mortality at 3 years (without severe OSA) | 96 (1 study) | ⨁⨁⨀⨀ LOW[1] due to imprecision | | RR 1 (0.43 to 2.3) | 0 fewer per 1000 (from 107 fewer to 244 more) |
| Cardiovascular events at 3 years (without severe OSA) | 96 (1 study) | ⨁⨁⨀⨀ LOW[1] due to imprecision | | RR 0.91 (0.43 to 1.94) | 21 fewer per 1000 (from 131 fewer to 215 more) |

1 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs . MID for machine usage (adherence)- 1 hour ; Established MIDs for SF-36 physical/mental- 2/3 ; FOSQ- 2 ; ESS –2.5; SAQLI – 2.. GRADE default MID (0.5XSD) used for all other continuous outcomes.
2 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
3 Downgraded by 1 or 2 incrementsfor heterogeneity unexplained by subgroup analysis. Random effects analysis used.

**Table 8: Clinical evidence summary: Non-invasive ventilation (NIV ) vs CPAP**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with CPAP | Risk difference with NIV (95% CI) |
| Change in SF-36 physical<br>Scale from: 0 to 100.<br>Higher is better | 213 (2 studies) 2-3 months and 3 years | ⨁⨁⨀⨀ LOW[1,2] due to risk of bias, imprecision | | The mean change in sf-36 physical in the control groups was 39.4 | The mean change in sf-36 physical in the intervention groups was 1.49 lower (4.88 lower to 1.9 higher) |
| Change in SF-36 mental<br>Scale from: 0 to 100. | 213 (2 studies) 2-3 months and 3 years | ⨁⨁⨀⨀ LOW[1,2] due to risk of bias, imprecision | | The mean change in sf-36 mental in the control groups was 47.29 | The mean change in sf-36 mental in the intervention groups was 0.21 higher (3.11 lower to 2.38 higher) |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with CPAP | Risk difference with NIV (95% CI) |
| Disease specific QoL<br>Severe Respiratory Insufficiency Questionnaire (SRI)<br>Scale from: 0 to 100.<br>Higher is better | 57<br>(1 study)<br>3 months | ⨁⨁⨁⊖<br>MODERATE[2]<br>due to imprecision | | The mean SRI in the control groups was<br>67.58 | The mean SRI in the intervention groups was<br>4.08 lower<br>(12.16 lower to 4 higher) |
| Change in FOSQ<br>Scale from: 5 to 30.<br>Higher is better | 156<br>(1 study)<br>2 months and 3 years | ⨁⊖⊖⊖<br>VERY LOW[1,2]<br>due to risk of bias, imprecision | | The mean change in FOSQ in the control groups was<br>77.3 | The mean change in FOSQ in the intervention groups was<br>5.4 higher<br>(0.3 lower to 11.1 higher) |
| Hours/night | 247<br>(3 studies)<br>2-3 months | ⨁⨁⨁⊖<br>MODERATE[1]<br>due to risk of bias | | The mean hours/night in the control groups was<br>5.3 | The mean hours/night in the intervention groups was<br>0.1 higher<br>(0.47 lower to 0.67 higher) |
| Change in AHI (events/hr) | 151<br>(1 study)<br>2 months | ⨁⨁⨁⊖<br>MODERATE[2] | | The mean change in ahi in the control groups was<br>-60 | The mean change in ahi in the intervention groups was<br>3 higher<br>(6.74 lower to 12.74 higher) |
| Change in ODI | 151<br>(1 study)<br>2 months | ⨁⨁⨁⊖<br>MODERATE[2]<br>due to imprecision | | The mean change in ODI in the control groups was<br>-58 | The mean change in ODI in the intervention groups was<br>12 higher<br>(1.95 to 22.05 higher) |
| Change in PaCO2 | 194<br>(2 studies)<br>2-3 months and 3 years | ⨁⨁⨁⨁<br>HIGH[2] | | The mean change in paco2 in the control groups was 19.1 | The mean change in paco2 in the intervention groups was<br>0.62 lower<br>(1.66 lower to 0.42 higher) |
| ESS<br>Scale from: 0 to 24.<br>Higher is worse | 253<br>(3 studies)<br>2-3 months and 3 years | ⨁⨁⊖⊖<br>LOW[1,2]<br>due to risk of bias, imprecision | | The mean ESS in the control groups was<br>1.9 | The mean ESS in the intervention groups was<br>0.8 lower<br>(3.34 lower to 1.75 higher) |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with CPAP | Risk difference with NIV (95% CI) |
| Systolic BP | 57<br>(1 study)<br>3 months | ⨁⨁⨀⨀<br>LOW[2]<br>due to imprecision | | The mean systolic bp in the control groups was<br>137 | The mean systolic bp in the intervention groups was<br>0 higher<br>(8.74 lower to 8.74 higher) |
| Mortality | 204<br>(1 study)<br>5.37 years | ⨁⨁⨀⨀<br>LOW[2]<br>due to imprecision | RR 0.76<br>(0.37 to 1.55) | Moderate | |
| | | | | 150 per 1000 | 36 fewer per 1000<br>(from 95 fewer to 82 more) |
| cardiovascular events | 204<br>(1 study) 3 years | ⨁⨁⨀⨀<br>LOW[2]<br>due to imprecision | RR 1.17<br>(0.63 to 2.19) | Moderate | |
| | | | | 150 per 1000 | 25 more per 1000<br>(from 56 fewer to 179 more) |
| hospitalisation per patient per year | 204<br>(1 study)<br>5.37 years | ⨁⨁⨁⨁<br>HIGH | | The mean hospitalisation in the control groups was 1.63 | The mean hospitalisation per patient per year in the intervention groups was<br>0.19 lower<br>(1.13 lower to 0.75 higher) |

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs . MID for machine usage (adherence)- 1 hour ; Established MIDs for SF-36 physical/mental- 2/3 ; ESS –2.5; SRI -6.. GRADE default MID (0.5XSD) used for all other continuous outcomes.

**Table 9: Clinical evidence summary: CPAP vs lifestyle**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Lifestyle | Risk difference with CPAP (fixed) (95% CI) |
| Change in SF-36 physical<br>Scale from: 0 to 100. | 150<br>(1 study)<br>2 months | ⨁⨁⨀⨀<br>LOW[1,2]<br>due to risk of bias, imprecision | | The mean change in sf-36 physical in the control groups was<br>0.2 | The mean change in sf-36 physical in the intervention groups was<br>1 higher<br>(1.52 lower to 3.52 higher) |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Lifestyle | Risk difference with CPAP (fixed) (95% CI) |
| Change in SF-36 mental<br>Scale from: 0 to 100. | 150<br>(1 study)<br>2 months | ⨁⨁⨀⨀<br>LOW[1,2]<br>due to risk of bias, imprecision | | The mean change in sf-36 mental in the control groups was<br>1.2 | The mean change in sf-36 mental in the intervention groups was<br>3.4 higher<br>(0.06 to 6.74 higher) |
| Change in FOSQ<br>Scale from: 5 to 20. | 150<br>(1 study)<br>2 months | ⨁⨁⨀⨀<br>LOW[1,2]<br>due to risk of bias, imprecision | | The mean change in FOSQ in the control groups was<br>-1.7 | The mean change in FOSQ in the intervention groups was<br>6.8 higher<br>(1.67 to 11.93 higher) |
| Change in ESS<br>Scale from 0-24 | 150<br>(1 study)<br>2 months | ⨁⨁⨀⨀<br>LOW[1,2]<br>due to risk of bias, imprecision | | The mean change in ESS in the control groups was<br>-1 | The mean change in ESS in the intervention groups was<br>3.3 lower<br>(4.76 to 1.84 lower) |
| Change in AHI | 150<br>(1 study)<br>2 months | ⨁⨁⨁⨁<br>HIGH | | The mean change in ahi in the control groups was<br>-6.8 | The mean change in ahi in the intervention groups was<br>53.2 lower<br>(62.97 to 43.43 lower) |
| Change in ODI | 150<br>(1 study)<br>2 months | ⨁⨁⨁⨁<br>HIGH | | The mean change in ODI in the control groups was<br>-4.7 | The mean change in ODI in the intervention groups was<br>53.3 lower<br>(62.75 to 43.85 lower) |
| Change in PaCO2 | 150<br>(1 study)<br>2 months | ⨁⨁⨁⨁<br>HIGH | | The mean change in paco2 in the control groups was<br>-3.2 | The mean change in paco2 in the intervention groups was<br>0.5 lower<br>(2.52 lower to 1.52 higher) |

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. MID for machine usage (adherence)- 1 hour ; Established MIDs for SF-36 physical/mental- 2/3 ; ESS –2.5; SRI -6.. GRADE default MID (0.5XSD) used for all other continuous outcomes.

See appendix F for full GRADE tables.

**Narrative results:**

Data on tolerability outcomes were measured and reported inconsistently across the studies. Data have been presented a narratively for studies where could not not be analysed (data were presented graphically or data could not be adjusted adequately for the crossover design). Narrative data was considered alongside the GRADE evidence by the committee when making recommendations. The overall study quality was taken into account as GRADE analysis for each outcome could not be performed.

## Auto CPAP vs fixed CPAP

***Nasal blockage*** *(very low quality)*

Four participants in Sériès 1997 suffered nasal blockage (two from auto-CPAP1 group, one from auto-CPAP2, and one from fixed CPAP), which resolved with the use of a heated humidifier. Nolan 2007 presented bar charts of those experiencing blocked or runny nose during both arms of treatment (just over 40% in those treated with auto-CPAP and just over 30% in those with fixed pressure CPAP based on visual inspection, N = 26).

Nussbaumer 2006 reported similar scores between treatment arms by participants who rated symptoms on a VAS (N = 38).

***Tolerance of treatment pressure*** *(very low quality)*

Massie 2003 reported a significant difference between auto and fixed CPAP in favour of the automatic pressure mode on feeling discomfort from pressure and experiencing less trouble getting to sleep (all values $P < 0.006$). Randerath 2001 reported no significant differences between the two groups who were treated with both auto and fixed CPAP (no numerical values presented). d'Ortho 2000 reported little difference on an un-validated questionnaire measuring tolerance of treatment pressure between auto-CPAP and fixed CPAP (N = 25). In Nussbaumer 2006 participant-rated tolerance of treatment pressure was better in the auto-CPAP arm than during fixed pressure CPAP treatment.

***Mask leak*** *(very low quality)*

Nolan 2007 presented data that indicated slightly fewer participants experiencing leak with auto-CPAP (just over 20% versus just under 25% based on visual inspection).

Teschler 2000 reported no significant difference in mask leak between fixed CPAP (13% mask on time with leak of 0.4 Ls-1) and auto-CPAP (10% mask on time with leak of 0.4 Ls-1). Hukins 2004, Damjanovic 2009, Galetke 2008 and West 2006 reported slightly fewer leaks as either number of leaks per person, leakage time or pressure leaked per second with auto-CPAP compared with CPAP. Nussbaumer 2006 found that mask leaks were perceived to be less problematic on auto-CPAP than on fixed pressure CPAP.

**NIV vs fixed CPAP**

***Tolerability outcomes*** *(very low quality)*

Reeves-Hoché 1995 reported five withdrawals due to either mask discomfort (n = 2) or therapy intolerance (n = 3). All were from the CPAP group. No withdrawals due to mask discomfort or therapy intolerance occurred from the bi-level PAP group. Twenty participants complained of nasal dryness (no distribution between the two groups reported). Three participants complained of rhinorrhoea and 15 participants complained of nasal bridge pressure (no distribution reported between the two groups).

Gay 2003 reported that telephone contact did not identify any complications that necessitated further interventions. Muir 1998 did not report data in terms of specific adverse effects. No difference in the rate of adverse effects was reported. Gulati 2015 used a global treatment comfort score on a 0-100 VAS but there was insufficient evidence to determine the effect (Bi-PAP: 69 versus fixed CPAP 60, P = 0.16).

## 1.5 Economic evidence

### 1.5.1 Included studies

Two health economic study were included in this review, one for OSAHS[23] and the other for OHS[141]. This is summarised in the health economic evidence profile below (Table 10) and the health economic evidence table in appendix H.

### 1.5.2 Excluded studies

No health economic studies that were relevant to this question were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in appendix G.

### 1.5.3 Summary of studies included in the economic evidence review

**Table 10: Health economic evidence profile: Auto-CPAP versus fixed level CPAP**

| Study | Applicability | Limitations | Other comments | Incremental cost | Incremental effects | Cost effectiveness | Uncertainty |
|---|---|---|---|---|---|---|---|
| Bloch 2018 [23] | Partially Applicable (a) | Potentially serious limitations (b) | Cost-consequences(c) analysis RCT with 2 year follow-up | **OSAHS costs** +£180 **All health care costs** -£60 | -0.03 QALYs(c) | **OSAHS costs** Fixed level dominated auto-CPAP **All health care costs** Fixed level cost £2,000 per QALY gained | Quality of life change was not sensitive to Intention-to-treat / per protocol analysis |

*Abbreviations: CPAP=continuous passive airway pressure; QALY= quality-adjusted life years; RCT= randomised controlled trial*
*(a) Quality of life measured by SF-6D not EQ-5D. Switzerland cost perspective.*
*(b) Costs were medians not means. Based on a single trial not a systematic review. Not double-blinded. Funding from manufacturers.*
*(c) QALYs estimated by National Guideline Centre*

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**Table 11: Health economic evidence profile: Non-invasive ventilation versus CPAP**

| Study | Applicability | Limitations | Other comments | Incremental cost | Incremental effects | Cost effectiveness | Uncertainty |
|---|---|---|---|---|---|---|---|
| Masa 2020[141] | Partially applicable (a) | Minor limitations (b) | • Within-RCT cost-effectiveness analysis (Pickwick study/Masa 2015[137])<br>• Population: Stable ambulatory patients with OHS and concomitant severe OSA (AHI ≥30)<br>• Time horizon: 3 years | £830 per year(c) | Hospitalisation days per year:<br>-0.24 | £3736 per hospital day averted | Probability CPAP cost saving: 99.5%<br><br>Results were robust to sensitivity analyses which included exploring the impact of a higher proportion of treatment dropouts in the CPAP group. |

*Abbreviations: RCT= randomised controlled trial; CPAP = Continuous positive airway pressure.*
*(a) Partially applicable; Spanish healthcare system; QALYs and clinical outcomes not included; no discounting.*
*(b)* Minor limitations; *Within RCT cost-effectiveness analysis; details regarding resource and cost* collection *not reported.*
*(c) 2018 Spanish Euros converted to 2018 UK pounds. [190] Cost components incorporated: The cost of hospitalisation days plus other hospital resources, including ICU days and ED visits; non-annual, baseline and annual clinic visits; NIV daytime adjustment and tests; medication for comorbid conditions; home care for PAP therapy.*

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### 1.5.4 Unit costs

Unit costs were presented to the guideline committee.

**Table 12: Unit costs of positive airway pressure devices with and without humidification**

| Device | Cost (including VAT) | Annuitised Device Costs (including VAT) [a] | Device Name[b] | Supply Chain Code |
|---|---|---|---|---|
| Fixed-level continuous positive airway pressure device (CPAP) | £216 - £280 | £34 - £44 | S9 Escape, Airsense10 Elite, Airsense Elite Standard sleepcube SystemOne Pro Dreamstation Pro | FDD2400, FDD5011, FAG1366 FAG2279 FAG4055 FAG4053 |
| Fixed-level CPAP + Humidifier | £360 - £370 | £58- £63 | Sleepstyle fixed SystemOne Pro Dreamstation | FDE897 FAG4056 FAG4054 |
| Automatic continuous positive airway pressure device (Auto-CPAP) | £367 - £400 | £57 - £58 | Airsense Autoset Dreamstation Auto SystemOne Auto | FAG1365 FAG3369 FAG4059 |
| Auto-CPAP + Humidifier | £450 - £485 | £71 - £77 | Airsense Autoset Dreamstation Auto SystemOne Auto Airesense Autoset for Her Sleepstyle Auto | FAG2246 FAG1364 FAG3372 FDE896 FAG4060 |

*(a) Assuming the equipment lasts 7 years and a discount rate of 3.5%.*

(b) *Example devices have been listed here.*[181] *There might be other devices available from the NHS supply chain. Costs for consumable products such as head masks have not been included here as these costs would be the same irrespective of which devices is preferred.*

**Table 13: Unit cost of non-invasive ventilation devices for obesity hypoventilation syndrome**

| Device Type | Device Cost (including VAT) | Annuitized device costs (including VAT) [a] | Supply Chain Codes[b] |
|---|---|---|---|
| Non-invasive ventilation (NIV) | £1620 - £3780 | £256 - £597 | FDD5016, FDD5020 FDD5013, FAG1720, FAG2145, FAG2146, FDD2437, FDD2438, |
| NIV with auto component or iVAPS | £2220-£3105 | £351 - £497 | FDD5017, FAG2144, FAG2148 |

*(a) Assuming the equipment lasts 7 years and a discount rate of 3.5%.*

*(b) Example devices have been listed her. There might be other available from the NHS supply chain. Costs for consumable products such as head masks have not been included here as these costs would be the same irrespective of which devices is preferred.*

### 1.5.5 Health economic modelling

This analysis was conducted as a sub-analysis of the main guideline model, which covered the diagnostic and treatment pathway for people suspected of having OSAHS (See Economic analysis report).

#### 1.5.5.1 Strategies compared

The cost of auto-CPAP devices are more expensive than the fixed level devices. However, this cost will be at least partially offset by reduced staff time required in re-titrating patients. Since the cost of re-titration can be reduced in the presence of telemonitoring, we considered costs in the presence and absence of telemonitoring.

#### 1.5.5.2 Methods and data sources (Summary)

- Health outcomes
    - We assumed no difference in patient outcomes between strategies.
- Costs
    - Set up costs, 3 month review and annual review costs were assumed to be the same for each strategy and only device costs, telemonitoring and retitration costs differ between strategies
    - The cost of the CPAP devices and consumables were extracted from the NHS Supply catalogue (and VAT removed). The unweighted mean of different devices (excluding VAT) was used in the model base case - £207 for fixed-CPAP and £320 for auto-CPAP. Higher and lower costs were used in a sensitivity analysis.
    - The device costs were annuitized using a discount rate of 3.5% and assuming the equipment is replaced after 7 years.
    - Telemonitoring costs were from ResMed (£45 for one year or £150 for 5 years).
    - Education and set up was costed as a respiratory consultant-led outpatient consultation and follow-up was a non-consultant-led outpatient consultation. The unit costs were 'NHS costs'.
- Re—titration
    - Re-titration using telemonitoring was assumed to take up 20 minutes of a physiologist's time (60 minutes in a sensitivity analysis).
    - Re-titration using auto-titration was assumed to require an auto-CPAP machine over 2 nights and analysis of the results was assumed to take 45 minutes of a physiologist's time (75 minutes in a sensitivity analysis) and 10 minutes of a medical consultant.
    - The unit cost of staff time used in re-titration were standard NHS costs from the PSSRU (£47 per hour for a band 6 physiologist and £109 per hour for a medical consultant)
    - It was assumed that 18% of patients using fixed-CPAP would require re-titration – based on the number of patients having an unplanned contact in one of the included trials.[23] This was increased to 30% in a sensitivity analysis.
- Lifetime costs
    - The lifetime costs were calculated from the main guideline model and include the cost of RTAs and the health care costs associated with treating cardiovascular events. However, these costs were assumed not to vary between strategies. The difference in lifetime cost between strategies is attributable to the differences in device, telemonitoring and retitration costs.
    - The lifetime costs were based on a cohort of men aged 50. This was calculated separately for men with mild OSAHS and for men with moderate

OSAHS. The only difference was that dropout from treatment was greater than for the men with mild OSAHS.

The resulting cost per year of treatment is shown in Table 14.

**Table 14: Cost (£) of each strategy per year of treatment**

| | Device Cost | Staff | Retitration staff time | Tele-monitoring access | Con-sumables | Total |
|---|---|---|---|---|---|---|
| **Year 1** | | | | | | |
| Fixed-level CPAP with auto-titration | 32.63 | 265.57 | 9.70 | | 101.21 | 409.11 |
| Fixed-level CPAP with telemonitoring | 32.63 | 265.57 | 2.82 | 30.00 | 101.21 | 432.23 |
| Fixed-level CPAP with telemonitoring (yr 1 only) | 32.63 | 265.57 | 2.82 | 45.00 | 101.21 | 447.23 |
| Auto-CPAP only | 50.55 | 265.57 | | | 101.21 | 417.33 |
| Auto-CPAP with telemonitoring | 50.55 | 265.57 | | 30.00 | 101.21 | 447.33 |
| **Year 2 onwards** | | | | | | |
| Fixed-level CPAP with auto-titration | 32.63 | 119.97 | 0.00 | | 101.21 | 253.81 |
| Fixed-level CPAP with telemonitoring | 32.63 | 119.97 | 0.00 | 30.00 | 101.21 | 283.81 |
| Fixed-level CPAP with telemonitoring (yr 1 only) | 32.63 | 119.97 | 0.00 | | 101.21 | 253.81 |
| Auto-CPAP only | 50.55 | 119.97 | | | 101.21 | 271.73 |
| Auto-CPAP with telemonitoring | 50.55 | 119.97 | | 30.00 | 101.21 | 301.73 |

### Results

The lowest cost strategy was Fixed-level CPAP with auto-titration followed by Fixed-level CPAP with telemonitoring for one year and then by auto-CPAP – see Table 15. The ranking was the same across all the sensitivity analyses.

**Table 15: Lifetime mean cost (£) per patient of each strategy**

| | Base case | Low auto-CPAP price and high fixed-level CPAP price | 30% require retitration in year 1 | Increased staff time for retitration | All 3 (least favourable to fixed-level CPAP) |
|---|---|---|---|---|---|
| **Mild OSAHS** | | | | | |
| Fixed-level CPAP with auto-titration | 9,646 | 9,698 | 9,652 | 9,650 | 9,712 |

| | Base case | Low auto-CPAP price and high fixed-level CPAP price | 30% require retitration in year 1 | Increased staff time for retitration | All 3 (least favourable to fixed-level CPAP) |
|---|---|---|---|---|---|
| Fixed-level CPAP with telemonitoring | 10,013 | 10,065 | 10,015 | 10,018 | 10,076 |
| Fixed-level CPAP with telemonitoring (yr 1 only) | 9,684 | 9,736 | 9,686 | 9,690 | 9,748 |
| Auto-CPAP only | 9,860 | 9,832 | 9,860 | 9,860 | 9,832 |
| Auto-CPAP with telemonitoring | 10,233 | 10,206 | 10,233 | 10,233 | 10,206 |
| **Moderate OSASHS** | | | | | |
| Fixed-level CPAP with auto-titration | 9,922 | 9,980 | 9,929 | 9,926 | 9,994 |
| Fixed-level CPAP with telemonitoring | 10,330 | 10,388 | 10,332 | 10,336 | 10,399 |
| Fixed-level CPAP with telemonitoring (yr 1 only) | 9,960 | 10,018 | 9,962 | 9,966 | 10,029 |
| Auto-CPAP only | 10,160 | 10,130 | 10,160 | 10,160 | 10,130 |
| Auto-CPAP with telemonitoring | 10,575 | 10,545 | 10,575 | 10,575 | 10,545 |

This analysis was assessed to be partially applicable because it does not include QALYs with potentially serious limitations, since resource use was based on expert opinion.

## 1.6 Economic evidence statements

- One cost-utility comparison based on a published cost consequences analysis found that:
  - Fixed-level CPAP dominated auto-CPAP for adults with OSAHS (based on OSAHS costs)
  - Fixed-level CPAP was cost effective compared with auto-CPAP for adults with OSAHS (£2000 per QALY gained) (based on all health care costs)

  This analysis was assessed to be partially applicable with potentially serious limitations.
- One cost analysis found that CPAP was cost saving compared to non-invasive ventilation for people with obesity hypoventilation syndrome.

  This analysis was assessed to be partially applicable with minor limitations.
- One original cost comparison found that:
  - Fixed-level CPAP (using auto-CPAP just for re-titration) was the lowest cost strategy
  - Fixed-level CPAP (with telemonitoring) was less costly than auto-CPAP *with* telemonitoring
  - Fixed-level CPAP (with telemonitoring for 1 year) was less costly than auto-CPAP *without* telemonitoring
  - Fixed-level CPAP (with telemonitoring) was more costly than auto-CPAP without telemonitoring

  This analysis was assessed to be partially applicable with potentially serious limitations.

# 1.7 The committee's discussion of the evidence

## 1.7.1 Interpreting the evidence

### 1.7.1.1 The outcomes that matter most

The committee considered the outcome of health-related quality of life as critical outcome for decision making. Other important outcomes included sleepiness scores (e.g. Epworth), Apnoea-Hypopnoea index, Oxygen desaturation index, hours of use, minor adverse effects of treatment, tolerability of the treatment (such as dry mouth, stuffy nose, mask intolerance), treatment pressure, expression of preference. The committee were also interested in the impact on co-existing conditions such as HbA1c for diabetes, cardiovascular events and systolic blood pressure for hypertension.

No evidence was identified for impact on cardiovascular events in the OSAHS population.

No evidence was identified for the outcomes of adverse effects of treatments, tolerability of the treatment, treatment pressure, expression of preference and impact on co-existing conditions for the OHS population.

### 1.7.1.2 The quality of the evidence

**OSAHS**

There was evidence from 48 studies: 36 studies compared auto-CPAP with fixed level CPAP, 6 studies compared non-invasive ventilation (NIV) with fixed level CPAP, and 6 studies compared addition of humidification to fixed CPAP with fixed level CPAP. The populations recruited to the studies were predominantly male with a recent diagnosis of OSAHS. At baseline, the study populations had high BMI and AHI scores, and symptom scores indicated that they had excessive daytime sleepiness.

Data on tolerability outcomes (nasal blockage, dry mouth, tolerance of treatment pressure and mask leak) used different scales to capture these outcomes. Data were presented narratively for studies where data could not be analysed. Hence the comparative effects on tolerability outcomes are uncertain. The committee took this very low quality data into account while interpreting the evidence for decision making.

All evidence was in people with moderate to severe sleep apnoea (AHI >/= 15 but <30 moderate and AHI >/= 30 severe); however the majority of the studies were in people with severe sleep apnoea.

The committee considered the clinical importance of AHI on a case by case basis, taking into consideration the baseline AHI and the improvement in severity of sleep apnoea.

The quality of the evidence varied from high to very low quality. The majority of the evidence was downgraded due to due to risk of bias, inconsistency and imprecision. Risk of bias was most commonly due to selection bias and lack of blinding. Where there was heterogeneity in the evidence for an outcome, outcomes were downgraded for inconsistency as sub-group analysis was not conducted as data was from the Cochrane review. The committee also acknowledged that some uncertainty existed across the effect sizes seen within the evidence, with some confidence intervals crossing the MID thresholds or line of no effect. The committee took into account the quality of the evidence, including the uncertainty in their interpretation of the evidence.

**OHS**

There was evidence from 9 studies - 3 studies compared non-invasive ventilation (NIV) with lifestyle advice only, 3 studies compared non-invasive ventilation (NIV) with CPAP, 1 study

compared non-invasive ventilation (NIV), CPAP and lifestyle advice and 2 studies compared volume assured non-invasive ventilation (NIV) with fixed non-invasive ventilation (NIV). All studies in the review included patients with severe sleep apnoea except for one study which had a mixed population including both moderate and severe sleep apnoea, and one that excluded patients with severe OSAHS. The quality of the evidence varied from high to very low quality; the majority of the evidence was downgraded due to risk of bias, inconsistency and imprecision. Risk of bias was most commonly due to selection bias and lack of blinding. Where there was heterogeneity in the evidence for an outcome, pre-specified subgroup analyses did not explain the variation in effect sizes. As a result, many outcomes were downgraded for inconsistency. The committee also acknowledged that some uncertainty existed across the effect sizes seen within the evidence, with some confidence intervals crossing the MID thresholds or line of no effect. The committee took this in to account in their interpretation of evidence.

**COPD-OSAHS overlap syndrome**

No evidence was identified for people with COPD-OSAHS overlap syndrome.

#### 1.7.1.3 Benefits and harms

## OSAHS

The evidence was available for people with moderate to severe OSAHS; however the majority of the studies in all three comparisons listed below were in people with severe OSAHS*.*

***Auto CPAP vs fixed level CPAP***

The evidence suggested that there was no clinically important difference between auto CPAP and fixed level CPAP for the outcomes of machine usage, number of participants who used CPAP therapy > 4 hours per night, symptoms (Epworth Sleepiness Scale), withdrawal, quality of life (measured by FOSQ, SAQLI and SF-36), Apnoea Hypopnoea Index (events/hr), arousals (events/hr), blood pressure, intolerable treatment pressure, mask leak and stuffy nose.

Overall there was no clinically important difference between auto CPAP and fixed level CPAP for the outcome treatment pressure, but there was a high degree of statistical variation. Despite the different mechanisms used to deliver mask pressure between the devices (auto CPAP and fixed level CPAP), in some studies the delivered treatment pressure was equivalent between auto-CPAP and fixed level CPAP, whilst in others the mean treatment pressure in auto-CPAP was between 3 and 5 cm H20 lower. Differences in algorithms used by the different machines used to alter pressure (e.g. forced oscillation), variation in peak treatment pressure within study populations and the selection of participants on the basis of high treatment pressure requirements, could contribute to the conflicting results. We consider the certainty of evidence for this outcome to be low because of this degree of variation. The committee acknowledged that in some OSAHS patients the lower mean pressure delivery from auto CPAP may be beneficial as it may lead to better tolerability, and in turn increase adherence to therapy.

There was also no clinically important difference between auto CPAP and fixed level CPAP for the outcome patient preference. However the results from the studies indicated wide variation between users of CPAP in terms of how they respond to the different modes of pressure delivery. In eight of the 14 studies reporting this outcome, there was a numerically superior preference for auto-CPAP over either fixed level CPAP, or neither treatment. However, in 6 studies the preference was in the opposite direction. There was no obvious explanation for this apparent discrepancy in terms of study design and technology of active

interventions. Narrative evidence for the outcomes mask leak, tolerance for treatment pressure and nasal blockage was inconsistent and this was based on very low quality evidence.

***Non-invasive ventilation (NIV) vs fixed level CPAP***

The evidence suggested that there was no clinically important difference between non-invasive ventilation (NIV) and fixed level CPAP for any of the following outcomes: machine usage (hours/night), symptoms (Epworth Sleepiness Scale), withdrawal, quality of life (measured by SAQLI and SF-36), Apnoea Hypopnoea Index (events/hr), patient preference, dry mouth, mask intolerance and treatment comfort.

There was clinically important benefit of non-invasive ventilation (NIV) compared to fixed level CPAP for the outcome dry mouth. The committee however were not confident of this outcome as there was some uncertainty around the effect estimate and it was based on one small study.

***Heated humidification with fixed pressure CPAP vs fixed level CPAP alone***

The evidence suggested that there was no clinically important difference between heated humidification with fixed level CPAP and fixed level CPAP alone for machine usage, symptoms (Epworth Sleepiness Scale), withdrawal, quality of life (measured by SF-36), Apnoea Hypopnoea Index (events/hr) and patient preference. There was a clinically important benefit of heated humidification + fixed level CPAP for nasal symptoms such as runny nose and congested nose (from dichotomous outcomes); however continuous data for the same outcomes did not show any clinically important difference between the two groups.

CPAP treatment options for mild/moderate/severe OSAHS-committee's consideration of the evidence to make recommendations

The NICE technology appraisal guidance TA139 on continuous positive airway pressure for the treatment of obstructive sleep apnoea/hypopnoea syndrome[175] recommends CPAP as a treatment option for moderate and severe OSAHS. In line with this, the committee agreed that CPAP should be first-line treatment for people with moderate and severe OSAHS. The evidence for use of CPAP in mild OSAHS is considered separately in Evidence Review E.

In the evidence reviewed for types of CPAP, most of the studies compared auto-CPAP with fixed level CPAP and measured machine usage, symptoms and AHI. There was weaker evidence (few studies) for quality of life. The evidence showed fixed level and auto CPAP to be equally effective and auto-CPAP to be more costly and therefore the committee recommended fixed level CPAP as first choice. However, some people, particularly those in whom high pressures are only needed part of the time, find auto-CPAP more comfortable and effective than fixed-level CPAP. For others, telemonitoring may not be possible because of technological constraints such as the lack of availability of internet or poor internet connection, auto-CPAP should be an option in these cases. The committee were also aware that some hospitals get significant discount on auto-CPAP devices which might make them more cost effective. Therefore, the committee agreed that if auto-CPAP is available at the same or lower cost than fixed-level CPAP, auto CPAP could be considered.

The committee based on their experience discussed the advantages of telemonitoring. These include early night-by-night access to data which can lead to early detection of problems such as mask leaks or persistent respiratory events of sleep apnoea, and the ability to monitor that OSAHS so that it continues to be effectively controlled and the individual is adherent to therapy. Telemonitoring makes managing a person's OSAHS more efficient for clinicians as they have ready access to the data should they need it. For example, if contacted by a person with an issue they can use the data to help identify the problem (for example, mask leak or inadequate pressure) and take appropriate action without the need for a scheduled appointment. The committee agreed that video and telephone consultations along with telemonitoring is also advantageous to people with

OSAHS as it can reduce the number of in-person visits needed to the sleep service. This can be particularly beneficial to patients who have difficulty in getting to clinics, for example, people who live in remote places or people with poor mobility, there would be fewer clinic visits in such cases. The reduction in the number of face-to-face consultations will also help reduce the risk of infection during the COVID-19 pandemic. Telemonitoring has facilitated remote assessment of patients during the coronavirus pandemic and has become a standard follow-up option in most sleep services. This use is likely to continue long term, because it is convenient for patients, enables them to assess progress themselves and allows access to efficacy and adherence data whenever needed, for example, for problem solving, routine follow-up and to complete DVLA reports.

The costs of telemonitoring were also discussed and the committee noted that in their experience, telemonitoring is included in the price of the machine for 12 months. Based on this they agreed that telemonitoring should be offered alongside CPAP for the first 12 months of treatment, and considered beyond 12 months where optimal control of symptoms and AHI has not been achieved, or to help with solving problems that people with OSAHS might experience. However, some people, particularly those in whom high pressures are only required for part of the time, find auto CPAP significantly more comfortable and effective than fixed level CPAP. For others, telemonitoring may not be possible because of technogical constraints such as the lack of availalblity of internet or poor internet connection. The committee agreed that auto-CPAP should be available in these cases.The committee discussed that initial pressure setting for CPAP is important to help ensure patient adherence to therapy and improve important outcomes, but they agreed that this should be a clinical decision individual to each person with OSAHS.

People who have previously used CPAP prior to study entry are under-represented in the studies included in the review. The results of the studies that recruited from this population do not provide evidence of substantially different results in terms of either usage or functional outcomes in these groups.

The evidence was available for people with moderate to severe OSAHS; the committee agreed that the data could be extrapolated to people with mild OSAHS as well.

The committee discussed that there was a variation in practice in the UK in the use of fixed level CPAP and auto CPAP, with bigger centres generally using fixed level CPAP and smaller centres using auto CPAP.

Given the low quality evidence and uncertainty about the cost-effectiveness between auto and fixed-level CPAP the committee made a research recommendation to help inform future guidelines (see Appendix J:). The committee did not make a research recommendation for long term use of telemonitoring as they believe telemonitoring is already becoming common practice and will remain so in the future. They agreed it is more convenient for CPAP users and clinicians. It also saves time as users do not need to download data and post or take it in to the sleep service.

Evidence suggested that there was clinically important benefit of addition of heated humidification for nasal symptoms such as runny nose and congested nose, but the results were not consistent. The committee from their experience of current practice agreed that addition of humidification to CPAP should be considered for people with all severities of OSAHS who have nasal symptoms, as it could reduce side effects causing upper airway symptoms and subsequently improve adherence and treatment effectiveness.

The evidence for CPAP compared to conservative management and other interventions in mild OSAHS population is in Evidence report E and the evidence for telemonitoring is in Evidence report L.

The committee agreed that all people with OSAHS should also be offered lifestyle advice including weight loss, smoking cessation, sleep hygiene and reduced alcohol intake

alongside the chosen treatment method as obesity increases the prevalence and severity of OSAHS, smoking causes upper airway inflammation which can exacerbate symptoms, and excess alcohol before sleep reduces upper airway tone increasing apnoeas, and reduces sleep quality. Sleep hygiene recommendations include ensuring adequate sleep time, avoiding caffeine and stimulants that interfere with sleep prior to bedtime, exercising regularly, having a quiet, comfortable, darkened bedroom, and winding down before sleep For lifestyle advice refer to NICE guidelines on stop smoking interventions and services, preventing excess weight gain , obesity and alcohol-use disorders: prevention.[170, 172-174]

The recommendations for CPAP reflect current practice in most centres. Some sleep services currently using auto CPAP, may switch to fixed level CPAP for new patients starting CPAP*,* which is likely to be cost saving.

## OHS

Where the severity of OSAHS associated with OHS was characterised, evidence was for severe rather than mild and moderate OSAHS. The committee noted that differentiation into OHS with OSAHS or OHS without OSAHS (usually with nocturnal hypoventilation) based on the diagnostic sleep study is helpful.

### *Non-invasive ventilation (NIV) vs lifestyle change*

In people with OHS (both with and without severe OSAHS), the evidence suggested that there was clinically important benefit of non-invasive ventilation for change in PaCO2, PaO2, change in AHI change in ODI, and symptoms (change in ESS), compared to lifestyle changes, although there was some uncertainty around the effect estimates. The evidence suggested that there were no clinically important differences between non-invasive ventilation and lifestyle for change in HbA1c and change in systolic blood pressure. There was inconsistency in quality of life outcomes with benefit of non-invasive ventilation for quality of life measured by FOSQ and no difference between non-invasive ventilation and lifestyle when measured by SF-36 . All outcomes were measured at 2 months follow-up.

In people with OHS without severe OSAHS at 3 years follow-up, the evidence suggested that there was clinically important benefit of non-invasive ventilation for PaCO2 and ESS compared to lifestyle changes, although there was some uncertainty around the effect estimates. The evidence suggested that there were no clinically important differences between non-invasive ventilation and lifestyle for systolic blood pressure, diastolic blood pressure, mortality and cardiovascular events, however there was some uncertainty around the effect estimates. There was inconsistency in quality of life outcomes with benefit of non-invasive ventilation for quality of life measured by FOSQ and SF-36 physical at 3 years and no difference between non-invasive ventilation and lifestyle for SF-36 mental. All outcomes were measured at 3 years follow-up.

It is important to note these studies included stable patients (who do not have acute ventilatory failure) who tolerated and showed an adequate response to CPAP. All studies excluded people with acute ventilatory failure, or who did not tolerate and respond to CPAP in a preliminary trial, and therefore recommendations for management in these people is based on expert opinion, with provision of NIV.

### *Non-invasive ventilation (NIV) vs CPAP*

In clinically stable patients with OHS (who do not have acute ventilatory failure) and severe OSAHS the evidence suggested that there was no clinically important difference between non-invasive ventilation and CPAP for quality of life (measured by SF-36), adherence, change in AHI, and change in ODI, change in PaCO2, change in symptoms, systolic blood pressure, cardiovascular events and hospitalisation per patient per year. There was clinically important benefit of non-invasive ventilation for mortality and the outcome FOSQ. The

apparent mortality benefit was based on a small number of events and the committee viewed this result with caution.

There were no studies of CPAP in patients with OHS in whom severe OSAHS had been excluded since conceptually CPAP is not a treatment for hypoventilation that is not a result of obstructive events. Therefore in this group, non-invasive ventilation is recommended. However the committee agreed that research of the efficacy of CPAP in this patient group would be of interest, since mechanisms of CPAP benefit may extend beyond simply splinting the upper airway. As the committee made a strong recommendation for this population, they did not make a research recommendation.

There were no studies of CPAP vs non-invasive ventilation in people with acute ventilatory failure; the committee recommended non-invasive ventilation in this patient group since rapid improvement in hypercapnia is a priority, and patients are often too unwell to discontinue treatment whilst sleep studies are carried out. The committee agreed there are no real harms if non-invasive ventilation is indicated and it is tolerated better than CPAP.

***Fixed NIV vs volume assured NIV***

The evidence suggested that there was no clinically important difference between fixed NIV and volume assured non-invasive ventilation for disease specific quality of life, symptoms (Epworth Sleepiness Scale), PaCO2, PaO2, Adherence (hours per night), AHI and ODI.

***CPAP vs lifestyle (dietary and lifestyle counselling)***

The evidence suggested that there was clinically important benefit of CPAP for change in symptoms (ESS), change in AHI, change in ODI compared to lifestyle (dietary and lifestyle counselling. However there was some uncertainty around the effect estimate for the outcome ESS. The evidence suggested that there was no clinically important difference between CPAP and lifestyle for change in PaCO2. There was inconsistency in quality of life outcomes with benefit of CPAP for quality of life SF-36 mental and FOSQ and no difference between NIV and lifestyle for SF-36 physical. There was no evidence for CPAP vs non-invasive ventilation for management of patients with obesity hypoventilation without severe OSAHS.

Treatment options for OHS-committee's consideration of the evidence to make recommendations

The committee's experience is that approximately 90% of the people with OHS have associated OSAHS of at least mild severity, and 70% severe OSAHS. The evidence was limited to people with OHS and severe OSAHS who were stable (who do not have acute ventilatory failure). It showed that both CPAP and non-invasive ventilation are beneficial compared with lifestyle changes, and that there was little difference in effectiveness between these treatments. There was no evidence comparing CPAP and non-invasive ventilation for people with acute ventilatory failure.

OSAHS and obesity are associated with increased cardiovascular disease, type 2 diabetes and mortality, and the committee therefore agreed that advice regarding weight loss should be offered to all people with OHS to reduce their risk. The committee agreed that all people with OHS should also be offered lifestyle advice including weight loss, smoking cessation, sleep hygiene and reduced alcohol intake alongside the chosen treatment method as obesity increases the prevalence and severity of OHS, smoking causes upper airway inflammation which can exacerbate symptoms, and excess alcohol before sleep reduces upper airway tone increasing apnoeas, and reduces sleep quality. Sleep hygiene recommendations include ensuring adequate sleep time, avoiding caffeine and stimulants that interfere with sleep prior to bedtime, exercising regularly, having a quiet, comfortable, darkened bedroom, and winding down before sleep. For lifestyle advice refer to NICE guidelines on stop smoking interventions and services,[173] preventing excess weight gain,[172] obesity[170] and alcohol-use disorders: prevention.[174]

People with OHS who do not have acute ventilatory failure

In people with stable OHS and severe OSAHS, based on the evidence and their experience, the committee agreed that CPAP should be offered as a first line treatment because it is more cost-effective, simpler to set up and may be better tolerated than non-invasive ventilation, and it is effective even in mild to moderate hypercapnia. The committee discussed that it seems probable that hypercapnic ventilatory failure in the obese with severe obstructive sleep apnoea is driven in part by the increased work of breathing due to upper airway obstruction of severe OSAHS, rather than the obesity itself. Therefore the committee agreed that stable patients (who do not have acute ventilatory failure) with severe OSAHS could be effectively treated with CPAP alone to alleviate upper airway obstruction and associated severe OSAHS.

If symptoms do not improve, hypercapnia persists, AHI or ODI are not sufficiently reduced or CPAP is poorly tolerated, the committee agreed that treatment should be changed to non-invasive ventilation to control nocturnal hypoventilation.

In line with current practice the committee agreed that non-invasive ventilation should be considered for people with OHS and nocturnal hypoventilation who do not have OSAHS, or in whom OSAHS is not severe.

People with OHS and acute ventilatory failure

All studies excluded people with acute ventilatory failure, and therefore the recommendations for their management is based on committee experience. Although there was no direct evidence available, the committee were clear that non-invasive ventilation should be the first-line treatment for people with OHS and acute ventilatory failure because rapid improvement in hypercapnia is a priority. People in whom hypercapnia resolves may have a trial without non-invasive ventilation. In this instance, they should remain under review in case hypercapnia recurs and re-started on non-invasive ventilation, if necessary. Assessement with respiratory polygrahy on recovery should be carried out to to determine the need to treat long-term with CPAP or non-invasive ventilation. The committee agreed that people with residual OSAHS but minimal hypoventilation when stable can be switched to CPAP.

For people with OHS, the committee made separate recommendations for people who were stable (who do not have acute ventilatory failure)) and OHS patients with acute ventilatory failure.

The committee noted from their experience that long-term non-invasive ventilation therapy should be considered if hypercapnia persists. People in whom hypercapnia resolves may have a trial without non-invasive ventilation. In this instance, they should remain under review in case hypercapnia recurs, and should be assessed with respiratory polygraphy on recovery to determine the need to treat long-term with CPAP or non-invasive ventilation. The committee agreed that people with residual OSAHS but minimal hypoventilation when stable can be switched to CPAP.

Due to lack of evidence comparing auto vs fixed level CPAP in OHS, the committee did not specify the type of CPAP. The committee discussed whether evidence from people with OSAHS could be used for people with OHS. They agreed that the differences between these two groups are too great to allow them to make a consensus recommendation based on the evidence in OSAHS. They discussed whether there should be a research recommendation for auto vs fixed CPAP in OHS but decided against this because auto CPAP is likely to be less effective in this patient group than fixed CPAP as less time is spent at therapeutic pressure.

The committee stated that in current practice a trial of discontinuing non-invasive ventilation, carrying out respiratory polygraphy and considering conservative management or step-down

to CPAP are not always undertaken, hence these steps would be a change in practice that is likely to result in less non-invasive ventilation use.

Based on the evidence reviewed for OSAHS and their experience of current practice, the committee agreed that addition of humidification to CPAP should be considered in people with OHS who have nasal symptoms, as it could reduce upper airway side effects and consequently improve adherence and treatment effectiveness.

### COPD-OSAHS overlap syndrome

There was no evidence available for this population. The committee used their collective experience to make the recommendations. The committee agreed that treatment for this population depends on the level of hypercapnia when awake and asleep. People with more severe daytime hypercapnia ($PaCO_2$ greater than 7 kPa) caused by nocturnal hypoventilation, are likely to need non-invasive ventilation. This is based on extrapolation from data, not reviewed for this guideline but, in whom definite benefit of non-invasive ventilation has not been demonstrated when hypercapnia is modest (PaCO2 between 6 and 7 kPa and not associated with exacerbation of COPD). The decision to treat with CPAP in the absence of a PaCO2 >7kPa is based upon clinical severity and symptom burden of OSAHS. The committee therefore recommended that CPAP should be considered in people with COPD-OSAHS overlap syndrome if they have confirmed OSAHS from a sleep study and if their PaCO2 is less than or equal to 7.0 kPa, and non-invasive ventilation should be considered if the PaCO2 is higher. Based on the evidence reviewed for OSAHS and their experience of current practice, the committee agreed that addition of humidification to CPAP should be considered for people with all COPD-OSAHS overlap syndrome who have nasal symptoms, because it may reduce upper airway side effects and consequently improve adherence and treatment effectiveness.

The committee agreed that all people with COPD-OSAHS overlap syndrome should also be offered lifestyle advice including weight loss, smoking cessation, sleep hygiene and reduced alcohol intake alongside the chosen treatment method as obesity increases the prevalence and severity of COPD-OSAHS overlap syndrome, smoking causes upper airway inflammation which can exacerbate symptoms, and excess alcohol before sleep reduces upper airway tone increasing apnoeas, and reduces sleep quality. Sleep hygiene recommendations include ensuring adequate sleep time, avoiding caffeine and stimulants that interfere with sleep prior to bedtime, exercising regularly, having a quiet, comfortable, darkened bedroom, and winding down before sleep. For lifestyle advice refer to NICE guidelines on stop smoking interventions and services,[173] preventing excess weight gain,[172] obesity[170] and alcohol-use disorders: prevention.[174]

The committee agreed that the recommendations reflect current actual practice.

As there was no evidence for CPAP compared to non-invasive ventilation for people with COPD-OSAHS overlap syndrome, the committee made a research recommendation to inform future guidance as to in which scenario CPAP or non-invasive ventilation is preferred for people with COPD-OSAHS overlap syndrome.

### Reducing the risk of transmission of infection when using CPAP or non-invasive ventilation

The committee agreed that CPAP and non-invasive ventilation are aerosol generating procedures and where there is a risk of airborne infection, such as during a time of COVID-19 risk, appropriate infection control precautions should be taken, which may include device modification.

## 1.7.2 Cost effectiveness and resource use

#### OSAHS

NICE's technology appraisal TA139[175] recommended positive airway pressure devices as a treatment option for adults with moderate or severe symptomatic OSAHS. However, TA139 does not specify the type of positive airway pressure devices that should be used. In the NHS supply catalogue, the acquisition cost of auto-CPAP was over £100 higher than fixed level CPAP, depending on the type and brand of device, although the committee are aware that some hospitals get significant discounts. Positive airway pressure devices are a lifetime intervention and a replacement device is required every 5-7 years or 10,000 hours). It has been estimated that the treated OSAHS population in the UK is 330,000[220] or even as high as 700,000[92] and the currently untreated population is considerably larger therefore there is potential for a significant resource impact.

As there was no important differences in the key clinical outcome measures, the committee agreed that costs were important when considering fixed-level CPAP versus auto-CPAP. Therefore, a cost-comparison analysis was incorporated into the economic model developed for the guideline to identify the least expensive device over a lifetime horizon. The committee identified five key strategies which sufficiently captured the different methods of using fixed-level CPAP or auto-CPAP. The lowest cost strategies were fixed-level CPAP with autotitration and fixed-level CPAP with telemonitoring for the first year. The committee decided to recommend telemonitoring as a tool for improving adherence but also to reduce contact with patients that might lead to transmission of infectious disease (see Evidence reports L and M).

After the development of this model, a published cost-consequences analysis was found that was based on a trial with one-year follow-up in Switzerland. This too found a trend towards lower OSAHS treatment costs for fixed-level CPAP, although the trend for all health care costs favoured auto-CPAP. Neither difference was statistically significant.

The committee concluded that fixed-level CPAP is generally likely to be less costly and more efficient than auto-CPAP but there is some uncertainty and this could be affected by local factors including the prices of devices and consumables or a need to reduce staff time spent on pressure adjustment.

The committee recommended that fixed-level be offered first-line. They recommended that auto-CPAP should be considered in situations when there is a need for high pressure only for certain times during sleep or if a patient is not tolerant to fixed-level CPAP. There might be local circumstances where auto-CPAP can be purchased and administered at the same or lower cost as fixed-level CPAP. In this circumstance, the committee decided that auto-CPAP could be considered, if this price is guaranteed for an extended period of time.

In the economic analyses of treatment for mild OSAHS and diagnostic strategies, CPAP was cost effective compared to both conservative management and mandibular advancement splints, regardless of whether the cost of fixed-level CPAP or auto-CPAP were used in the model (see Evidence reports D and E).

There was no cost effectiveness evidence for the use of humidification and the clinical evidence was mainly related to increased machine usage. The committee formed a consensus recommendation that humidification need not be offered first line but that it should be added to CPAP for people with OSAHS who have nasal or oral symptoms, to improve the quality of their sleep and optimise adherence to treatment. This addition is current practice (the committee estimated that it would apply to 30% to 50% of people receiving CPAP devices for OSAHS).

**OHS**

A single published economic evaluation was found comparing CPAP with non-invasive ventilation (NIV) for people with OHS. This study in a Spanish setting did not evaluate patient outcomes but found that CPAP was cost saving compared to NIV

The clinical evidence showed significant benefits for CPAP over lifestyle intervention for a number of outcomes including quality of life, which the committee considered were likely to be cost effective. The clinical evidence did not show important benefits for NIV over CPAP. The committee divided the obesity hypoventilation population into two categories: 1) a stable population 2) a population with acute ventilatory failure.

In the population who are stable and have severe OSAHS, the committee recommended the provision of CPAP as a first line treatment and only a switch to NIV if hypercapnia persists after follow up. The committee suggested that this would be a significant change in practice as historically, NIV would usually have been offered as first line. The committee explained this would achieve substantial cost savings. If there is no OSAHS in the stable OHS population, the committee formed a consensus recommendation based on their experience, that people in this group should be considered for NIV. As this is already occurring in current practice, the recommendation is expected to be cost-neutral. The committee also considered whether CPAP devices would be appropriate for this stable OHS group (without OSAHS) over the more expensive NIV, however, the committee concluded that in the absence of OSA, alveolar ventilation must be augmented using pressure support ventilation and therefore it would be physiologically inappropriate to use CPAP in this situation.

For people with acute ventilatory failure, as the absence of NIV would have the potential to result in death, the committee were of the strong view that all people in this category should be offered NIV. As this is already routinely offered in current practice, this recommendation would be cost-neutral. In those instances where hypercapnia is resolved, the committee recommended that the need for ongoing NIV, as opposed to CPAP, be reviewed. However follow-up including respiratory polygraphy to ensure that sleep disordered breathing *is well controlled,* and hypercapnia has not r*e*curred, wasconsidered advisable.

The recommendations on the choice of pressure variant device for the OHS population as a whole is likely to result in cost-savings for the NHS from reduced use of NIV but this will be partly offset by the need for additional sleep studies and $CO_2$ testing.

**COPD-OSAHS overlap syndrome**

There was no relevant published clinical or economic evidence found for this population.

The committee made consensus recommendations that are in line with current practice and therefore there is not expected to be significant resource impact:

- The less costly treatment CPAP as the first-line treatment
- Consideration of non-invasive ventilation for people with hypercapnia
- Consideration of supplemental oxygen therapy in people whose symptoms persist.

### 1.7.3 Other factors the committee took into account

The views of lay members were taken into consideration when reviewing types of devices such as fixed level CPAP, auto CPAP, non-invasive ventilation and whether humidification is used or not. The lay member's emphasised above all that it is important to provide a personalised therapy. This is as much a consideration of which device should be used in conjunction with the best evidence available but also and more importantly when considering mask interfaces.

There are a number of different services throughout the country providing fixed level CPAP, auto CPAP and non-invasive ventilation. Some of the services have historically chosen particular device options due to other resource limitations. For example using an auto CPAP may mean that less clinic appointments are needed for device titration. The advent of more effective telemonitoring ability and reduction in cost means that remote monitoring is available across all devices. Therefore the ability to clinically manage and change patient therapy can be provided without a face to face clinic appointment but though telephone,

telemonitoring or other electronic communication strategy. This ability to use telemonitor as well as use virtual clinics can change the way that services provide ongoing follow up support for patients. This will be particularly helpful in rural and logistically challenging regions of the country (see evidence report for detailed discussion of telemonitoring in chapter L).

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# Appendices

# Appendix A: Review protocols

**Table 16: Review protocol: Positive Airway Pressure therapy variants for OSAHS/OHS/ COPD-OSAHS overlap syndrome**

| Field | Content |
|---|---|
| PROSPERO registration number | Not registered |
| Review title | Positive Airway Pressure therapy variants for OSAHS/OHS/ COPD-OSAHS overlap syndrome |
| Review question | What is the comparative clinical and cost effectiveness of different types of positive airway pressure devices (for example, fixed-pressure CPAP, variable-pressure CPAP, bi-level positive airway pressure or other modes of non-invasive ventilation for managing obstructive sleep apnoea/hypopnoea syndrome, obesity hypoventilation syndrome and COPD-OSAHS overlap syndrome?<br><br>What is the clinical and cost effectiveness of the addition of humidification to positive airway pressure therapy for managing obstructive sleep apnoea/hypopnoea syndrome, obesity hypoventilation syndrome and COPD-OSAHS overlap syndrome? |
| Objective | To determine the most clinical and cost effective variants of positive airway pressure devices to use in OSAHS, OHS and COPD-OSAHS overlap syndrome |
| Searches | The following databases (from inception) will be searched:<br>• Cochrane Central Register of Controlled Trials (CENTRAL)<br>• Cochrane Database of Systematic Reviews (CDSR)<br>• Embase<br>• MEDLINE<br>• EPISTEMONIKOS<br><br>Searches will be restricted by:<br>• English language studies<br><br>The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant.<br><br>The full search strategies will be published in the final review. |
| Condition or domain being studied | Obstructive sleep apnoea/hypopnoea syndrome is the most common form of sleep disordered breathing. The guideline will also cover obesity hypoventilation syndrome and COPD-OSAHS overlap syndrome (the coexistence of obstructive sleep apnoea/hypopnoea syndrome and chronic obstructive pulmonary disease |
| Population | Inclusion: People (16 and older) with OSAHS, OHS or COPD-OSAHS overlap syndrome (only if formal diagnosis methods) |

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| | Population will be stratified by:<br>• population: OSAHS, OHS, COPD-OSAHS overlap syndrome<br>• severity: Mild, moderate, severe (based on AHI/ODI)<br><br>Severity:<br>• Mild OSAHS: AHI >5 but <15<br>• Moderate OSAHS: AHI >/= 15 but <30<br>• Severe OSAHS: AHI >/= 30<br>When a mixed severity population is included the severity of the majority of the population will be used by taking the mean AHI of the patients included and the study will be downgraded for indirectness.<br><br>Exclusion: Children and young adults (under 16 years old) |
| Intervention/Exposure/Test | • Fixed pressure (default) CPAP with humidification<br>• Fixed pressure CPAP without humidification |
| Comparator/Reference standard/Confounding factors | • Variable pressure CPAP with humidification<br>• Variable pressure CPAP without humidification<br>• Bi-level positive airwaypressure*/Non-invasive ventilation (NIV) with humidification<br>• Bi-level positive airway pressure/ non-invasive ventilation (NIV) without humidification<br>• No positive airway pressure device (for OHS and mild OSAHS only)<br><br>Compare fixed CPAP with variable pressure CPAP (with or without humidification) and bilevel positive airway pressure<br><br>* Non-invasive ventilation is the preferred terminology |
| Types of study to be included | Published NMAs and IPDs will be considered for inclusion.<br>• RCTs only<br>• Systematic review of RCTs<br>• Parallel or crossover to be included<br><br>Minimum duration of follow-up 1 months |
| Other exclusion criteria | Non-English language studies.<br><br>Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available. |
| Context | - |
| Primary outcomes (critical outcomes) | • Generic or disease specific quality of life measures (continuous)<br><br>Minimum follow up: 1 month |
| Secondary outcomes (important outcomes) | • Sleepiness scores (continuous, e.g. Epworth)<br>• Apnoea-Hypopnoea index (continuous)<br>• Oxygen desaturation index (continuous)<br>• Hours of use (adherence measure, continuous)<br>• Minor adverse effects of treatment (rates or dichotomous)<br>• Impact on co-existing conditions:<br>o HbA1c for diabetes (continuous)<br>o Cardiovascular events for cardiovascular disease (dichotomous)<br>o Systolic blood pressure for hypertension (continuous) |

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| | • tolerability of the treatment<br>• treatment pressure<br>• expression of preference<br><br>Minimum follow up: 1 month |
| Data extraction (selection and coding) | EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above.<br>EviBASE will be used for data extraction. |
| Risk of bias (quality) assessment | Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual.<br>For Intervention reviews<br>• Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS)<br>• Randomised Controlled Trial: Cochrane RoB (2.0)<br><br>10% of all evidence reviews are quality assured by a senior research fellow. This includes checking:<br>• papers were included /excluded appropriately<br>• a sample of the data extractions<br>• correct methods are used to synthesise data<br>• a sample of the risk of bias assessments<br>Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. |
| Strategy for data synthesis | • Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5).<br>• GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome.<br>The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/<br><br>Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome.<br>• WinBUGS will be used for network meta-analysis, if possible given the data identified.<br>Heterogeneity between the studies in effect measures will be assessed using the $I^2$ statistic and visually inspected. An $I^2$ value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to |

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| | explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects. | |
| Analysis of sub-groups | Subgroups that will be investigated if heterogeneity is present:<br>• High risk occupational groups (for example heavy goods vehicle drivers, pilots) vs general population<br>• Sleepiness – Epworth >9 vs Epworth 9 or less<br>• Coexisting conditions – type 2 diabetes vs atrial fibrillation vs hypertension vs none<br>• Precise humidification – HME vs cold passover water baths<br>• BMI – obese vs non-obese | |
| Type and method of review | ☒ | Intervention |
| | ☐ | Diagnostic |
| | ☐ | Prognostic |
| | ☐ | Qualitative |
| | ☐ | Epidemiologic |
| | ☐ | Service Delivery |
| | ☐ | Other (please specify) |
| Language | English | |
| Country | England | |
| Anticipated or actual start date | NA – not registered on PROSPERO | |
| Anticipated completion date | NA – not registered on PROSPERO | |
| Named contact | 5a. Named contact<br>National Guideline Centre<br><br>5b Named contact e-mail<br>SleepApnoHypo@nice.org.uk<br>5e Organisational affiliation of the review<br>National Institute for Health and Care Excellence (NICE) and the National Guideline Centre | |
| Review team members | From the National Guideline Centre:<br>Carlos Sharpin, Guideline lead<br>Sharangini Rajesh, Senior systematic reviewer<br>Audrius Stonkus, Systematic reviewer<br>Emtiyaz Chowdhury (until January 2020), Health economist<br>David Wonderling, Head of health economics<br>Agnes Cuyas, Information specialist (till December 2019)<br>Jill Cobb, Information specialist | |

| | |
|---|---|
| Funding sources/sponsor | This systematic review is being completed by the National Guideline Centre which receives funding from NICE. |
| Conflicts of interest | All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline. |
| Collaborators | Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10098 |
| Other registration details | NA – not registered A |
| Reference/URL for published protocol | NA – not registered |
| Dissemination plans | NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as:<br>• notifying registered stakeholders of publication<br>• publicising the guideline through NICE's newsletter and alerts<br>• issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE. |
| Keywords | - |
| Details of existing review of same topic by same authors | NA |
| Additional information | - |
| Details of final publication | www.nice.org.uk |

**Table 17: Health economic review protocol-OSAHS**

| Review question | All questions – health economic evidence |
|---|---|
| **Objectives** | To identify health economic studies relevant to any of the review questions. |
| **Search criteria** | • Populations, interventions and comparators must be as specified in the clinical review protocol above.<br>• Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis).<br>• Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) |

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|---|---|
| | • Unpublished reports will not be considered unless submitted as part of a call for evidence.<br>• Studies must be in English. |
| **Search strategy** | A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below. |
| **Review strategy** | Studies not meeting any of the search criteria above will be excluded. Studies published before 2003, abstract-only studies and studies from non-OECD countries or the USA will also be excluded.<br>Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[171]<br><br>**Inclusion and exclusion criteria**<br>• If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile.<br>• If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile.<br>• If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included.<br><br>**Where there is discretion**<br>The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.<br><br>The health economist will be guided by the following hierarchies.<br>*Setting:*<br>• UK NHS (most applicable).<br>• OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).<br>• OECD countries with predominantly private health insurance systems (for example, Switzerland).<br>• Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.<br>*Health economic study type:*<br>• Cost–utility analysis (most applicable).<br>• Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).<br>• Comparative cost analysis.<br>• Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.<br>*Year of analysis:*<br>• The more recent the study, the more applicable it will be. |

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| | • Studies published in 2003 or but that depend on unit costs and resource data entirely or predominantly from before 2003 will be rated as 'Not applicable'.<br>• Studies published before 2003 will be excluded before being assessed for applicability and methodological limitations.<br>*Quality and relevance of effectiveness data used in the health economic analysis:*<br>• The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline. |

OHS

**Table 18: Health economic review protocol**

| Review question | All questions – health economic evidence |
|---|---|
| **Objectives** | To identify health economic studies relevant to any of the review questions. |
| **Search criteria** | • Populations, interventions and comparators must be as specified in the clinical review protocol above.<br>• Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis).<br>• Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.)<br>• Unpublished reports will not be considered unless submitted as part of a call for evidence.<br>• Studies must be in English. |
| **Search strategy** | A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below. |
| **Review strategy** | Studies not meeting any of the search criteria above will be excluded. Studies published before 2003, abstract-only studies and studies from non-OECD countries or the USA will also be excluded.<br>Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[171]<br><br>**Inclusion and exclusion criteria**<br>• If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile.<br>• If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile.<br>• If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included.<br><br>**Where there is discretion**<br>The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in |

discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.

The health economist will be guided by the following hierarchies.

*Setting:*

- UK NHS (most applicable).
- OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).
- OECD countries with predominantly private health insurance systems (for example, Switzerland).
- Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.

*Health economic study type:*

- Cost–utility analysis (most applicable).
- Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).
- Comparative cost analysis.
- Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.

*Year of analysis:*

- The more recent the study, the more applicable it will be.
- Studies published in 2003 or later but that depend on unit costs and resource data entirely or predominantly from before 2003 will be rated as ‘Not applicable’.
- Studies published before 2003 will be excluded before being assessed for applicability and methodological limitations.

*Quality and relevance of effectiveness data used in the health economic analysis:*

- The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

# Appendix B: Literature search strategies

Sleep Apnoea search strategy 8  positive airway pressure devices

This literature search strategy was used for the following reviews;

- What is the comparative clinical and cost effectiveness of different types of positive airway pressure devices (for example, fixed-pressure CPAP, variable-pressure CPAP, bi-level positive airway pressure or other modes of non-invasive ventilation) for managing obstructive sleep apnoea/hypopnoea syndrome, obesity hypoventilation syndrome and COPD-OSAHS overlap syndrome?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[171]

For more information, please see the Methods Report published as part of the accompanying documents for this guideline.

# B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

**Table 19: Database date parameters and filters used**

| Database | Dates searched | Search filter used |
|---|---|---|
| Medline (OVID) | 1946 – 20 November 2019 | Exclusions<br>Randomised controlled trials<br>Systematic review studies |
| Embase (OVID) | 1974 – 20 November 2019 | Exclusions<br>Randomised controlled trials<br>Systematic review studies |
| The Cochrane Library (Wiley) | Cochrane Reviews to 2019 Issue 11 of 12<br>CENTRAL to 2019 Issue 11 of 12 | None |
| Epistemonikos (Epistemonikos Foundation) | Inception – 29 November 2018 | None |

**Medline (Ovid) search terms**

| | |
|---|---|
| 1. | exp Sleep Apnea Syndromes/ |
| 2. | (sleep* adj4 (apn?ea* or hypopn?ea*)).ti,ab. |
| 3. | (sleep* adj4 disorder* adj4 breath*).ti,ab. |
| 4. | (OSAHS or OSA or OSAS).ti,ab. |
| 5. | (obes* adj3 hypoventil*).ti,ab. |
| 6. | pickwick*.ti,ab. |
| 7. | or/1-6 |
| 8. | limit 7 to English language |
| 9. | letter/ |
| 10. | editorial/ |
| 11. | news/ |
| 12. | exp historical article/ |

| | |
|---|---|
| 13. | Anecdotes as Topic/ |
| 14. | comment/ |
| 15. | case report/ |
| 16. | (letter or comment*).ti. |
| 17. | or/9-16 |
| 18. | randomized controlled trial/ or random*.ti,ab. |
| 19. | 17 not 18 |
| 20. | animals/ not humans/ |
| 21. | exp Animals, Laboratory/ |
| 22. | exp Animal Experimentation/ |
| 23. | exp Models, Animal/ |
| 24. | exp Rodentia/ |
| 25. | (rat or rats or mouse or mice).ti. |
| 26. | or/19-25 |
| 27. | 8 not 26 |
| 28. | Continuous Positive Airway Pressure/ |
| 29. | positive airway* pressure.ti,ab. |
| 30. | Continuous Positive Airway* Pressure.kw. |
| 31. | Positive-Pressure Respiration/ |
| 32. | (positive adj3 pressure adj (therapy or device* or ventilat*)).ti,ab. |
| 33. | (PAP or CPAP or aPAP or nCPAP or autoCPAP or auto-CPAP).ti,ab. |
| 34. | (biPAP or BPAP or NBiPAP or NBPAP or NIV).ti,ab. |
| 35. | ((noninvasive or non-invasive) adj3 ventilat*).ti,ab. |
| 36. | or/28-35 |
| 37. | 27 and 36 |
| 38. | randomized controlled trial.pt. |
| 39. | controlled clinical trial.pt. |
| 40. | randomi#ed.ti,ab. |
| 41. | placebo.ab. |
| 42. | randomly.ti,ab. |
| 43. | Clinical Trials as topic.sh. |
| 44. | trial.ti. |
| 45. | or/38-44 |
| 46. | Meta-Analysis/ |
| 47. | exp Meta-Analysis as Topic/ |
| 48. | (meta analy* or metanaly* or metaanaly* or meta regression).ti,ab. |
| 49. | ((systematic* or evidence*) adj3 (review* or overview*)).ti,ab. |
| 50. | (reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab. |
| 51. | (search strategy or search criteria or systematic search or study selection or data extraction).ab. |
| 52. | (search* adj4 literature).ab. |
| 53. | (medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab. |
| 54. | cochrane.jw. |
| 55. | ((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab. |

| | |
|---|---|
| 56. | or/46-55 |
| 57. | 37 and (45 or 56) |

**Embase (Ovid) search terms**

| | |
|---|---|
| 1. | exp Sleep Disordered Breathing/ |
| 2. | (sleep* adj4 (apn?ea* or hypopn?ea*)).ti,ab. |
| 3. | (sleep* adj4 disorder* adj4 breath*).ti,ab. |
| 4. | (OSAHS or OSA or OSAS).ti,ab. |
| 5. | (obes* adj3 hypoventil*).ti,ab. |
| 6. | pickwick*.ti,ab. |
| 7. | or/1-6 |
| 8. | limit 7 to English language |
| 9. | letter.pt. or letter/ |
| 10. | note.pt. |
| 11. | editorial.pt. |
| 12. | case report/ or case study/ |
| 13. | (letter or comment*).ti. |
| 14. | or/9-13 |
| 15. | randomized controlled trial/ or random*.ti,ab. |
| 16. | 14 not 15 |
| 17. | animal/ not human/ |
| 18. | nonhuman/ |
| 19. | exp Animal Experiment/ |
| 20. | exp Experimental Animal/ |
| 21. | animal model/ |
| 22. | exp Rodent/ |
| 23. | (rat or rats or mouse or mice).ti. |
| 24. | or/16-23 |
| 25. | 8 not 24 |
| 26. | positive end expiratory pressure/ |
| 27. | positive airway pressure.ti,ab. |
| 28. | Continuous Positive Airway Pressure.kw. |
| 29. | (positive pressure adj2 (therapy or device* or ventilation)).ti,ab. |
| 30. | (PAP or CPAP or aPAP or nCPAP or autoCPAP or auto-CPAP).ti,ab. |
| 31. | (biPAP or BPAP or NBiPAP or NBPAP or NIV).ti,ab. |
| 32. | ((noninvasive or non-invasive) adj3 ventilation).ti,ab. |
| 33. | or/26-32 |
| 34. | 25 and 33 |
| 35. | random*.ti,ab. |
| 36. | factorial*.ti,ab. |
| 37. | (crossover* or cross over*).ti,ab. |
| 38. | ((doubl* or singl*) adj blind*).ti,ab. |
| 39. | (assign* or allocat* or volunteer* or placebo*).ti,ab. |
| 40. | crossover procedure/ |
| 41. | single blind procedure/ |
| 42. | randomized controlled trial/ |

| | |
|---|---|
| 43. | double blind procedure/ |
| 44. | or/35-43 |
| 45. | systematic review/ |
| 46. | meta-analysis/ |
| 47. | (meta analy* or metanaly* or metaanaly* or meta regression).ti,ab. |
| 48. | ((systematic* or evidence*) adj3 (review* or overview*)).ti,ab. |
| 49. | (reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab. |
| 50. | (search strategy or search criteria or systematic search or study selection or data extraction).ab. |
| 51. | (search* adj4 literature).ab. |
| 52. | (medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab. |
| 53. | cochrane.jw. |
| 54. | ((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab. |
| 55. | or/45-54 |
| 56. | 34 and (44 or 55) |

**Cochrane Library (Wiley) search terms**

| | |
|---|---|
| #1. | MeSH descriptor: [Sleep Apnea Syndromes] explode all trees |
| #2. | (sleep* near/4 (apnea* or apnoea* or hypopnea* or hypopnoea* )):ti,ab |
| #3. | (sleep* near/4 disorder* near/4 breath*):ti,ab |
| #4. | (OSAHS or OSA or OSAS):ti,ab |
| #5. | (obes* near/3 hypoventil*):ti,ab |
| #6. | pickwick*:ti,ab |
| #7. | (OR #1-#6) |
| #8. | MeSH descriptor: [Continuous Positive Airway Pressure] explode all trees |
| #9. | positive airway* pressure:ti,ab |
| #10. | Continuous Positive Airway* Pressure:kw |
| #11. | (positive near/3 pressure near/3 (therapy or device* or ventilat*)):ti,ab |
| #12. | (PAP or CPAP or aPAP or nCPAP or autoCPAP or auto-CPAP):ti,ab |
| #13. | (biPAP or BPAP or NBiPAP or NBPAP or NIV):ti,ab |
| #14. | ((noninvasive or non-invasive) near/3 ventilat*):ti,ab |
| #15. | MeSH descriptor: [Positive-Pressure Respiration] this term only |
| #16. | (or #8-#15) |
| #17. | #7 and #16 |

**Epistemonikos search terms**

| | |
|---|---|
| 1. | ((title:((sleep apnea syndromes) OR (sleep* AND (apn?ea* OR hypopn?ea*)) OR (sleep* AND (apn?ea* OR hypopn?ea*)) OR (sleep* AND (disorder* OR breath*)) OR (OSAHS OR OSA OR OSAS) OR (obes* AND hypoventil*) OR pickwick*) OR abstract:((sleep apnea syndromes) OR (sleep* AND (apn?ea* OR hypopn?ea*)) OR (sleep* AND (apn?ea* OR hypopn?ea*)) OR (sleep* AND (disorder* OR breath*)) OR (OSAHS OR OSA OR OSAS) OR (obes* AND hypoventil*) OR pickwick*))) |

## B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to sleep apnoea population in NHS Economic Evaluation Database (NHS EED – this ceased to be

updated after March 2015) and the Health Technology Assessment database (HTA – this ceased to be updated after March 2018) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics and quality of life studies.

### B.2.1 Health economic studies strategy

**Table 20: Database date parameters and filters used**

| Database | Dates searched | Search filter used |
|---|---|---|
| Medline | 2014 – 26 November 2019 | Exclusions<br>Health economics studies |
| Embase | 2014 – 26 November 2019 | Exclusions<br>Health economics studies |
| Centre for Research and Dissemination (CRD) | HTA - Inception – 31 March 2018<br>NHSEED - Inception to March 2015 | None |

Medline (Ovid) search terms

| | |
|---|---|
| | exp Sleep Apnea Syndromes/ |
| 1. | (sleep* adj4 (apn?ea* or hypopn?ea*)).ti,ab. |
| 2. | (sleep* adj4 disorder* adj4 breath*).ti,ab. |
| 3. | (OSAHS or OSA or OSAS).ti,ab. |
| 4. | (obes* adj3 hypoventil*).ti,ab. |
| 5. | pickwick*.ti,ab. |
| 6. | or/1-6 |
| 7. | limit 7 to English language |
| 8. | letter/ |
| 9. | editorial/ |
| 10. | news/ |
| 11. | exp historical article/ |
| 12. | Anecdotes as Topic/ |
| 13. | comment/ |
| 14. | case report/ |
| 15. | (letter or comment*).ti. |
| 16. | or/9-16 |
| 17. | randomized controlled trial/ or random*.ti,ab. |
| 18. | 17 not 18 |
| 19. | animals/ not humans/ |
| 20. | exp Animals, Laboratory/ |
| 21. | exp Animal Experimentation/ |
| 22. | exp Models, Animal/ |
| 23. | exp Rodentia/ |
| 24. | (rat or rats or mouse or mice).ti. |
| 25. | or/19-25 |

| | |
|---|---|
| 26. | 8 not 26 |
| 27. | Economics/ |
| 28. | Value of life/ |
| 29. | exp "Costs and Cost Analysis"/ |
| 30. | exp Economics, Hospital/ |
| 31. | exp Economics, Medical/ |
| 32. | Economics, Nursing/ |
| 33. | Economics, Pharmaceutical/ |
| 34. | exp "Fees and Charges"/ |
| 35. | exp Budgets/ |
| 36. | budget*.ti,ab. |
| 37. | cost*.ti. |
| 38. | (economic* or pharmaco?economic*).ti. |
| 39. | (price* or pricing*).ti,ab. |
| 40. | (cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab. |
| 41. | (financ* or fee or fees).ti,ab. |
| 42. | (value adj2 (money or monetary)).ti,ab. |
| 43. | or/28-43 |
| 44. | 27 and 44 |

**Embase (Ovid) search terms**

| | |
|---|---|
| 1. | exp Sleep Disordered Breathing/ |
| 2. | (sleep* adj4 (apn?ea* or hypopn?ea*)).ti,ab. |
| 3. | (sleep* adj4 disorder* adj4 breath*).ti,ab. |
| 4. | (OSAHS or OSA or OSAS).ti,ab. |
| 5. | (obes* adj3 hypoventil*).ti,ab. |
| 6. | pickwick*.ti,ab. |
| 7. | or/1-6 |
| 8. | limit 7 to English language |
| 9. | letter.pt. or letter/ |
| 10. | note.pt. |
| 11. | editorial.pt. |
| 12. | case report/ or case study/ |
| 13. | (letter or comment*).ti. |
| 14. | or/9-13 |
| 15. | randomized controlled trial/ or random*.ti,ab. |
| 16. | 14 not 15 |
| 17. | animal/ not human/ |
| 18. | nonhuman/ |
| 19. | exp Animal Experiment/ |
| 20. | exp Experimental Animal/ |
| 21. | animal model/ |
| 22. | exp Rodent/ |

| | |
|---|---|
| 23. | (rat or rats or mouse or mice).ti. |
| 24. | or/16-23 |
| 25. | 8 not 24 |
| 26. | health economics/ |
| 27. | exp economic evaluation/ |
| 28. | exp health care cost/ |
| 29. | exp fee/ |
| 30. | budget/ |
| 31. | funding/ |
| 32. | budget*.ti,ab. |
| 33. | cost*.ti. |
| 34. | (economic* or pharmaco?economic*).ti. |
| 35. | (price* or pricing*).ti,ab. |
| 36. | (cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab. |
| 37. | (financ* or fee or fees).ti,ab. |
| 38. | (value adj2 (money or monetary)).ti,ab. |
| 39. | or/26-38 |
| 40. | 25 and 39 |

**NHS EED and HTA (CRD) search terms**

| | |
|---|---|
| #1. | MeSH DESCRIPTOR Sleep Apnea Syndromes EXPLODE ALL TREES |
| #2. | (sleep* adj4 (apn?ea* or hypopn?ea*)) |
| #3. | (sleep* adj4 disorder* adj4 breath*) |
| #4. | (OSAHS or OSA or OSAS) |
| #5. | (obes* adj3 hypoventil*) |
| #6. | (pickwick*) |
| #7. | #1 OR #2 OR #3 OR #4 OR #5 OR #6 |

## B.2.2 Quality of life studies strategy

**Table 21: Database date parameters and filters used**

| Database | Dates searched | Search filter used |
|---|---|---|
| Medline | 1946 – 26 November 2019 | Exclusions<br>Quality of life studies |
| Embase | 1974 – 26 November 2019 | Exclusions<br>Quality of life studies |

**Medline (Ovid) search terms**

| | |
|---|---|
| 1. | exp Sleep Apnea Syndromes/ |
| 2. | (sleep* adj4 (apn?ea* or hypopn?ea*)).ti,ab. |
| 3. | (sleep* adj4 disorder* adj4 breath*).ti,ab. |
| 4. | (OSAHS or OSA or OSAS).ti,ab. |
| 5. | (obes* adj3 hypoventil*).ti,ab. |
| 6. | pickwick*.ti,ab. |

| | |
|---|---|
| 7. | or/1-6 |
| 8. | limit 7 to English language |
| 9. | letter/ |
| 10. | editorial/ |
| 11. | news/ |
| 12. | exp historical article/ |
| 13. | Anecdotes as Topic/ |
| 14. | comment/ |
| 15. | case report/ |
| 16. | (letter or comment*).ti. |
| 17. | or/9-16 |
| 18. | randomized controlled trial/ or random*.ti,ab. |
| 19. | 17 not 18 |
| 20. | animals/ not humans/ |
| 21. | exp Animals, Laboratory/ |
| 22. | exp Animal Experimentation/ |
| 23. | exp Models, Animal/ |
| 24. | exp Rodentia/ |
| 25. | (rat or rats or mouse or mice).ti. |
| 26. | or/19-25 |
| 27. | 8 not 26 |
| 28. | quality-adjusted life years/ |
| 29. | sickness impact profile/ |
| 30. | (quality adj2 (wellbeing or well being)).ti,ab. |
| 31. | sickness impact profile.ti,ab. |
| 32. | disability adjusted life.ti,ab. |
| 33. | (qal* or qtime* or qwb* or daly*).ti,ab. |
| 34. | (euroqol* or eq5d* or eq 5*).ti,ab. |
| 35. | (qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab. |
| 36. | (health utility* or utility score* or disutilit* or utility value*).ti,ab. |
| 37. | (hui or hui1 or hui2 or hui3).ti,ab. |
| 38. | (health* year* equivalent* or hye or hyes).ti,ab. |
| 39. | discrete choice*.ti,ab. |
| 40. | rosser.ti,ab. |
| 41. | (willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab. |
| 42. | (sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab. |
| 43. | (sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab. |
| 44. | (sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab. |
| 45. | (sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab. |
| 46. | (sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab. |
| 47. | or/28-46 |

| | |
|---|---|
| 48. | 27 and 47 |

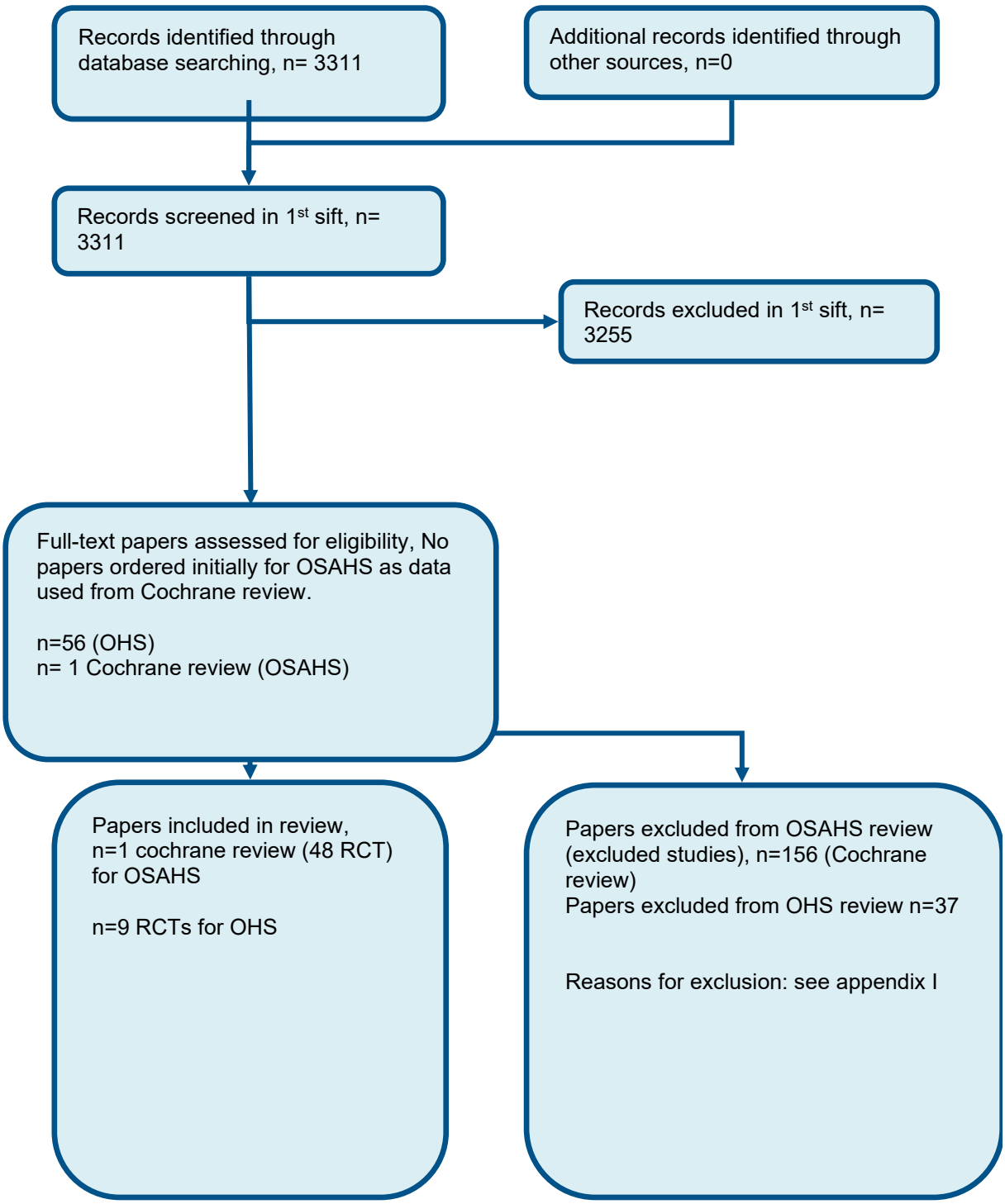
**Embase (Ovid) search terms**

| | |
|---|---|
| 1. | exp Sleep Disordered Breathing/ |
| 2. | (sleep* adj4 (apn?ea* or hypopn?ea*)).ti,ab. |
| 3. | (sleep* adj4 disorder* adj4 breath*).ti,ab. |
| 4. | (OSAHS or OSA or OSAS).ti,ab. |
| 5. | (obes* adj3 hypoventil*).ti,ab. |
| 6. | pickwick*.ti,ab. |
| 7. | or/1-6 |
| 8. | limit 7 to English language |
| 9. | letter.pt. or letter/ |
| 10. | note.pt. |
| 11. | editorial.pt. |
| 12. | case report/ or case study/ |
| 13. | (letter or comment*).ti. |
| 14. | or/9-13 |
| 15. | randomized controlled trial/ or random*.ti,ab. |
| 16. | 14 not 15 |
| 17. | animal/ not human/ |
| 18. | nonhuman/ |
| 19. | exp Animal Experiment/ |
| 20. | exp Experimental Animal/ |
| 21. | animal model/ |
| 22. | exp Rodent/ |
| 23. | (rat or rats or mouse or mice).ti. |
| 24. | or/16-23 |
| 25. | 8 not 24 |
| 26. | quality adjusted life year/ |
| 27. | "quality of life index"/ |
| 28. | short form 12/ or short form 20/ or short form 36/ or short form 8/ |
| 29. | sickness impact profile/ |
| 30. | (quality adj2 (wellbeing or well being)).ti,ab. |
| 31. | sickness impact profile.ti,ab. |
| 32. | disability adjusted life.ti,ab. |
| 33. | (qal* or qtime* or qwb* or daly*).ti,ab. |
| 34. | (euroqol* or eq5d* or eq 5*).ti,ab. |
| 35. | (qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab. |
| 36. | (health utility* or utility score* or disutilit* or utility value*).ti,ab. |
| 37. | (hui or hui1 or hui2 or hui3).ti,ab. |
| 38. | (health* year* equivalent* or hye or hyes).ti,ab. |
| 39. | discrete choice*.ti,ab. |
| 40. | rosser.ti,ab. |
| 41. | (willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab. |

| | |
|---|---|
| 42. | (sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab. |
| 43. | (sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab. |
| 44. | (sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab. |
| 45. | (sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab. |
| 46. | (sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab. |
| 47. | or/26-46 |
| 48. | 25 and 47 |

# Appendix C: Clinical evidence selection

**Figure 1: Flow chart of clinical study selection for the review of PA variants for OSAHS and OHS**



# Appendix D: Clinical evidence tables

## OSAHS

| Study | Kennedy 2019[110] |
|---|---|
| Study type | Systematic Review |
| Number of studies (number of participants) | N=48 studies<br><br>Studies that were randomised and controlled, either parallel group or cross-over design, including those that were single-blind. |
| Countries and setting | Conducted in Multiple countries; Setting: Hospital |
| Line of therapy | Mixed line |
| Duration of study | Intervention + follow up: 2 weeks to 2 years |
| Method of assessment of guideline condition | Yes |
| Stratum | -Moderate<br><br>-severe |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | Randomised parallel group or crossover trials in people with OSA. studies that compared auto-titrating CPAP (auto-CPAP), Bi-level PAP (non-invasive ventilation), or the addition of heated humidification to CPAP with fixed pressure CPAP alone |
| Exclusion criteria | Trials assessing interventions in people with central sleep apnoea and where sleep apnoea was related to sleeping position. Excluded studies that were conducted as short-term laboratory based interventions, since |

| | |
|---|---|
| | they did not intend to capture the effects of interventions administered on a nightly basis at home. Excluded studies that were less than two weeks in duration because we were primarily interested in the effects of pressure modification in the context of ongoing use of CPAP. |
| Recruitment/selection of patients | Participants had to be randomised in trials assessing one of the following comparisons:<br>1. Automatically adjusted-CPAP (auto-CPAP including forced oscillation technique) versus fixed CPAP (fixed pressure setting);<br>2. Bi-level PAP (non-invasive ventilation) versus fixed CPAP;<br>3. Humidification plus CPAP versus fixed CPAP; |
| Age, gender and ethnicity | Average age of the study populations ranged between 49 and 55 and average body mass index was between 32 and 35 kg/m2. Baseline sleep disruption as measured by AHI was severe and ESS scores indicated that the study populations had excessive daytime sleepiness (11 to 16). One study recruited people with co-existing sleep apnoea and obesity hypoventilation syndrome (Masa 2015). |
| Further population details | Participants were adults of either sex with a diagnosis of OSA, based on history and results of sleep studies. The sleep studies were either oximetry studies showing desaturation index (DI) of at least 5 per hour or of respiratory movements and airflow to give an apnoea hypopnoea index (AHI) of at least 5 per hour. |
| Extra comments | The majority of studies excluded participants who had previously used CPAP. Most studies were conducted in Europe and North America. A smaller number of trials were conducted in Australia, Hong Kong ,New Zealand and Thailand.<br>The median study sample size is 40 (range 10 to 322).<br>Average study duration was between 12 and 16 weeks in studies comparing auto-CPAP or Bi-level PAP with fixed pressure CPAP. Studies comparing additional humidification with fixed pressure CPAP had shorter average durations (6 weeks respectively).<br>The use of standard CPAP titration protocols was common across the studies. Most were conducted over one or two nights, with the exception of Pépin 2016 where home based pressure titration occurred over eight nights |

| | |
|---|---|
| Indirectness of population | No indirectness |
| Interventions | Intervention 1 :Automatically adjusted CPAP (auto-CPAP) compared with fixed CPAP<br><br>(n=36 studies; 2135 participants):<br>Duration between 12 and 16 weeks<br>Indirectness: No indirectness<br><br>Intervention 2 Non-invasive ventilation with fixed pressure CPAP<br>(n= 6 studies ; 325 participants)<br>Duration between 12 and 16 weeks<br>Indirectness: No indirectness<br><br>Intervention 3 addition of humidification to fixed pressure CPAP<br>(n= 6 studies ; 359 participants)<br>Duration 6 weeks.<br><br>Indirectness: No indirectness |
| Funding | The majority of the included studies were funded by industry |

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: Auto-CPAP versus fixed CPAP

Protocol outcome 1: Machine usage (hours/night)
- Actual outcome: Machine usage (hours/night); MD 0.21 [95% CI 0.11 to 0.31];

Risk of bias: All domain - high, Selection - high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Number of participants who used CPAP therapy > 4 hours per night
- Actual outcome: Number of participants who used CPAP therapy > 4 hours per night; RR; 1.06 [95% CI 0.90, 1.24]
Risk of bias: All domain - high, Selection - high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Machine usage (frequency of usage as % of days)
- Actual outcome: Machine usage (frequency of usage as % of days); MD;  1.60 [95% CI -0.83 to 4.03]

Risk of bias: All domain - high, Selection - high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 4: Machine usage (% of nights of > 4 hours of use) - crossover studies
- Actual outcome: Machine usage (% of nights of > 4 hours of use) - crossover studies; MD; 6.25 [95% CI -0.05 to12.54]

Risk of bias: All domain - high, Selection - high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 5: Symptoms (Epworth Sleepiness Scale)
- Actual outcome: Symptoms (Epworth Sleepiness Scale); MD; -0.44 [95% CI -0.72, to -0.16]

Risk of bias: All domain - high, Selection - high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 6: Withdrawals (parallel group trials/first arm crossover trials)
- Actual outcome: Withdrawals (parallel group trials/first arm crossover trials); RR 0.91 [95% CI 0.67, 1.24]

Risk of bias: All domain - high, Selection - high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 7: Quality of life (Functional Outcome of Sleep Questionnaire)
- Actual outcome: Quality of life (Functional Outcome of Sleep Questionnaire); MD 0.12 [95% CI -0.21, 0.46]

Risk of bias: All domain - high, Selection - high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness.

Protocol outcome 8: Quality of life (Sleep Association Quality of Life Index)
- Actual outcome: Quality of life (Sleep Association Quality of Life Index); MD -0.14 [95% CI -0.54, 0.27]

Risk of bias: All domain - high, Selection - high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 9: Quality of life (SF-36 questionnaire) physical
- Actual outcome: 0.76 [-3.50, 5.01]; MD 0.76 [-3.50, 5.01]

Risk of bias: All domain - high, Selection - high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 10: QOL (SF-36)
- Actual outcome: Role physical ; MD -3.73 [95% CI -13.46, 6.01]

Risk of bias: All domain - high, Selection - high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 11: QOL SF-36
- Actual outcome: bodily pain ; MD 4.21 [95% CI -4.23, 12.64]

Risk of bias: All domain - high, Selection - high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 12: QOL SF-36
- Actual outcome: general health; MD 2.49 [955 CI -4.99, 9.97]

Risk of bias: All domain - high, Selection - high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 13: QOL SF-36
- Actual outcome: vitality ; MD 1.32 [-1.25, 3.88]

Risk of bias: All domain - high, Selection - high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 14: QOL SF-36
- Actual outcome: social functioning ; MD 3.31 [-4.29, 10.92]

Risk of bias: All domain - high, Selection - high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 15: QOL SF-36
- Actual outcome: role emotional ; MD 0.70 [-4.19, 5.59]

Risk of bias: All domain - high, Selection - high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 16: QOL SF-36
- Actual outcome: mental health ; MD; 0.20 [95% CI -1.88 to 2.27]
Risk of bias: All domain - high, Selection - high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 17: Apnoea Hypopnoea Index (events/hr)
- Actual outcome: Apnoea Hypopnoea Index (events/hr); MD 0.48 [95% CI 0.16, 0.80]

Risk of bias: All domain - high, Selection - high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 18: Arousals (events/hr)
- Actual outcome: Arousals (events/hr); MD -0.66 [955 CI -2.90, 1.58]

Risk of bias: All domain - high, Selection - high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 19: Pressure of CPAP treatment (cm $H_2O$)
- Actual outcome: Pressure of CPAP treatment (cm $H_2O$); MD -1.49 [-2.12, -0.85]

Risk of bias: All domain - high, Selection - high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 20: Systolic blood pressure [mmHg]
- Actual outcome: Systolic blood pressure [mmHg]; MD ; 1.87 [-1.08, 4.82]

Risk of bias: All domain - high, Selection - high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 21: Diastolic blood pressure [mmHg]
- Actual outcome: Diastolic blood pressure [mmHg]; MD 4.01 [-1.46, 9.49]

Risk of bias: All domain - high, Selection - high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 22: 24 hour mean BP
- Actual outcome: 24 hour mean BP; MD 0.59 [95% CI -1.05, 2.22]

Risk of bias: All domain - low, Selection - low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 23: 24 hour systolic BP
- Actual outcome: 24 hour systolic BP; MD -0.15 [95% CI -2.21, 1.91]

Risk of bias: All domain - low, Selection - low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 24: 24 hour diastolic BP
- Actual outcome: 24 hour diastolic BP; MD  0.90 [-0.65, 2.44]

Risk of bias: All domain - low, Selection - low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 25: Tolerability outcomes
- Actual outcome Intolerable treatment pressure; RR 0.90 (0.66 , 1.23);
Risk of bias: All domain - low, Selection - low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 26: Tolerability outcomes
- Actual outcome: mask leak ;RR 1.11 (0.74, 1.66)
Risk of bias: All domain - low, Selection - low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 27: Tolerability outcomes
- Actual outcome: dry mouth ; RR 0.82 (0.61, 1.10); ;
Risk of bias: All domain - low, Selection - low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 28: Tolerability outcomes
- Actual outcome: stufyf nose; RR 0.98 (0.63, 1.54);
Risk of bias: All domain - low, Selection - low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 29: Patient preference (auto-CPAP/not auto-CPAP)
- Actual outcome: Patient preference (auto-CPAP/not auto-CPAP); RR 0.99 [0.64, 1.56] ;
Risk of bias: All domain - high, Selection - high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: Non-invasive ventilation versus fixed CPAP
Protocol outcome 1: Machine usage (hours/night)
-Actual outcome: Machine usage (hours/night); MD 0.14 [-0.17, 0.45]

Risk of bias: All domain - high, Selection - high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Symptoms (Epworth Sleepiness Scale)
- Actual outcome: Symptoms (Epworth Sleepiness Scale); MD -0.49 [-1.46, 0.48]

Risk of bias: All domain - high, Selection - high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Withdrawals (parallel group trials/first arm cross-over trials)
- Actual outcome: Withdrawals (parallel group trials/first arm cross-over trials); RR 0.61 [0.33, 1.15]

Risk of bias: All domain - high, Selection - high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 4: Quality of life (Functional Outcome of Sleep Questionnaire)
- Actual outcome: Quality of life (Functional Outcome of Sleep Questionnaire); MD 1.00 (0.56, 1.79);
Risk of bias: All domain - high, Selection - high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 5: Quality of life (Sleep Association Quality of Life Index)
- Actual outcome: Quality of life (Sleep Association Quality of Life Index); MD 0.40 (-0.34, 1.14);
Risk of bias: All domain - high, Selection - high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 6: Quality of life (SF-36 questionnaire

- Actual outcome: Quality of life (SF-36 questionnaire) Physical ; MD 0.60 (-2.21, 3.41); ;
Risk of bias: All domain - high, Selection - high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 7: Quality of life (SF-36 questionnaire)
- Actual outcome: Quality of life (SF-36 questionnaire) Mental; MD -2.90 (-7.09, 1.29); ;
Risk of bias: All domain - high, Selection - high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 8: Apnoea Hypopnoea Index (events/hr)
- Actual outcome: Apnoea Hypopnoea Index (events/hr); MD 1.36 [95% CI -6.92, 9.63]

Risk of bias: All domain - high, Selection - high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 9: Patient preference - BiPAP/no preference or CPAP
- Actual outcome: Patient preference - BiPAP/no preference or CPAP; RR 0.88 [0.47, 1.65]

Risk of bias: All domain - high, Selection - high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 10: Tolerability outcomes
- Actual outcome: dry mouth; RR;  0.56 (0.15, 2.17)
Risk of bias: All domain - high, Selection - high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 11: Tolerability outcomes
- Actual outcome: mask intolerance ; RR; 1.1.3 (0.45, 2.85)
Risk of bias: All domain - high, Selection - high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 12: Treatment comfort score
- Actual outcome Treatment comfort score; MD; ; 9 (-3.54, 21.54)

Risk of bias: All domain - high, Selection - high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: Heated humidification + fixed pressure CPAP versus fixed pressure CPAP alone

Protocol outcome 1: Machine usage (hours/night)
- Actual outcome: Machine usage (hours/night); MD 0.37 [0.10, 0.64]

Risk of bias: All domain - high, Selection - high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Symptoms (Epworth Sleepiness Scale)
- Actual outcome: Symptoms (Epworth Sleepiness Scale); MD; -0.34 [-0.93, 0.26]
Risk of bias: All domain - high, Selection - high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Withdrawals (parallel group trials/first arm cross-over trials)
- Actual outcome: Withdrawals (parallel group trials/first arm cross-over trials); RR 1.00 [0.56, 1.79]

Risk of bias: All domain - high, Selection - high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 4: Apnoea Hypopnoea Index (events/hr)
- Actual outcome: Apnoea Hypopnoea Index (events/hr); MD 0.30 (-0.95, 1.55) ;
Risk of bias: All domain - high, Selection - high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 5: Quality of life (SF-36 questionnaire) [SF-36 ]
- Actual outcome: Quality of life (SF-36 questionnaire) [SF-36 ]; MD 0.11 [-6.97, 7.18]
Risk of bias: All domain - high, Selection - high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 6: Nasal symptoms (parallel group trials)
- Actual outcome: runny nose; RR 0.39 [0.13, 1.15]

Risk of bias: All domain - low, Selection - low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 7: Nasal symptoms (parallel group trials)

- Actual outcome: blocked nose ;RR 0.37 [0.20, 0.70]

Risk of bias: All domain - low, Selection - low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 8: Nasal symptoms (parallel group trials)
- Actual outcome: dry nose; MD; -0.38 [-0.78, 0.01]

Risk of bias: All domain - high, Selection - high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 9: Nasal symptoms (parallel group trials)
- Actual outcome runny nose:; MD ; -0.30 [-0.69, 0.09]
Risk of bias: All domain - high, Selection - high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 10: Nasal symptoms (parallel group trials)
- Actual outcome: blocked nose; MD -0.38 [-0.78, 0.01]

Risk of bias: All domain - high, Selection - high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 11: Nasal symptoms (parallel group trials)
- Actual outcome: bleeding nose; MD;  -0.45 [-0.99, 0.10]
Risk of bias: All domain - high, Selection - high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness

Protocol outcome 12: Preference

| | |
|---|---|
| - Actual outcome: Preference; RR; 1.06 (0.67, 1.67)<br>Risk of bias: All domain - high, Selection - high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness | |
| Protocol outcomes not reported by the study | None |

# OHS

| **Study** | **Borel 2012[25]** |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=37) |
| Countries and setting | Conducted in France; Setting: Grenoble University Hospital sleep department |
| Line of therapy | Unclear |
| Duration of study | Intervention + follow up: 1 month |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis |
| Stratum | Severe |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | Patients aged 20 to 75 years with a BMI. 30 kg/$m^2$ and a Pa co 2 45 mm Hg on daytime blood gas assessment were included unless they declined. |

| | |
|---|---|
| Exclusion criteria | Exclusion criteria: any significant airway obstruction (FEV1 /FVC , 70%), scoliosis, cardiac failure, or progressive neuromuscular disease. |
| Recruitment/selection of patients | A screening of OHS was proposed to all ambulatory obese patients recruited from advertisements in local newspaper or attending the sleep department referred for diagnosis of sleep disordered breathing |
| Age, gender and ethnicity | Age - Mean (SD): 56 (7). Gender (M:F): 15/22. Ethnicity: unclear |
| Further population details | 1. BMI: BMI of 30 2 kg/$m^2$ or more. Co-existing conditions: HTN 3. High risk occupation group: Not stated / Unclear 4. Sleepiness: ESS >9 |
| Indirectness of population | No indirectness |
| Interventions | (n=19) Intervention 1: Bi-level positive airway pressure/ non-invasive ventilation (NIV) without humidification. NIV treatment was initiated over three to four nights spent in the respiratory ward in individual rooms. Patients were set on bilevel positive pressure ventilation (GoodKnight-425ST; Covidien). After discharge, the patients were asked to use NIV every night.<br>Duration 1 month. Concurrent medication/care: none reported. Indirectness: No indirectness<br>Further details: 1. Precise humidification – : Not stated / Unclear<br><br>(n=18) Intervention 2: No positive airway pressure device (for OHS and mild OSAHS only) . 1 hour education session, focused on general health risks of OSA and obesity, given dietary and lifestyle counselling by<br>specialist nurse including recommendations for a healthier diet and more exercise. Duration 1 month. Concurrent medication/care: none reported. Indirectness: No indirectness<br>Further details: 1. Precise humidification – : Not applicable |
| Funding | Study funded by industry |

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BI-LEVEL POSITIVE AIRWAY PRESSURE/ NON-INVASIVE VENTILATION (NIV) WITHOUT HUMIDIFICATION versus NO POSITIVE AIRWAY PRESSURE DEVICE (FOR OHS AND MILD OSAHS

ONLY)

Protocol outcome 1: Sleepiness score at >1 month
- Actual outcome for Severe: ESS change score at 1 month; Group 1: mean -3.4 (SD 5.2284); n=18, Group 2: mean -2.1 (SD 4.6679); n=17
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: difference between groups for age; Group 1 Number missing: 1, Reason: cardiac pacing during FU; Group 2 Number missing: 1, Reason: acute respiratory failure

Protocol outcome 2: AHI/RDI at >1 month
- Actual outcome for Severe: AHI change score at 1 month; Group 1: mean -34.1 (SD 35.3919); n=18, Group 2: mean 6.3 (SD 27.6183); n=17
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: difference between groups for age; Group 1 Number missing: 1, Reason: cardiac pacing during FU; Group 2 Number missing: 1, Reason: acute respiratory failure

Protocol outcome 3: Systolic blood pressure for hypertension at >1 month
- Actual outcome for Severe: systolic BP change score at 1 month; Group 1: mean -1.3 (SD 21.7178); n=18, Group 2: mean -5.4 (SD 10.8917); n=17
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: difference between groups for age; Group 1 Number missing: 1, Reason: cardiac pacing during FU; Group 2 Number missing: 1, Reason: acute respiratory failure

Protocol outcome 4: HbA1c for diabetes at >1 month
- Actual outcome for Severe: HbA1c change score at 1 month; Group 1: mean 0.04 (SD 0.2212); n=18, Group 2: mean -0.12 (SD 0.4668); n=17
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: difference between groups for age; Group 1 Number missing: 1, Reason: cardiac pacing during FU; Group 2 Number missing: 1, Reason: acute respiratory failure

Protocol outcome 5: PaCO2 at >1 month
- Actual outcome for Severe: paco2 change score at 1 month; Group 1: mean -4.9 (SD 3.8207); n=18, Group 2: mean -1.4 (SD 4.2789); n=17
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: difference between groups for age; Group 1 Number missing: 1, Reason: cardiac pacing during FU; Group 2 Number missing: 1, Reason: acute respiratory failure

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| Protocol outcome 6: Pa02 at >1 month<br>- Actual outcome for Severe: pa02 at 1 month; Group 1: mean 2.4 (SD 10.1663); n=18, Group 2: mean 0.15 (SD 13.9758); n=17<br>Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: difference between groups for age; Group 1 Number missing: 1, Reason: cardiac pacing during FU; Group 2 Number missing: 1, Reason: acute respiratory failure | |
| Protocol outcomes not reported by the study | Quality of life at >1 month; ODI at >1 month; CO2 control at >1 month; Adverse effects of treatment at >1 month; Adherence in hours of use at >1 month; Mortality at >1 month; Cardiovascular events at >1 month |

| Study | Howard 2017[95] |
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| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=60) |
| Countries and setting | Conducted in Australia; Setting: the Alfred hospital (Melbourne) and the Royal Prince Alfred hospital (Sydney) |
| Line of therapy | Unclear |
| Duration of study | Intervention + follow up: 3 months |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis |
| Stratum | Undefined severity |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | Participants with a primary diagnosis of OHS (body mass index (BMI) over 30 kg/$m^2$ and daytime PaCO2 >45 mm Hg) were recruited from the ventilatory failure services at Austin Health, the Alfred Hospital (Melbourne) and The Royal Prince Alfred Hospital (Sydney), Australia. |
| Exclusion criteria | Potential participants were excluded if they had another condition that may contribute to hypoventilation including neuromuscular disease, chest wall abnormalities, respiratory depressant medications, COPD or an FEV1/FVC ratio <70% after bronchodilators. Participants presented either as a stable outpatient referral or following a hospital admission with an acute respiratory acidosis and initial stabilisation on Bi-level PAP. Arterial blood pH was in the normal range (7.35 –7.45) at randomisation for both groups. Diagnostic polysomnography was not required for diagnosis, but undertaken as clinically indicated outside the protocol. Prior ventilatory support (Bi-level PAP or CPAP) was permitted provided the duration was <1 month in the 3 months prior to enrolment. |

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| Age, gender and ethnicity | Age - Mean (SD): 53 (10). Gender (M:F): 32/28. Ethnicity: unclear |
| Further population details | 1. BMI: BMI of 30 2 kg/$m^2$ or more. Co-existing conditions: Not stated / Unclear 3. High risk occupation group: Not stated / Unclear 4. Sleepiness: Not stated / Unclear |
| Indirectness of population | No indirectness |
| Interventions | (n=29) Intervention 1: Bi-level positive airway pressure/ non-invasive ventilation (NIV) without humidification. The Bi-level PAP group received non-invasive ventilation using a spontaneous timed mode of ventilatory support for 3 months. The protocol included a planned change to Bi-level PAP in the event of treatment failure in the CPAP group. Polysomnography was used to facilitate titration of PAP settings at randomisation. In the Bi-level PAP group, the ventilator rate and pressure support were titrated to overcome nocturnal hypoventilation. Supplemental oxygen was added to maintain SpO2 ≥90%. The devices used<br>were able to deliver both CPAP and Bi-level PAP (VPAP III STA, ResMed, Bella Vista, Australia; Harmony, Philips Respironics, USA).<br>Duration 3 months.<br><br>Concurrent medication/care: CPAP or Bi-level expiratory pressure was titrated to overcome obstructive events. No formal dietary advice or exercise programme was prescribed. The devices used were able to deliver both CPAP and Bi-level PAP (VPAP III STA, ResMed, Bella Vista, Australia; Harmony, Philips Respironics,USA)<br>Indirectness: No indirectness<br>Further details: 1. Precise humidification – : Not stated / Unclear (n=31)<br><br>Intervention 2: Fixed pressure CPAP without humidification. Fixed pressure CPAP was used in the CPAP group. The protocol included a planned change to Bi-level PAP in the event of treatment failure in the CPAP group. The devices used were able to deliver both CPAP and Bi-level PAP (VPAP III STA, ResMed, Bella Vista, Australia; Harmony, Philips Respironics, USA)<br>Duration 3 months.<br><br>Concurrent medication/care: CPAP or Bi-level expiratory pressure was titrated to overcome obstructive events. No formal dietary advice or exercise programme was prescribed. The devices used were able to deliver both CPAP and Bi-level PAP (VPAP III STA, ResMed, Bella Vista, Australia; Harmony, Philips Respironics, USA). |

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| | Indirectness: No indirectness<br>Further details: 1. Precise humidification – : Not stated / Unclear |
| Funding | Study funded by industry |

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BI-LEVEL POSITIVE AIRWAY PRESSURE/ NON-INVASIVE VENTILATION (NIV) WITHOUT HUMIDIFICATION versus FIXED PRESSURE CPAP WITHOUT HUMIDIFICATION

Protocol outcome 1: Quality of life at >1 month
- Actual outcome for Severe: SF36 physical at 3 months; Group 1: mean 37.96 (SD 8.061); n=27, Group 2: mean 40.48 (SD 7.5095); n=30
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: withdrew; Group 2 Number missing: 1, Reason: withdrew
- Actual outcome for Severe: SF36 mental at 3 months; Group 1: mean 45.68 (SD 11.3279); n=27, Group 2: mean 47.08 (SD 10.5217); n=30
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: withdrew; Group 2 Number missing: 1, Reason: withdrew
- Actual outcome for Severe: SRI at 3 months; Group 1: mean 63.5 (SD 15.8675); n=27, Group 2: mean 67.58 (SD 15.1887); n=30
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: withdrew; Group 2 Number missing: 1, Reason: withdrew

Protocol outcome 2: Sleepiness score at >1 month
- Actual outcome for Severe: ESS at 3 months; Group 1: mean 7.6 (SD 6.5699); n=29, Group 2: mean 7.26 (SD 6.2988); n=30
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: withdrew; Group 2 Number missing: 1, Reason: withdrew

Protocol outcome 3: Adherence in hours of use at >1 month
- Actual outcome for Severe: adherence hours per night at 3 months; Group 1: mean 5.3 (SD 2.63); n=29, Group 2: mean 5 (SD 2.4); n=31
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: withdrew; Group 2 Number missing: 1, Reason: withdrew

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| Protocol outcome 4: Systolic blood pressure for hypertension at >1 month<br>- Actual outcome for Severe: systolic BP at 3 months; Group 1: mean 137 (SD 17.3948); n=27, Group 2: mean 137 (SD 16.122); n=30<br>Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: withdrew; Group 2 Number missing: 1, Reason: withdrew | |
| Protocol outcomes not reported by the study | AHI/RDI at >1 month; ODI at >1 month; CO2 control at >1 month; Adverse effects of treatment at >1 month; HbA1c for diabetes at >1 month; Mortality at >1 month; Pa02 at >1 month; PaCO2 at >1 month; Cardiovascular events at >1 month |

| **Study (subsidiary papers)** | **Pickwick Project trial: Masa 2015[137], Masa, 2019 [142], Masa 2016[139], Masa 2020 [135]** |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 3; (2 with severe OSA (n=221)) (1 without severe OSA (n=86)) (1 without severe OSA, n=98) |
| Countries and setting | Conducted in Spain; Setting: 16 tertiary hospitals in Spain |
| Line of therapy | Unclear |
| Duration of study | Intervention + follow up: 2 months,5.44 years and 8.4 years |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis |
| Stratum | Severe and Mild (Severe and without severe OSA) |
| Subgroup analysis within study | N/A |
| Inclusion criteria | Patients with suspected OHS or OSA with substantial experience with NIV and CPAP treatments. OHS was defined as obesity, with a body mass index (BMI) greater than or equal to 30; stable hypercapnic respiratory failure (PaCO2>45 mm Hg, pH>7.35, and no clinical worsening during the 2 previous months). Other inclusion criteria were as follows: (1) severe OSA (apnea–hypopnea index [AHI] >30), (2) an absence of narcolepsy or restless leg syndrome, and (3) a correctly executed 30-minute CPAP/NIV treatment test.<br><br>Patients without severe OSA were included in the without severe OSA study.<br><br>For without severe OSA study:<br><br>(1) nonsevere OSA (apnea-hypopnea index < 30 events/h), (2) an absence of narcolepsy or restless legs syndrome, and (3) a correctly executed 30-min NIV treatment test |

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| Exclusion criteria | The exclusion criteria were as follows: (1) a psychophysical inability to complete questionnaires, (2) severe chronic debilitating illness, (3) severe chronic nasal obstruction, and (4) a lack of informed consent. Patients without severe OSA (AHI<30) were referred to the parallel study protocol. Additional exclusions were; no relevant chronic obstructive pulmonary disease (FEV1>70% predicted when FEV 1/FVC<70) or neuromuscular, chest wall, or metabolic disease. |
| Recruitment/selection of patients | From May 2009 to March 2013 patients between 15 and 80 years of age who were referred for pulmonary consultations for suspected OHS or OSA at 16 tertiary hospitals in Spain with substantial experience with NIV and CPAP treatments were screened.<br><br>From April 2013 to December 2014 patients with OHS without severe OSA continued to be included. The study was stopped after 8.4 years of follow-up (May 2009 to November 2017) with the agreement of the 16 clinical centers because of the prespecified criterion of absence of new patient enrollment in the last year. |
| Age, gender and ethnicity | Age - Mean (SD): 60 (13). Gender (M:F): 97/124. Ethnicity: unclear |
| Further population details | 1. BMI: BMI of 30 2 kg/$m^2$ or more. Co-existing conditions: HTN 3. High risk occupation group: Not stated / Unclear 4. Sleepiness: ESS >9 |
| Indirectness of population | No indirectness |
| Interventions | (n=71) severe population Intervention, (n=40 non severe OSA population at 2 months; n=48 non severe population at 3 years) 1: Bi-level positive airway pressure/ non-invasive ventilation (NIV) without humidification. In addition to lifestyle modification and oxygen (if required), patients were instructed to use NIV treatment during the entire sleep period. The ventilator mode was set at bilevel pressure with assured volume. While the patient was awake, the expiratory positive airway pressure (EPAP) was set between 4 and 8 cm H2O, and the inspiratory positive airway pressure (IPAP) was set between 18 and 22 cm H2O (EPAP included). The respiratory rate was adjusted to 12 to 15 breaths/min (close to the spontaneous respiratory rate, if possible), and the target volume was set at between 5 and 6 ml/kg of actual weight, allowing for an increase in the maximum pressure over the previously fixed IPAP, if necessary.<br>Duration 2 months and 3 years. Concurrent medication/care: all patients received lifestyle modification advice and oxygen (if required). |

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| | Indirectness: No indirectness<br>Further details: 1. Precise humidification: Not applicable<br><br>(n=80) severe population only. Intervention 2: Fixed pressure CPAP without humidification. In addition to lifestyle modification and oxygen (if required), patients were instructed to use at-home fixed CPAP during the entire sleep period before conventional CPAP titration.<br><br>Duration 2 months. Concurrent medication/care: all patients received lifestyle modification advice and oxygen (if required).<br><br>Indirectness: No indirectness<br>Further details: 1. Precise humidification: Not stated / Unclear<br><br>(n=70) severe population, (n=46 non severe population at 2 months; n=48 non severe population at 3 years) Intervention 3: No positive airway pressure device (for OHS and mild OSAHS only). The lifestyle modification consisted of a 1,000-calorie diet and the maintenance of correct sleep hygiene and habits (avoiding the supine decubitus position; maintaining regular sleep habits and exercise; not consuming sedatives, stimulants, or alcohol; not smoking tobacco; and avoiding heavy meals within 4 hours before bedtime). Oxygen therapy was added if the daytime PaO2 was less than 55 mm Hg (18), with the necessary flow to maintain waking arterial oxygen saturation between 88 and 92% or PAO2 greater than or equal to 55 mm Hg for at least 17 h/d.<br>Duration 2 months and 3 years. Concurrent medication/care: all patients received lifestyle modification advice and oxygen (if required).<br><br>Indirectness: No indirectness<br>Further details: 1. Precise humidification : Not applicable |
| Funding | Study funded by industry (study had a mix of academic, government and industry funding) |
| Severe OSA population<br><br>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BI-LEVEL POSITIVE AIRWAY PRESSURE/ NON-INVASIVE VENTILATION (NIV) WITHOUT HUMIDIFICATION versus FIXED PRESSURE CPAP WITHOUT HUMIDIFICATION | |

Protocol outcome 1: AHI/RDI at >1 month
- Actual outcome for Severe: change in AHI (severe OSAHS) at 2 months; Group 1: mean -57 (SD 30); n=71, Group 2: mean -60 (SD 31); n=80
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: ODI at >1 month
- Actual outcome for Severe: change in ODI (severe OSAHS) at 2 months; Group 1: mean -46 (SD 30); n=71, Group 2: mean -58 (SD 33); n=80
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Adherence in hours of use at >1 month
- Actual outcome for Severe: adherence (severe OSAHS) at 2 months; Group 1: mean 5.3 hours per night (SD 2.3); n=72, Group 2: mean 5.3 hours per night (SD 2.1); n=80
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BI-LEVEL POSITIVE AIRWAY PRESSURE/ NON-INVASIVE VENTILATION (NIV) WITHOUT HUMIDIFICATION versus NO POSITIVE AIRWAY PRESSURE DEVICE (FOR OHS AND MILD OSAHS ONLY)

Protocol outcome 1: Quality of life at >1 month
- Actual outcome for Severe: change in SF-36 physical (severe OSAHS) at 2 months; Group 1: mean 1.1 (SD 8.7); n=71, Group 2: mean 0.2 (SD 6.8); n=70
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for Severe: change in SF-36 mental (severe OSAHS) at 2 months; Group 1: mean 1.7 (SD 14); n=71, Group 2: mean 1.2 (SD 88); n=70
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for Severe: change in FOSQ (severe OSAHS) at 2 months; Group 1: mean 4.3 (SD 17); n=71, Group 2: mean -1.7 (SD 16); n=70
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Sleepiness score at >1 month
- Actual outcome for Severe: change in ESS (severe OSAHS) at 2 months; Group 1: mean -4.8 (SD 5); n=71, Group 2: mean -1 (SD 4.4); n=70
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: AHI/RDI at >1 month
- Actual outcome for Severe: change in AHI (severe OSAHS) at 2 months; Group 1: mean -57 (SD 30); n=71, Group 2: mean -6.8 (SD 30); n=70
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: ODI at >1 month
- Actual outcome for Severe: change in ODI (severe OSAHS) at 2 months; Group 1: mean -46 (SD 30); n=71, Group 2: mean -4.7 (SD 26); n=70
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 5: PaCO2 at >1 month
- Actual outcome for Severe: change in PACO2 (severe OSAHS) at 2 months; Group 1: mean -5.5 (SD 7); n=71, Group 2: mean -3.2 (SD 6); n=70
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FIXED PRESSURE CPAP WITHOUT HUMIDIFICATION versus NO POSITIVE AIRWAY PRESSURE DEVICE (FOR OHS AND MILD OSAHS ONLY)

Protocol outcome 1: Quality of life at >1 month
- Actual outcome for Severe: change in SF36 physical (severe OSAHS) at 2 months; Group 1: mean 1.2 (SD 8.9); n=80, Group 2: mean 0.2 (SD 6.8); n=70
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for Severe: change in SF36 mental (severe OSAHS) at 2 months; Group 1: mean 4.6 (SD 12); n=80, Group 2: mean 1.2 (SD 8.8); n=70

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for Severe: change in FOSQ (severe OSAHS) at 2 months; Group 1: mean 5.1 (SD 16); n=80, Group 2: mean 1.7 (SD 16); n=70
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Sleepiness score at >1 month
- Actual outcome for Severe: change in ESS (severe OSAHS) at 2 months; Group 1: mean -4.3 (SD 4.7); n=80, Group 2: mean -1 (SD 4.4); n=70
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: AHI/RDI at >1 month
- Actual outcome for Severe: change in AHI (severe OSAHS) at 2 months; Group 1: mean -60 (SD 31); n=80, Group 2: mean -6.8 (SD 30); n=70
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: ODI at >1 month
- Actual outcome for Severe: change in ODI (severe OSAHS) at 2 months; Group 1: mean -58 (SD 33); n=80, Group 2: mean -4.7 (SD 26); n=70
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 5: PaCO2 at >1 month
- Actual outcome for Severe: change in PaCO2 (severe OSAHS) at 2 months; Group 1: mean -3.7 (SD 6.6); n=80, Group 2: mean -3.2 (SD 6); n=70
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Without severe OSA population

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BI-LEVEL POSITIVE AIRWAY PRESSURE/ NON-INVASIVE VENTILATION (NIV) WITHOUT HUMIDIFICATION versus NO POSITIVE AIRWAY PRESSURE DEVICE/LIFE STYLE MODIFICATION – 2 months follow-up

Protocol outcome 1: Quality of life at >1 month
- Actual outcome for Mild (without severe): change in SF-36 mental (Mild OSAHS) at 2 months; Group 1: mean 4.1 (SD 12.8); n=40, Group 2: mean -0.9 (SD 9.4); n=46
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for Mild (without severe): change in FOSQ (Mild OSAHS) at 2 months; Group 1: mean 4.4 (SD 19); n=40, Group 2: mean -2.7 (SD 18.2); n=46
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Sleepiness score at >1 month
- Actual outcome for Mild ( without severe OSA): change in ESS (Mild OSAHS) at 2 months; Group 1: mean -2.9 (SD 3.8); n=40, Group 2: mean -1.2 (SD 3.4); n=46
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: AHI/RDI at >1 month
- Actual outcome for Mild (without Severe): change in AHI (Mild OSAHS) at 2 months; Group 1: mean -11 (SD 12.5); n=40, Group 2: mean 0.1 (SD 9.4); n=46
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: ODI at >1 month
- Actual outcome for Mild (without severe) : change in ODI (Mild OSAHS) at 2 months; Group 1: mean -19 (SD 18.8); n=40, Group 2: mean -0.4 (SD 14.1); n=46
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 5: PaCO2 at >1 month

- Actual outcome for Mild (without severe): change in PACO2 (Mild OSAHS) at 2 months; Group 1: mean -6 (SD 5.3); n=40, Group 2: mean -2.8 (SD 5.1); n=46
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 6: Systolic blood pressure for hypertension at >1 month
- Actual outcome for Mild: systolic BP change score (mild) at 1 month; Group 1: mean -4.2 (SD 21.3); n=40, Group 2: mean -4.3 (SD 19.2); n=46
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Without severe OSA population

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BI-LEVEL POSITIVE AIRWAY PRESSURE/ NON-INVASIVE VENTILATION (NIV) WITHOUT HUMIDIFICATION versus NO POSITIVE AIRWAY PRESSURE DEVICE/LIFE STYLE MODIFICATION – 3 years follow-up

Protocol outcome 1: Hospitalisation
- Actual outcome : mean hospitalization days per year at 3 years; Group 1: mean 2.71 (SD 4.52) ; n=48, Group 2: mean 2.60 (SD 5.31); n=48
Risk of bias: All domain - low, Selection - Low, Blinding - low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Quality of life at >1 month
- Actual outcome : SF-36 physical at 3 years; Group 1: mean 37.31 (SD 13.57 ); n=48, Group 2: mean 34.96 (SD 14.89 ); n=48
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Quality of life at >1 month
- Actual outcome : SF-36 mental at 3 years; Group 1: mean 42.82 (SD 17.86 ); n=48, Group 2: mean 44.29 (SD 19.7 ); n=48

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

- Actual outcome : FOSQ at 3 years; Group 1: mean 77.21 (SD 26.5); n=48, Group 2: mean 72.16 (SD 28.5 ); n=48
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Sleepiness score at >1 month
- Actual outcome: ESS at 3 years; Group 1: mean 4.16 (SD 6.18 ); n=48, Group 2: mean 7.13 (SD 6.78 ); n=48
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 5: PaCO2 at >1 month
- Actual outcome : PACO2 at 3 years; Group 1: mean 44.26 (SD 5.97 ); n= n=48, Group 2: mean 47.54 (SD 5.76); n=48
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 6: Systolic blood pressure for hypertension at >1 month
- Actual outcome for Mild: systolic BP at 3 years; Group 1: mean 135.37 (SD 19.26); n=48, Group 2: mean 132.04 (SD 18.31); n=48
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 7: Diastolic blood pressure for hypertension at >1 month
- Actual outcome : diastolic BP at 3 years; Group 1: mean77.51 (SD 13.52 ); n=48, Group 2: mean 74.04 (SD 12.88); n=48
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 8: Cardiovascular events
- Actual outcome : cardiovascular events at 3 years; Group 1: 10; n=48, Group 2: 11; n=48
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 9: Mortality
- Actual outcome : Mortality at 3 years; Group 1: 9; n=48, Group 2: 9 n=48

| | |
|---|---|
| Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 | |
| Narartive results:<br>Oral dryness (3 years)- 3% in NIV group. No other adverse events with NIV at 3 years. | |
| Protocol outcomes not reported by the study | HbA1c for diabetes at >1 month; |

| Study | Murphy 2012[168] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=50) |
| Countries and setting | Conducted in United Kingdom; Setting: respiratory unit in hospitals in UK |
| Line of therapy | Unclear |
| Duration of study | Intervention + follow up: 3 months |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis |
| Stratum | Undefined severity |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | Study inclusion criteria were body mass index >40 kg/m2; daytime stable respiratory failure with PaCO2 >6 kPa and pH >7.35; absence of another identifiable cause of hypoventilation; ratio of forced expiratory volume in 1 s (FEV1) to forced vital capacity (FVC) >0.70; and FVC <70% predicted. |
| Exclusion criteria | The exclusion criterion was an inability to provide written informed consent. |
| Recruitment/selection of patients | Patients admitted to the Lane Fox Respiratory Unit, St Thomas' Hospital and to the Sleep and Ventilation Unit, Royal Brompton Hospital for either elective assessment of stable OHS or assessment following an episode of acute decompensated respiratory failure secondary to OHS were screened for study inclusion. |
| Age, gender and ethnicity | Age - Mean (SD): AVAPS = 53 (9) Fixed level PS = 56 (11). Gender (M:F): 23/27. Ethnicity: unclear |

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|---|---|
| Further population details | 1. BMI: BMI of 30 2 kg/m$^2$ or more. Co-existing conditions: Not stated / Unclear 3. High risk occupation group: Not stated / Unclear 4. Sleepiness: ESS >9 |
| Indirectness of population | No indirectness |
| Interventions | (n=25) Intervention 1: Bi-level positive airway pressure/ non-invasive ventilation (NIV) without humidification. Volume assured NIV. AVAPS (average volume-assured pressure support) mode, mean Vte 657ml. 2/25 required supplemental oxygen.<br><br>Duration 3 months.<br><br>Concurrent medication/care: Both modes were delivered by a BiPAP synchrony device (Philips-Respironics, Murrysville, Pennsylvania, USA).<br>Supplementary oxygen was provided to patients who met the criteria for daytime hypoxaemia (PaO2 <7.3 kPa or <8 kPa with secondary features of hypoxia or right heart failure) at the lowest flow rate that corrected hypoxaemia (PaO2>8 kPa).<br>Indirectness: No indirectness<br>Further details: 1. Precise humidification – : Not stated / Unclear<br><br>(n=25) Intervention 2: Bi-level positive airway pressure/ non-invasive ventilation (NIV) without humidification. Fixed NIV bi-level PS mean IPAP 25cm H2O, 4/25 required supplemental oxygen. Duration 3 months.<br><br>Concurrent medication/care: Ventilator set-up done over two days in both groups. Both modes were delivered by a BiPAP synchrony device (Philips-Respironics, Murrysville, Pennsylvania, USA). Supplementary oxygen was provided to patients who met the criteria for daytime hypoxaemia (Po2 <7.3 kPa or <8 kPa with secondary features of hypoxia or right heart failure) at the lowest flow rate that corrected hypoxaemia (PaO2>8 kPa). Indirectness: No indirectness<br>Further details: 1. Precise humidification – : Not stated / Unclear |
| Funding | Study funded by industry |

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BI-LEVEL POSITIVE AIRWAY PRESSURE/ NON-INVASIVE VENTILATION (NIV) WITHOUT HUMIDIFICATION versus BI-LEVEL POSITIVE AIRWAY PRESSURE/ NON-INVASIVE VENTILATION (NIV)

| | |
|---|---|
| WITHOUT HUMIDIFICATION<br><br>Protocol outcome 1: Quality of life at >1 month<br>- Actual outcome for Undefined severity: SRI at 3 months; Group 1: mean 11 (SD 12); n=23, Group 2: mean 7 (SD 13); n=23<br>Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 2<br><br>Protocol outcome 2: Sleepiness score at >1 month<br>- Actual outcome for Undefined severity: ESS at 3 months; Group 1: mean -5 (SD 6); n=23, Group 2: mean -6 (SD 6); n=23<br>Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 2<br><br>Protocol outcome 3: Adherence in hours of use at >1 month<br>- Actual outcome for Undefined severity: adherence hours per night at 3 months; Group 1: mean 4.2 (SD 2.9); n=23, Group 2: mean 5.1 (SD 2.4); n=23<br>Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 2<br><br>Protocol outcome 4: PaCO2 at >1 month<br>- Actual outcome for Undefined severity: PaCO2 at 3 months; Group 1: mean 6.4 (SD 0.8); n=23, Group 2: mean 6.2 (SD 0.8); n=23<br>Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 2<br><br>Protocol outcome 5: Pa02 at >1 month<br>- Actual outcome for Undefined severity: PaO2 at 3 months; Group 1: mean 9.1 (SD 1.2); n=23, Group 2: mean 9.3 (SD 1.2); n=23<br>Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 2 | |
| Protocol outcomes not reported by the study | AHI/RDI at >1 month; ODI at >1 month; CO2 control at >1 month; Adverse effects of treatment at >1 month; HbA1c for diabetes at >1 month; Mortality at >1 month; Systolic blood pressure for hypertension at >1 month; Cardiovascular events at >1 month |

| Study | Piper 2008[206] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=36) |
| Countries and setting | Conducted in Australia; Setting:<br>Sleep Investigation Unit at Royal Prince Alfred<br><br>Hospital Australia. |
| Line of therapy | Unclear |
| Duration of study | Intervention + follow up: 3 months |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis |
| Stratum | Undefined severity |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | Inclusion criteria included: (1) obesity with a BMI over 30 kg/$m^2$; (2) stable awake compensated respiratory failure with arterial carbon dioxide tension (PaCO2) >45 mm Hg and pH>7.34; (3) the absence of any significant respiratory, neuromuscular or other disorder that could account for the hypercapnia; (4) ratio of forced expiratory volume in 1 s/forced vital capacity (FEV1/FVC)>70%; (5) no major psychiatric illness that would affect the patient's ability to participant in the study; and (6) not currently being treated with positive pressure therapy. |
| Exclusion criteria | Based on clinical consensus and safety concerns, a priori criteria were set so that patients who displayed significant and prolonged desaturation or significant carbon dioxide retention during an |

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| | initial CPAP trial were excluded from the study. These criteria were: (1) oxygen saturation remaining below 80% continuously (10 min) in the absence of frank apnoea; (2) an acute rise in transcutaneous carbon dioxide pressure (TcCO2) (TCM3, Radiometer, Copenhagen, Denmark) during episodes of rapid eye movement (REM) sleep>10 mm Hg; or (3) an increase in afternoon to morning Pa CO2 of >10 mm Hg in those patients with an awake Pa CO2 .55 mm Hg. |
| Recruitment/selection of patients | Patients with obesity and daytime hypercapnia were recruited from the Sleep Disorders Clinic and Sleep Investigation Unit at Royal Prince Alfred Hospital. |
| Age, gender and ethnicity | Age - Mean (SD): 50 (15). Gender (M:F): 23/13. Ethnicity: unclear |
| Further population details | 1. BMI: BMI of 30 2 kg/$m^2$ or more. Co-existing conditions: Not stated / Unclear 3. High risk occupation group: Not stated / Unclear 4. Sleepiness: ESS >9 |
| Indirectness of population | No indirectness |
| Interventions | (n=18) Intervention 1: Bi-level positive airway pressure/ non-invasive ventilation (NIV) without humidification. Overnight titration of CPAP was performed in all patients in a sleep laboratory using manual titration. Pressure was increased in 1cmH2O increments with the aim of preventing obstruction, flow limitation, desaturation and arousal. Those patients randomised to BVS then underwent a further trial to titrate appropriate bilevel pressure settings. During the bilevel titration, the EPAP was commenced at 2cmH2O below the pressure needed to abolish obstructive events during the CPAP titration or at 5cmH2O, whichever was higher. The EPAP was then increased in 1cmH2O increments if inspiratory efforts did not consistently trigger IPAP. The IPAP was initially set 4cmH2O higher than EPAP, and then increased to eliminate hypopneas and improve saturation. A spontaneous mode of bilevel support was used in all patients.<br><br>Duration 3 months. Concurrent medication/care: patients were encouraged to contact the clinical service if they were experiencing any problems with therapy, and to return to their local doctor and referring physician for ongoing medical management. All patients received general information and advice about of life style changes including weight loss and diet.<br>The protocol permitted the administration of supplemental home oxygen at 1-2L/min to maintain a SpO2>90% if SpO2 remained <88% in NREM sleep during the patient's allocated home treatment |

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| | study at the maximum pressure that eliminated obstructive apneic or hypopneic events. patients were discharged home for 3 months with Duet LX bilevel devices: Respironics, Murrysville or VPAP II bilevel machines ResMed.<br>Indirectness: No indirectness<br>Further details: 1. Precise humidification – : Not stated / Unclear<br><br>(n=18) Intervention 2: Fixed pressure (default) CPAP with humidification. A short period of CPAP acclimatisation prior to the titration night was undertaken, which included mask fitting and use of CPAP at a range of pressures from 5-10cmH2O to ensure the patient understood the sensations they were likely to experience when using the therapy overnight. Overnight titration of CPAP was performed in all patients in a sleep laboratory using manual titration. Pressure was increased in 1cmH2O increments with the aim of preventing obstruction, flow limitation, desaturation and arousal. Patients were then discharged home on positive pressure therapy REMstar CPAP.<br><br>Duration 3 months. Concurrent medication/care: Patients were encouraged to contact the clinical service if they were experiencing any problems with therapy, and to return to their local doctor and referring physician for ongoing medical management. All patients received general information and advice about of life style changes including weight loss and diet. The protocol permitted the administration of supplemental home oxygen at 1-2L/min to maintain a SpO2>90%<br>if SpO2 remained <88% in NREM sleep during the patient's allocated home treatment study at the maximum pressure that eliminated obstructive apneic or hypopneic events. patients were discharged home for 3 months with Duet LX bilevel devices: Respironics, Murrysville or VPAP II bilevel machines ResMed. Indirectness: No indirectness<br>Further details: 1. Precise humidification – : Not stated / Unclear |
| Funding | Academic or government funding |

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BI-LEVEL POSITIVE AIRWAY PRESSURE/ NON-INVASIVE VENTILATION (NIV) WITHOUT HUMIDIFICATION versus FIXED PRESSURE (DEFAULT) CPAP WITH HUMIDIFICATION

Protocol outcome 1: Sleepiness score at >1 month
- Actual outcome for Undefined severity: ESS change score at 3 months; Group 1: mean -9 (SD 5); n=18, Group 2: mean -6 (SD 8); n=18;

| | |
|---|---|
| ESS 0-24 Top=High is poor outcome<br>Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0<br><br>Protocol outcome 2: Adherence in hours of use at >1 month<br>- Actual outcome for Undefined severity: adherence hours per night at 3 months; Group 1: mean 6.1 hours (SD 2.1); n=18, Group 2: mean 5.8 hours (SD 2.4); n=18<br>Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0<br><br>Protocol outcome 3: PaCO2 at >1 month<br>- Actual outcome for Undefined severity: PaCO2 change score at 3 months; Group 1: mean -6.9 (SD 6.7); n=18, Group 2: mean -5.8 (SD 8.4); n=18<br>Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 | |
| Protocol outcomes not reported by the study | Quality of life at >1 month; AHI/RDI at >1 month; ODI at >1 month; CO2 control at >1 month; Adverse effects of treatment at >1 month; HbA1c for diabetes at >1 month; Mortality at >1 month; Pa02 at >1 month; Systolic blood pressure for hypertension at >1 month; Cardiovascular events at >1 month |

| **Study** | **Storre 2006[249]** |
|---|---|
| Study type | RCT (Patient randomised; Crossover: no details provided) |
| Number of studies (number of participants) | 1 (n=10) |

| | |
|---|---|
| Countries and setting | Conducted in Germany; Setting: university hospital Freiburg Germany |
| Line of therapy | Unclear |
| Duration of study | Intervention time: 6 weeks |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis |
| Stratum | Undefined severity |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | Clinically stable OHS patients with a BMI over 30 kg/$m^2$ and daytime hypercapnia (i.e. paco2 >45mmhg) who had failed to respond to CPAP therapy were enrolled. |
| Exclusion criteria | Excluded if had signs of respiratory infection or acute respiratory failure (eg. RR>30; pH < 7.35) or had any previous ventilatory support or had been intubated in the past 3 months. |
| Age, gender and ethnicity | Age - Mean (SD): 53.5 (11.7). Gender (M:F): 8/2. Ethnicity: unclear |
| Further population details | 1. BMI: BMI of 30 2 kg/$m^2$ or more. Co-existing conditions: Not stated / Unclear 3. High risk occupation group: Not stated / Unclear 4. Sleepiness: Not stated / Unclear |
| Indirectness of population | No indirectness |
| Interventions | (n=10) Intervention 1: Bi-level positive airway pressure/ non-invasive ventilation (NIV) without humidification. Voume assured (NIV) Bilevel pressure ventilation device with AVAPS (average volume-assured pressure support) enabled.<br><br>Duration 6 weeks. Concurrent medication/care: no patient received supplemental oxygen. Indirectness: No indirectness<br>Further details: 1. Precise humidification – : Not stated / Unclear |

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| | (n=10) Intervention 2: Bi-level positive airway pressure/ non-invasive ventilation (NIV) without humidification. Fixed NIV Bilevel pressure ventilation device without AVAPS (average volume-assured pressure support) enabled<br><br>Duration 6 weeks. Concurrent medication/care: no patient received supplemental oxygen.<br>Indirectness: No indirectness<br>Further details: 1. Precise humidification – : Not stated / Unclear |
| Funding | Study funded by industry |

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BI-LEVEL POSITIVE AIRWAY PRESSURE/ NON-INVASIVE VENTILATION (NIV) WITHOUT HUMIDIFICATION versus BI-LEVEL POSITIVE AIRWAY PRESSURE/ NON-INVASIVE VENTILATION (NIV) WITHOUT HUMIDIFICATION

Protocol outcome 1: Quality of life at >1 month
- Actual outcome for Undefined severity: QOL - SRI at 6 weeks; Group 1: mean 75 (SD 16); n=10,
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: AHI/RDI at >1 month
- Actual outcome for Undefined severity: AHI at 6 weeks; Group 1: mean 0 (SD 0); n=10, Group 2: mean 0 (SD 0); n=10
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: ODI at >1 month
- Actual outcome for Undefined severity: ODI at 6 weeks; Group 1: mean 33 (SD 17); n=10, Group 2: mean 27 (SD 15); n=10
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: PaCO2 at >1 month
- Actual outcome for Undefined severity: PaCO2 at 6 weeks; Group 1: mean 5.6 (SD 0.7); n=10, Group 2: mean 6.1 (SD 0.5); n=10

| | |
|---|---|
| Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 | |
| Protocol outcomes not reported by the study | Sleepiness score at >1 month; CO2 control at >1 month; Adverse effects of treatment at >1 month; Adherence in hours of use at >1 month; HbA1c for diabetes at >1 month; Mortality at >1 month; Pa02 at >1 month; Systolic blood pressure for hypertension at >1 month; Cardiovascular events at >1 month |

# Appendix E: Forest plots

# OSAHS

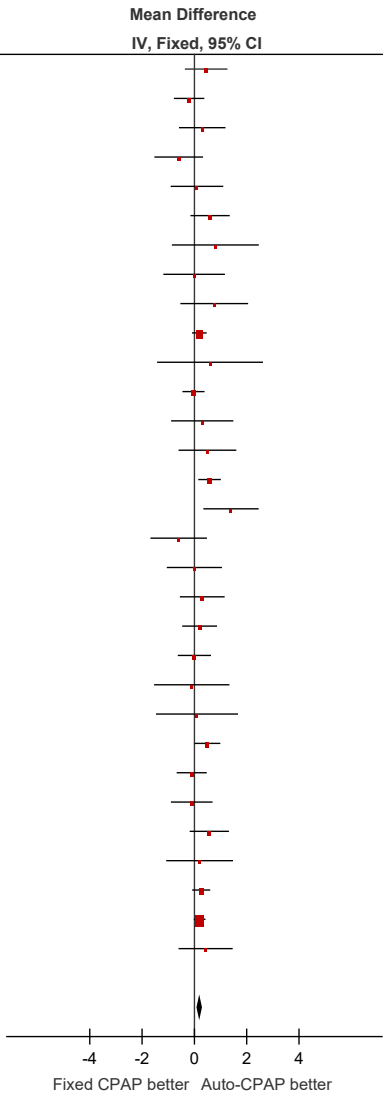
## E.1 Auto-CPAP versus fixed level CPAP- severe OSAHS

### Figure 2: Machine usage (hours/night)

| Study or Subgroup | Mean Difference | SE | Auto-CPAP Total | Fixed CPAP Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Berry 2014 | 0.45 | 0.402 | 67 | 64 | 1.6% | 0.45 [-0.34, 1.24] |
| Bloch 2018 | -0.2 | 0.2828 | 113 | 95 | 3.2% | -0.20 [-0.75, 0.35] |
| Chang 2015 | 0.3 | 0.4407 | 19 | 0 | 1.3% | 0.30 [-0.56, 1.16] |
| d'Ortho 2000 | -0.6 | 0.4617 | 25 | 0 | 1.2% | -0.60 [-1.50, 0.30] |
| Damjanovic 2009 | 0.1 | 0.498935 | 25 | 25 | 1.0% | 0.10 [-0.88, 1.08] |
| Ficker 2003 | 0.6 | 0.369373 | 50 | 50 | 1.9% | 0.60 [-0.12, 1.32] |
| Fietze 2007 | 0.8 | 0.8343 | 10 | 11 | 0.4% | 0.80 [-0.84, 2.44] |
| Galetke 2008 | -0.01 | 0.587 | 20 | 0 | 0.7% | -0.01 [-1.16, 1.14] |
| Hudgel 2000 | 0.76 | 0.647 | 29 | 0 | 0.6% | 0.76 [-0.51, 2.03] |
| Hukins 2004 | 0.19 | 0.13 | 46 | 0 | 15.3% | 0.19 [-0.06, 0.44] |
| Hussain 2004 | 0.6 | 1.02 | 10 | 0 | 0.2% | 0.60 [-1.40, 2.60] |
| Jarvis 2006 | -0.035 | 0.2015 | 20 | 0 | 6.4% | -0.04 [-0.43, 0.36] |
| Konermann 1998 | 0.3 | 0.593633 | 25 | 23 | 0.7% | 0.30 [-0.86, 1.46] |
| Marrone 2004 | 0.5 | 0.55 | 22 | 0 | 0.9% | 0.50 [-0.58, 1.58] |
| Massie 2003 | 0.58 | 0.2066 | 44 | 0 | 6.0% | 0.58 [0.18, 0.98] |
| Meurice 1996 | 1.4 | 0.525595 | 8 | 8 | 0.9% | 1.40 [0.37, 2.43] |
| Meurice 2007 | -0.6 | 0.537993 | 51 | 17 | 0.9% | -0.60 [-1.65, 0.45] |
| Nolan 2007 | 0 | 0.525 | 29 | 0 | 0.9% | 0.00 [-1.03, 1.03] |
| Nussbaumer 2006 | 0.3 | 0.4234 | 30 | 0 | 1.4% | 0.30 [-0.53, 1.13] |
| Patruno 2007 | 0.2 | 0.3266 | 16 | 15 | 2.4% | 0.20 [-0.44, 0.84] |
| Randerath 2001 | 0 | 0.31 | 45 | 0 | 2.7% | 0.00 [-0.61, 0.61] |
| Resta 2004 | -0.1 | 0.72111 | 10 | 10 | 0.5% | -0.10 [-1.51, 1.31] |
| Rochford 2006 | 0.1 | 0.7857 | 13 | 0 | 0.4% | 0.10 [-1.44, 1.64] |
| Rostig 2003 | 0.5 | 0.2379 | 30 | 0 | 4.6% | 0.50 [0.03, 0.97] |
| Senn 2003 | -0.1 | 0.28 | 29 | 0 | 3.3% | -0.10 [-0.65, 0.45] |
| Sériès 1997 | -0.1 | 0.392641 | 12 | 12 | 1.7% | -0.10 [-0.87, 0.67] |
| Sériès 2001 | 0.57 | 0.369678 | 17 | 16 | 1.9% | 0.57 [-0.15, 1.29] |
| Teschler 2000 | 0.2 | 0.6377 | 10 | 0 | 0.6% | 0.20 [-1.05, 1.45] |
| To 2008 | 0.26 | 0.16326 | 41 | 0 | 9.7% | 0.26 [-0.06, 0.58] |
| Vennelle 2010 | 0.2 | 0.10035 | 181 | 0 | 25.6% | 0.20 [0.00, 0.40] |
| West 2006 | 0.43 | 0.51463 | 28 | 31 | 1.0% | 0.43 [-0.58, 1.44] |
| **Total (95% CI)** | | | **1075** | **377** | **100.0%** | **0.21 [0.11, 0.31]** |

Heterogeneity: Chi² = 26.09, df = 30 (P = 0.67); I² = 0%

Test for overall effect: Z = 4.22 (P < 0.0001)

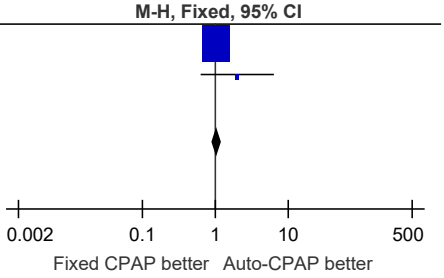


## Figure 3: Number of participants who used CPAP therapy > 4 hours per night

| Study or Subgroup | Auto-CPAP Events | Auto-CPAP Total | Fixed CPAP Events | Fixed CPAP Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Pépin 2016 | 107 | 161 | 104 | 161 | 97.2% | 1.03 [0.88, 1.21] |
| Sériès 1997 | 6 | 12 | 3 | 12 | 2.8% | 2.00 [0.65, 6.20] |
| **Total (95% CI)** | | **173** | | **173** | **100.0%** | **1.06 [0.90, 1.24]** |
| Total events | 113 | | 107 | | | |

Heterogeneity: Chi² = 1.33, df = 1 (P = 0.25); I² = 25%

Test for overall effect: Z = 0.68 (P = 0.50)

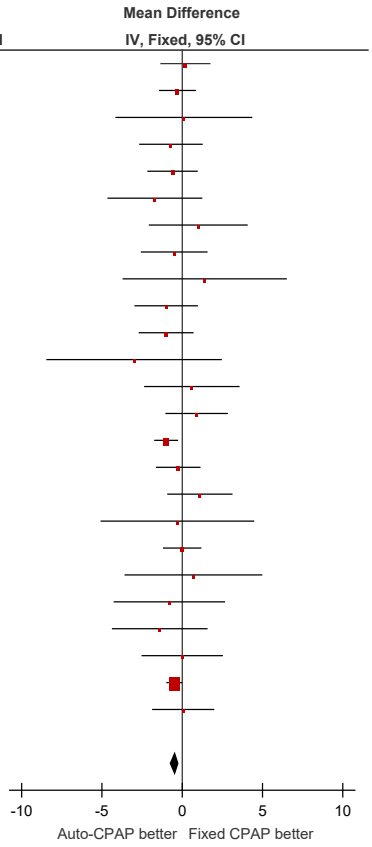



## Figure 4: Symptoms (Epworth Sleepiness Scale) (0 to 24, higher is worse)

| Study or Subgroup | Mean Difference | SE | Auto-CPAP Total | Fixed CPAP Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Berry 2014 | 0.2 | 0.7757 | 67 | 64 | 3.4% | 0.20 [-1.32, 1.72] |
| Bloch 2018 | -0.3 | 0.5657 | 113 | 95 | 6.4% | -0.30 [-1.41, 0.81] |
| d'Ortho 2000 | 0.1 | 2.155 | 25 | 0 | 0.4% | 0.10 [-4.12, 4.32] |
| Damjanovic 2009 | -0.7 | 0.99 | 25 | 25 | 2.1% | -0.70 [-2.64, 1.24] |
| Ficker 2003 | -0.6 | 0.781567 | 50 | 50 | 3.3% | -0.60 [-2.13, 0.93] |
| Galetke 2008 | -1.7 | 1.487 | 20 | 0 | 0.9% | -1.70 [-4.61, 1.21] |
| Hudgel 2000 | 1 | 1.55 | 29 | 0 | 0.8% | 1.00 [-2.04, 4.04] |
| Hukins 2004 | -0.5 | 1.04 | 46 | 0 | 1.9% | -0.50 [-2.54, 1.54] |
| Hussain 2004 | 1.4 | 2.59 | 10 | 0 | 0.3% | 1.40 [-3.68, 6.48] |
| Marrone 2004 | -1 | 0.989 | 22 | 0 | 2.1% | -1.00 [-2.94, 0.94] |
| Massie 2003 | -1 | 0.8521 | 44 | 0 | 2.8% | -1.00 [-2.67, 0.67] |
| Meurice 1996 | -3 | 2.768122 | 8 | 8 | 0.3% | -3.00 [-8.43, 2.43] |
| Meurice 2007 | 0.6 | 1.495816 | 51 | 17 | 0.9% | 0.60 [-2.33, 3.53] |
| Nolan 2007 | 0.9 | 0.97 | 29 | 0 | 2.2% | 0.90 [-1.00, 2.80] |
| Noseda 2004 | -1 | 0.36 | 24 | 0 | 15.7% | -1.00 [-1.71, -0.29] |
| Nussbaumer 2006 | -0.25 | 0.6888 | 30 | 0 | 4.3% | -0.25 [-1.60, 1.10] |
| Resta 2004 | 1.1 | 1.018332 | 10 | 10 | 2.0% | 1.10 [-0.90, 3.10] |
| Rochford 2006 | -0.3 | 2.4235 | 13 | 0 | 0.3% | -0.30 [-5.05, 4.45] |
| Rohling 2011 | 0 | 0.5908 | 33 | 0 | 5.8% | 0.00 [-1.16, 1.16] |
| Senn 2003 | 0.7 | 2.17 | 29 | 0 | 0.4% | 0.70 [-3.55, 4.95] |
| Sériès 1997 | -0.8 | 1.749524 | 12 | 12 | 0.7% | -0.80 [-4.23, 2.63] |
| Sériès 2001 | -1.4 | 1.499786 | 17 | 16 | 0.9% | -1.40 [-4.34, 1.54] |
| To 2008 | 0 | 1.2728 | 41 | 0 | 1.3% | 0.00 [-2.49, 2.49] |
| Vennelle 2010 | -0.5 | 0.23 | 181 | 0 | 38.6% | -0.50 [-0.95, -0.05] |
| West 2006 | 0.06 | 0.968246 | 28 | 31 | 2.2% | 0.06 [-1.84, 1.96] |
| **Total (95% CI)** | | | **957** | **328** | **100.0%** | **-0.44 [-0.72, -0.16]** |

Heterogeneity: Chi² = 13.53, df = 24 (P = 0.96); I² = 0%

Test for overall effect: Z = 3.11 (P = 0.002)

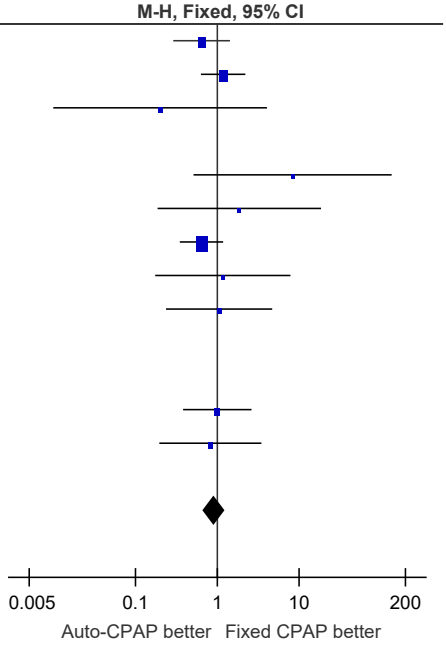


## Figure 5: Withdrawals (parallel group trials/first arm crossover trials)

| Study or Subgroup | Auto-CPAP Events | Auto-CPAP Total | Fixed CPAP Events | Fixed CPAP Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Berry 2014 | 9 | 78 | 14 | 78 | 18.4% | 0.64 [0.30, 1.40] |
| Bloch 2018 | 21 | 113 | 15 | 95 | 21.4% | 1.18 [0.64, 2.15] |
| Konermann 1998 | 0 | 25 | 2 | 25 | 3.3% | 0.20 [0.01, 3.97] |
| Meurice 1996 | 0 | 8 | 0 | 8 | | Not estimable |
| Meurice 2007 | 15 | 66 | 0 | 17 | 1.0% | 8.33 [0.52, 132.60] |
| Noseda 2004 | 2 | 14 | 1 | 13 | 1.4% | 1.86 [0.19, 18.13] |
| Pépin 2016 | 16 | 161 | 25 | 161 | 32.8% | 0.64 [0.36, 1.15] |
| Randerath 2001 | 2 | 24 | 2 | 28 | 2.4% | 1.17 [0.18, 7.67] |
| Rohling 2011 | 3 | 19 | 3 | 20 | 3.8% | 1.05 [0.24, 4.59] |
| Sériès 1997 | 0 | 12 | 0 | 12 | | Not estimable |
| Sériès 2001 | 0 | 17 | 0 | 16 | | Not estimable |
| Vennelle 2010 | 8 | 100 | 8 | 100 | 10.5% | 1.00 [0.39, 2.56] |
| West 2006 | 3 | 31 | 4 | 34 | 5.0% | 0.82 [0.20, 3.39] |
| **Total (95% CI)** | | **668** | | **607** | **100.0%** | **0.91 [0.67, 1.24]** |
| Total events | 79 | | 74 | | | |

Heterogeneity: Chi² = 6.84, df = 9 (P = 0.65); I² = 0%

Test for overall effect: Z = 0.58 (P = 0.56)

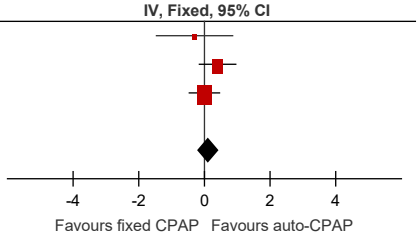



## Figure 6: Quality of life (Functional Outcome of Sleep Questionnaire) (5-20, higher is better)

| Study or Subgroup | Mean Difference | SE | Auto-CPAP Total | Fixed CPAP Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Berry 2014 | -0.3 | 0.5925 | 67 | 64 | 8.5% | -0.30 [-1.46, 0.86] |
| Bloch 2018 | 0.4 | 0.2828 | 113 | 95 | 37.3% | 0.40 [-0.15, 0.95] |
| Rochford 2006 | 0 | 0.2347 | 13 | 0 | 54.2% | 0.00 [-0.46, 0.46] |
| **Total (95% CI)** | | | **193** | **159** | **100.0%** | **0.12 [-0.21, 0.46]** |

Heterogeneity: Chi² = 1.74, df = 2 (P = 0.42); I² = 0%

Test for overall effect: Z = 0.72 (P = 0.47)

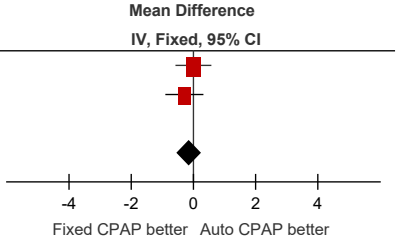



## Figure 7: Quality of life (Sleep Association Quality of Life Index) (1-7, higher is better)

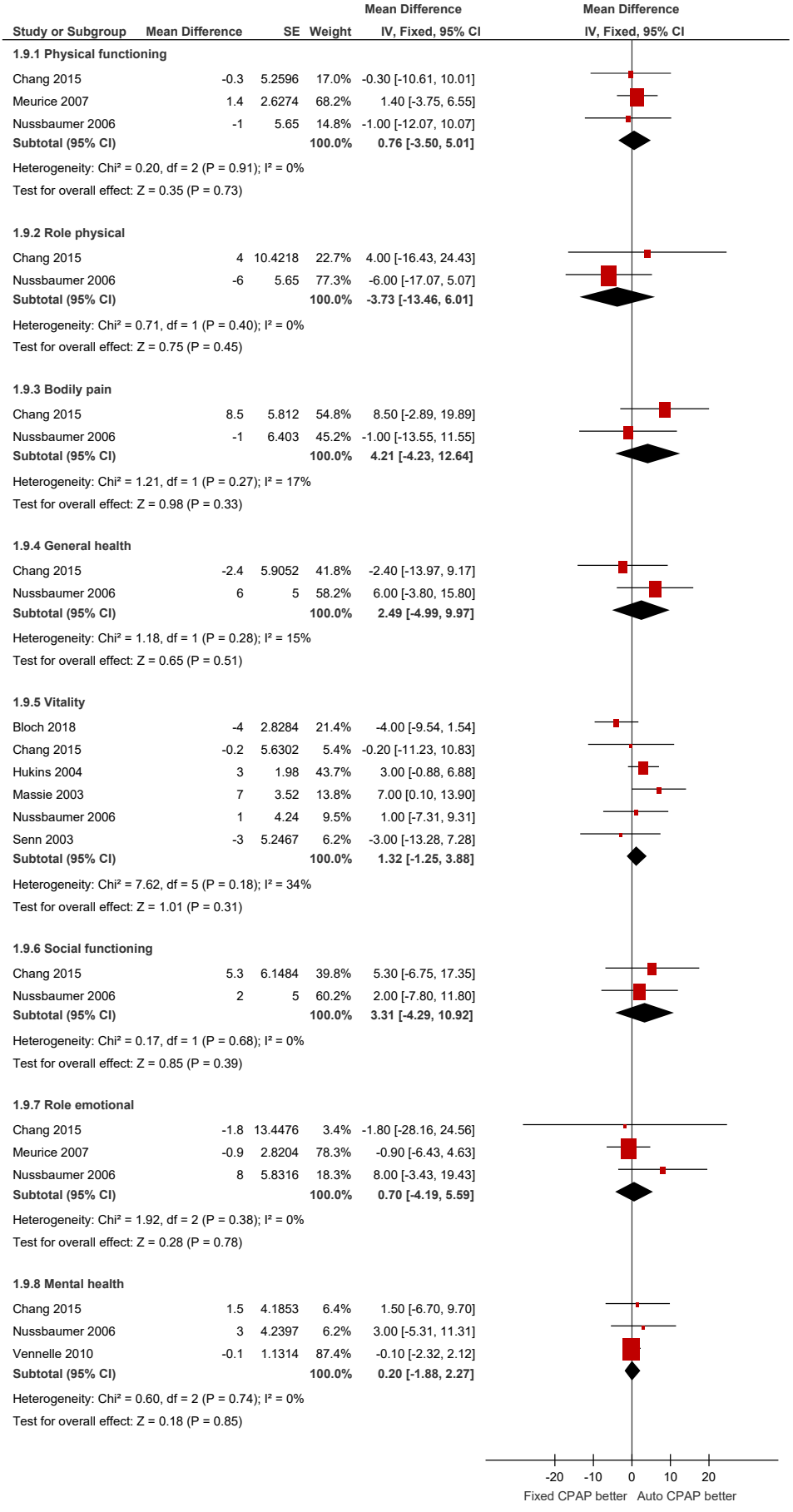
| Study or Subgroup | Mean Difference | SE | Auto-CPAP Total | Fixed CPAP Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| To 2008 | 0 | 0.2828 | 41 | 0 | 53.1% | 0.00 [-0.55, 0.55] |
| West 2006 | -0.29 | 0.301 | 26 | 30 | 46.9% | -0.29 [-0.88, 0.30] |
| **Total (95% CI)** | | | **67** | **30** | **100.0%** | **-0.14 [-0.54, 0.27]** |

Heterogeneity: Chi² = 0.49, df = 1 (P = 0.48); I² = 0%

Test for overall effect: Z = 0.66 (P = 0.51)



## Figure 8: Quality of life (SF-36) (0-100, higher is better)

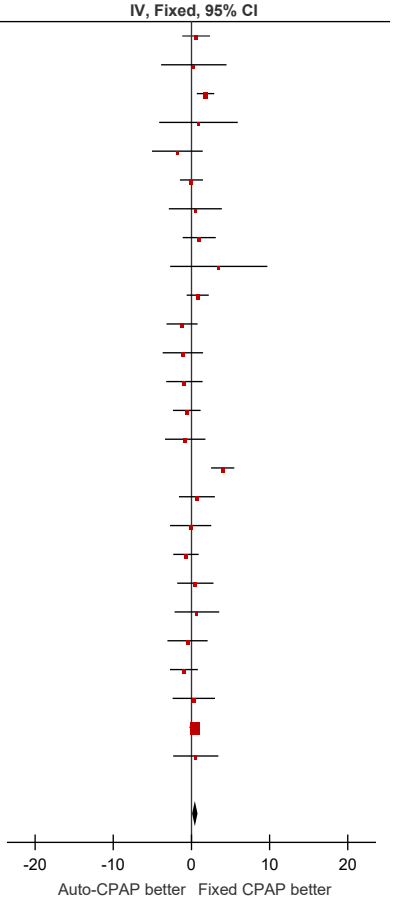


## Figure 9: Apnoea Hypopnoea Index (events/hr) (lower is better)

| Study or Subgroup | Mean Difference | SE | Auto-CPAP Total | Fixed CPAP Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Berry 2014 | 0.6 | 0.8612 | 67 | 64 | 3.7% | 0.60 [-1.09, 2.29] |
| Bloch 2018 | 0.3 | 2.0919 | 113 | 95 | 0.6% | 0.30 [-3.80, 4.40] |
| Chang 2015 | 1.8 | 0.5231 | 19 | 0 | 9.9% | 1.80 [0.77, 2.83] |
| d'Ortho 2000 | 0.9 | 2.52 | 25 | 0 | 0.4% | 0.90 [-4.04, 5.84] |
| Damjanovic 2009 | -1.8 | 1.612734 | 25 | 25 | 1.0% | -1.80 [-4.96, 1.36] |
| Ficker 2003 | 0 | 0.709282 | 50 | 50 | 5.4% | 0.00 [-1.39, 1.39] |
| Fietze 2007 | 0.5 | 1.6843 | 10 | 11 | 1.0% | 0.50 [-2.80, 3.80] |
| Galetke 2008 | 1 | 1.0357 | 20 | 0 | 2.5% | 1.00 [-1.03, 3.03] |
| Hussain 2004 | 3.5 | 3.13 | 10 | 10 | 0.3% | 3.50 [-2.63, 9.63] |
| Jarvis 2006 | 0.805 | 0.677 | 20 | 0 | 5.9% | 0.81 [-0.52, 2.13] |
| Konermann 1998 | -1.2 | 0.971668 | 25 | 23 | 2.9% | -1.20 [-3.10, 0.70] |
| Massie 2003 | -1.1 | 1.2755 | 44 | 0 | 1.7% | -1.10 [-3.60, 1.40] |
| Meurice 1996 | -0.9 | 1.142366 | 8 | 8 | 2.1% | -0.90 [-3.14, 1.34] |
| Nolan 2007 | -0.6 | 0.8571 | 29 | 0 | 3.7% | -0.60 [-2.28, 1.08] |
| Nussbaumer 2006 | -0.8 | 1.2755 | 30 | 0 | 1.7% | -0.80 [-3.30, 1.70] |
| Patruno 2007 | 4 | 0.716007 | 16 | 15 | 5.3% | 4.00 [2.60, 5.40] |
| Randerath 2001 | 0.7 | 1.13 | 45 | 0 | 2.1% | 0.70 [-1.51, 2.91] |
| Resta 2004 | -0.1 | 1.302306 | 10 | 10 | 1.6% | -0.10 [-2.65, 2.45] |
| Rochford 2006 | -0.7 | 0.7857 | 13 | 0 | 4.4% | -0.70 [-2.24, 0.84] |
| Rostig 2003 | 0.5 | 1.14 | 30 | 0 | 2.1% | 0.50 [-1.73, 2.73] |
| Senn 2003 | 0.7 | 1.414 | 29 | 0 | 1.4% | 0.70 [-2.07, 3.47] |
| Sériès 1997 | -0.5 | 1.267544 | 12 | 12 | 1.7% | -0.50 [-2.98, 1.98] |
| Sériès 2001 | -0.96 | 0.866589 | 17 | 16 | 3.6% | -0.96 [-2.66, 0.74] |
| Teschler 2000 | 0.3 | 1.34 | 10 | 0 | 1.5% | 0.30 [-2.33, 2.93] |
| Vennelle 2010 | 0.4 | 0.2905 | 181 | 0 | 32.2% | 0.40 [-0.17, 0.97] |
| West 2006 | 0.55 | 1.431536 | 28 | 31 | 1.3% | 0.55 [-2.26, 3.36] |
| **Total (95% CI)** | | | **886** | **370** | **100.0%** | **0.48 [0.16, 0.80]** |

Heterogeneity: Chi² = 49.01, df = 25 (P = 0.003); I² = 49%

Test for overall effect: Z = 2.91 (P = 0.004)

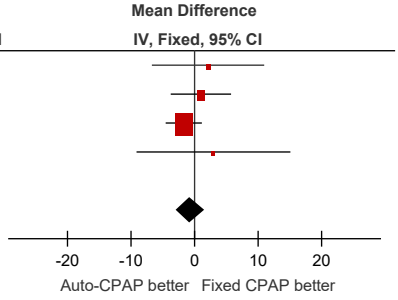



## Figure 10: Arousals (events/hr)

| Study or Subgroup | Mean Difference | SE | Auto-CPAP Total | Fixed CPAP Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Damjanovic 2009 | 2.12066 | 4.45642 | 25 | 25 | 6.6% | 2.12 [-6.61, 10.86] |
| Hussain 2004 | 1 | 2.367 | 10 | 0 | 23.3% | 1.00 [-3.64, 5.64] |
| Randerath 2001 | -1.7 | 1.3979 | 52 | 0 | 66.7% | -1.70 [-4.44, 1.04] |
| Sériès 1997 | 2.972092 | 6.12519 | 12 | 12 | 3.5% | 2.97 [-9.03, 14.98] |
| **Total (95% CI)** | | | **99** | **37** | **100.0%** | **-0.66 [-2.90, 1.58]** |

Heterogeneity: Chi² = 1.79, df = 3 (P = 0.62); I² = 0%

Test for overall effect: Z = 0.58 (P = 0.56)

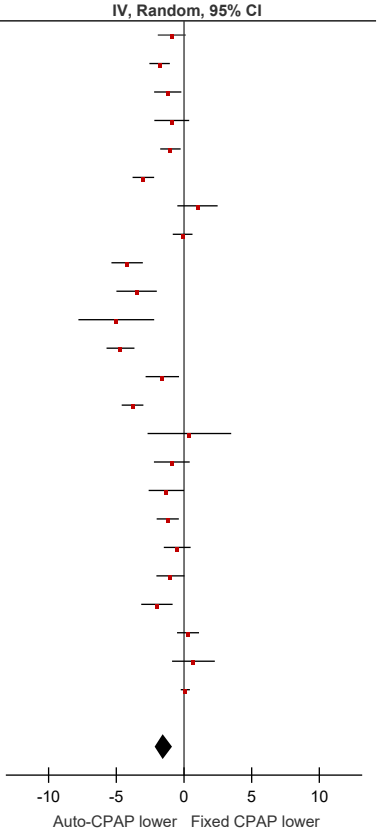


## Figure 11: Pressure of CPAP treatment (cm $H_2O$)

| Study or Subgroup | Mean Difference | SE | Auto-CPAP Total | Fixed CPAP Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Berry 2014 | -0.9 | 0.5015 | 67 | 64 | 4.4% | -0.90 [-1.88, 0.08] |
| Bloch 2018 | -1.8 | 0.3606 | 113 | 95 | 4.6% | -1.80 [-2.51, -1.09] |
| Chang 2015 | -1.2 | 0.4877 | 19 | 0 | 4.4% | -1.20 [-2.16, -0.24] |
| d'Ortho 2000 | -0.9 | 0.6327 | 25 | 0 | 4.1% | -0.90 [-2.14, 0.34] |
| Damjanovic 2009 | -1 | 0.360069 | 25 | 25 | 4.6% | -1.00 [-1.71, -0.29] |
| Ficker 2003 | -3 | 0.380526 | 50 | 50 | 4.6% | -3.00 [-3.75, -2.25] |
| Fietze 2007 | 1 | 0.7343 | 10 | 11 | 3.9% | 1.00 [-0.44, 2.44] |
| Galetke 2008 | -0.1 | 0.3469 | 20 | 0 | 4.6% | -0.10 [-0.78, 0.58] |
| Hudgel 2000 | -4.2 | 0.5663 | 29 | 0 | 4.2% | -4.20 [-5.31, -3.09] |
| Hukins 2004 | -3.5 | 0.7347 | 46 | 0 | 3.9% | -3.50 [-4.94, -2.06] |
| Hussain 2004 | -5 | 1.4031 | 10 | 0 | 2.5% | -5.00 [-7.75, -2.25] |
| Jarvis 2006 | -4.69 | 0.5 | 20 | 0 | 4.4% | -4.69 [-5.67, -3.71] |
| Konermann 1998 | -1.6 | 0.604649 | 25 | 23 | 4.2% | -1.60 [-2.79, -0.41] |
| Massie 2003 | -3.8 | 0.3827 | 22 | 0 | 4.6% | -3.80 [-4.55, -3.05] |
| Meurice 1996 | 0.4 | 1.55 | 8 | 8 | 2.3% | 0.40 [-2.64, 3.44] |
| Noseda 2004 | -0.9 | 0.648 | 24 | 0 | 4.1% | -0.90 [-2.17, 0.37] |
| Nussbaumer 2006 | -1.3 | 0.6429 | 30 | 0 | 4.1% | -1.30 [-2.56, -0.04] |
| Randerath 2001 | -1.2 | 0.3929 | 45 | 0 | 4.5% | -1.20 [-1.97, -0.43] |
| Rohling 2011 | -0.5 | 0.4802 | 33 | 0 | 4.4% | -0.50 [-1.44, 0.44] |
| Rostig 2003 | -1 | 0.5051 | 30 | 0 | 4.4% | -1.00 [-1.99, -0.01] |
| Senn 2003 | -2 | 0.5663 | 29 | 0 | 4.2% | -2.00 [-3.11, -0.89] |
| Sériès 1997 | 0.3 | 0.388373 | 12 | 12 | 4.5% | 0.30 [-0.46, 1.06] |
| Teschler 2000 | 0.7 | 0.7806 | 10 | 0 | 3.8% | 0.70 [-0.83, 2.23] |
| Vennelle 2010 | 0.1 | 0.1474 | 181 | 0 | 4.8% | 0.10 [-0.19, 0.39] |
| **Total (95% CI)** | | | **883** | **288** | **100.0%** | **-1.49 [-2.12, -0.85]** |

Heterogeneity: Tau² = 2.17; Chi² = 284.69, df = 23 (P < 0.00001); I² = 92%

Test for overall effect: Z = 4.58 (P < 0.00001)

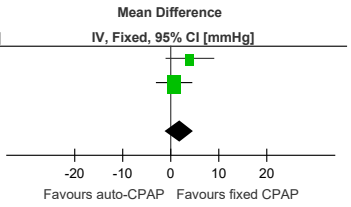



## Figure 12: Systolic blood pressure [mmHg]

| Study or Subgroup | Auto-CPAP Mean [mmHg] | SD [mmHg] | Total | Fixed pressure CPAP Mean [mmHg] | SD [mmHg] | Total | Weight | Mean Difference IV, Fixed, 95% CI [mmHg] |
|---|---|---|---|---|---|---|---|---|
| Patruno 2007 | 136 | 6 | 15 | 132 | 8 | 16 | 35.5% | 4.00 [-0.96, 8.96] |
| Pépin 2016 | 134.3 | 17.7 | 161 | 133.6 | 15.9 | 161 | 64.5% | 0.70 [-2.98, 4.38] |
| **Total (95% CI)** | | | **176** | | | **177** | **100.0%** | **1.87 [-1.08, 4.82]** |

Heterogeneity: Chi² = 1.10, df = 1 (P = 0.29); I² = 9%

Test for overall effect: Z = 1.24 (P = 0.21)

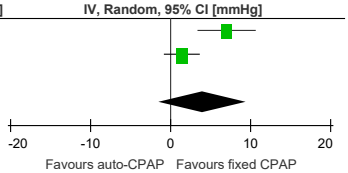



## Figure 13: Diastolic blood pressure [mmHg]

| Study or Subgroup | Auto-CPAP Mean [mmHg] | SD [mmHg] | Total | Fixed pressure CPAP Mean [mmHg] | SD [mmHg] | Total | Weight | Mean Difference IV, Random, 95% CI [mmHg] |
|---|---|---|---|---|---|---|---|---|
| Patruno 2007 | 86 | 4 | 15 | 79 | 6 | 16 | 46.7% | 7.00 [3.43, 10.57] |
| Pépin 2016 | 78.2 | 9.5 | 161 | 76.8 | 10.4 | 161 | 53.3% | 1.40 [-0.78, 3.58] |
| **Total (95% CI)** | | | **176** | | | **177** | **100.0%** | **4.01 [-1.46, 9.49]** |

Heterogeneity: Tau² = 13.41; Chi² = 6.89, df = 1 (P = 0.009); I² = 85%

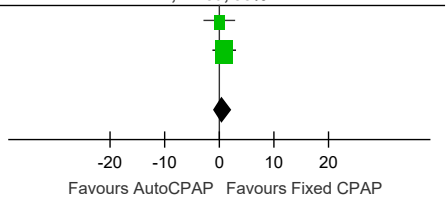
Test for overall effect: Z = 1.44 (P = 0.15)



## Figure 14: 24 hour mean BP

| Study or Subgroup | AutoCPAP Mean | AutoCPAP SD | AutoCPAP Total | Fixed CPAP Mean | Fixed CPAP SD | Fixed CPAP Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Bloch 2018 | 92 | 10.6301 | 113 | 92 | 9.7468 | 95 | 35.0% | 0.00 [-2.77, 2.77] |
| Pépin 2016 | 94.5 | 9.1 | 161 | 93.6 | 9.5 | 161 | 65.0% | 0.90 [-1.13, 2.93] |
| **Total (95% CI)** | | | **274** | | | **256** | **100.0%** | **0.59 [-1.05, 2.22]** |

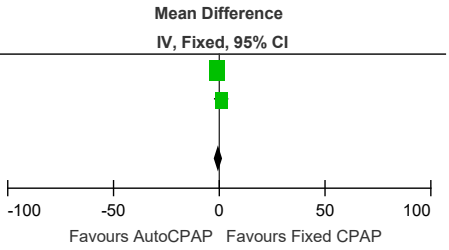
Heterogeneity: Chi² = 0.26, df = 1 (P = 0.61); I² = 0%
Test for overall effect: Z = 0.70 (P = 0.48)




## Figure 15: 24 hour systolic BP

| Study or Subgroup | AutoCPAP Mean | AutoCPAP SD | AutoCPAP Total | Fixed CPAP Mean | Fixed CPAP SD | Fixed CPAP Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Bloch 2018 | 126 | 10.6301 | 113 | 127 | 9.7468 | 95 | 55.3% | -1.00 [-3.77, 1.77] |
| Pépin 2016 | 128.1 | 14.2 | 161 | 127.2 | 14 | 161 | 44.7% | 0.90 [-2.18, 3.98] |
| **Total (95% CI)** | | | **274** | | | **256** | **100.0%** | **-0.15 [-2.21, 1.91]** |

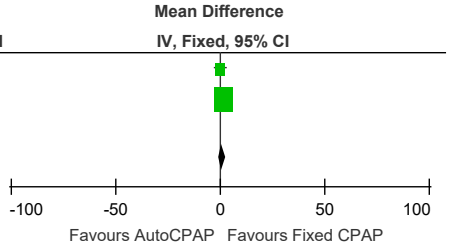
Heterogeneity: Chi² = 0.81, df = 1 (P = 0.37); I² = 0%
Test for overall effect: Z = 0.14 (P = 0.89)




## Figure 16: 24 hour diastolic BP

| Study or Subgroup | AutoCPAP Mean | AutoCPAP SD | AutoCPAP Total | Fixed CPAP Mean | Fixed CPAP SD | Fixed CPAP Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Bloch 2018 | 75 | 10.6301 | 113 | 75 | 9.7468 | 95 | 31.0% | 0.00 [-2.77, 2.77] |
| Pépin 2016 | 78.1 | 8 | 161 | 76.8 | 9 | 161 | 69.0% | 1.30 [-0.56, 3.16] |
| **Total (95% CI)** | | | **274** | | | **256** | **100.0%** | **0.90 [-0.65, 2.44]** |

Heterogeneity: Chi² = 0.58, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 1.14 (P = 0.26)




## Figure 17: Tolerability outcomes

| Study or Subgroup | Auto-CPAP Events | Auto-CPAP Total | Fixed CPAP Events | Fixed CPAP Total | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|
| **1.24.1 Intolerable treatment pressure** | | | | | |
| Bloch 2018 | 42 | 91 | 41 | 80 | 0.90 [0.66, 1.23] |
| **1.24.2 Mask Leak** | | | | | |
| Bloch 2018 | 34 | 91 | 27 | 80 | 1.11 [0.74, 1.66] |
| **1.24.3 Dry mouth** | | | | | |
| Bloch 2018 | 42 | 91 | 45 | 80 | 0.82 [0.61, 1.10] |
| **1.24.4 Stuffy nose** | | | | | |
| Bloch 2018 | 28 | 91 | 25 | 80 | 0.98 [0.63, 1.54] |

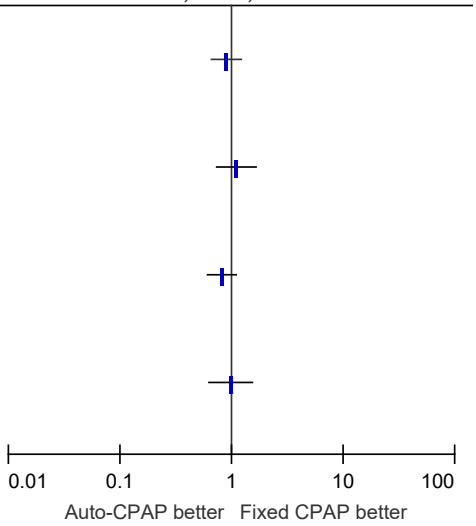
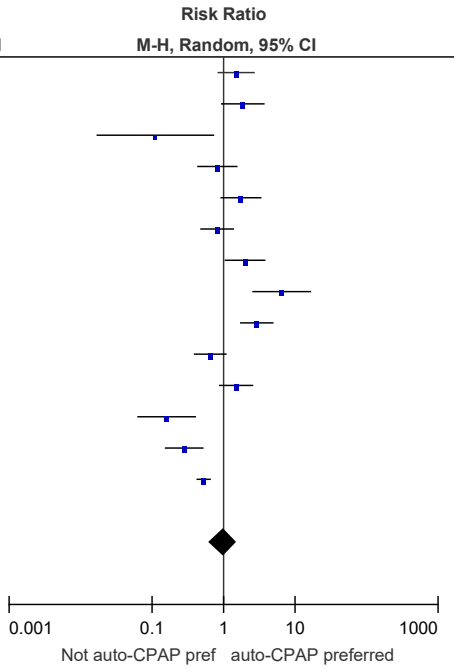


**Figure 18: Patient preference (auto-CPAP/not auto-CPAP)**

| Study or Subgroup | Auto-CPAP Events | Auto-CPAP Total | Not auto-CPAP Events | Not auto-CPAP Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| d'Ortho 2000 | 15 | 25 | 10 | 25 | 7.6% | 1.50 [0.84, 2.67] |
| Galetke 2008 | 13 | 20 | 7 | 20 | 7.2% | 1.86 [0.94, 3.66] |
| Hussain 2004 | 1 | 10 | 9 | 10 | 3.4% | 0.11 [0.02, 0.72] |
| Jarvis 2006 | 9 | 20 | 11 | 20 | 7.4% | 0.82 [0.44, 1.53] |
| Marrone 2004 | 14 | 22 | 8 | 22 | 7.4% | 1.75 [0.93, 3.31] |
| Nolan 2007 | 13 | 29 | 16 | 29 | 7.7% | 0.81 [0.48, 1.37] |
| Noseda 2004 | 16 | 24 | 8 | 24 | 7.4% | 2.00 [1.06, 3.76] |
| Nussbaumer 2006 | 26 | 30 | 4 | 30 | 6.3% | 6.50 [2.58, 16.36] |
| Randerath 2001 | 35 | 47 | 12 | 47 | 7.8% | 2.92 [1.74, 4.89] |
| Rohling 2011 | 13 | 33 | 20 | 33 | 7.8% | 0.65 [0.39, 1.08] |
| Rostig 2003 | 18 | 30 | 12 | 30 | 7.7% | 1.50 [0.89, 2.54] |
| Senn 2003 | 4 | 29 | 25 | 29 | 6.3% | 0.16 [0.06, 0.40] |
| To 2008 | 9 | 41 | 32 | 41 | 7.5% | 0.28 [0.15, 0.51] |
| Vennelle 2010 | 69 | 181 | 131 | 181 | 8.5% | 0.53 [0.43, 0.65] |
| **Total (95% CI)** | | **541** | | **541** | **100.0%** | **0.99 [0.64, 1.56]** |
| Total events | 255 | | 305 | | | |

Heterogeneity: Tau² = 0.60; Chi² = 117.71, df = 13 (P < 0.00001); I² = 89%

Test for overall effect: Z = 0.02 (P = 0.98)




# E.2 Non-invasive ventilation versus fixed level CPAP- severe OSAHS

**Figure 19: Machine usage (hours/night) (higher is better)**

| Study or Subgroup | Mean Difference | SE | Non invasive ventilation Total | Fixed CPAP Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Gay 2003 | 0 | 0.609508 | 12 | 15 | 6.7% | 0.00 [-1.19, 1.19] |
| Gulati 2015 | 0.49 | 0.26 | 28 | 0 | 36.9% | 0.49 [-0.02, 1.00] |
| Masa 2015 | 0 | 0.36 | 71 | 80 | 19.2% | 0.00 [-0.71, 0.71] |
| Reeves-Hoché 1995 | -0.1 | 0.25894 | 26 | 36 | 37.2% | -0.10 [-0.61, 0.41] |
| **Total (95% CI)** | | | **137** | **131** | **100.0%** | **0.14 [-0.17, 0.45]** |

Heterogeneity: Chi² = 2.87, df = 3 (P = 0.41); I² = 0%

Test for overall effect: Z = 0.91 (P = 0.36)

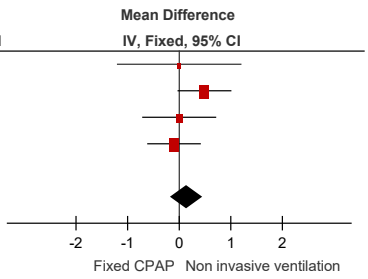
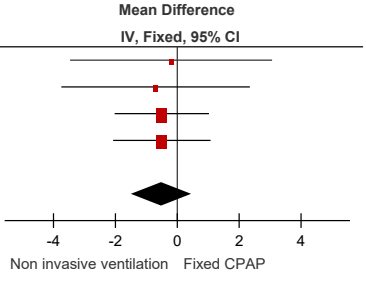



**Figure 20: Symptoms (Epworth Sleepiness Scale) (0 to 24, higher is worse)**

| Study or Subgroup | Mean Difference | SE | Non invasive ventilation Total | Fixed CPAP Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Gay 2003 | -0.2 | 1.6551 | 12 | 15 | 9.0% | -0.20 [-3.44, 3.04] |
| Gonzalez-Moro 2005 | -0.7 | 1.5443 | 10 | 10 | 10.3% | -0.70 [-3.73, 2.33] |
| Gulati 2015 | -0.5 | 0.767 | 28 | 0 | 41.7% | -0.50 [-2.00, 1.00] |
| Masa 2015 | -0.5 | 0.7926 | 71 | 80 | 39.1% | -0.50 [-2.05, 1.05] |
| **Total (95% CI)** | | | **121** | **105** | **100.0%** | **-0.49 [-1.46, 0.48]** |

Heterogeneity: Chi² = 0.05, df = 3 (P = 1.00); I² = 0%

Test for overall effect: Z = 1.00 (P = 0.32)

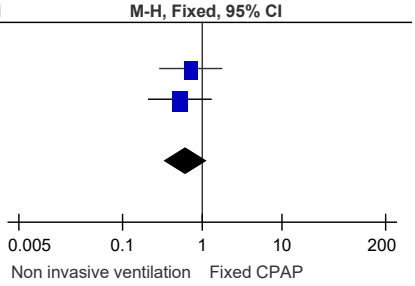


## Figure 21: Withdrawals (parallel group trials/first arm cross-over trials)

| Study or Subgroup | Non invasive ventilation Events | Total | Fixed CPAP Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Gay 2003 | 0 | 15 | 0 | 12 | | Not estimable |
| Masa 2015 | 7 | 71 | 11 | 80 | 46.4% | 0.72 [0.29, 1.75] |
| Reeves-Hoché 1995 | 5 | 31 | 16 | 52 | 53.6% | 0.52 [0.21, 1.29] |
| **Total (95% CI)** | | **117** | | **144** | **100.0%** | **0.61 [0.33, 1.15]** |
| Total events | 12 | | 27 | | | |

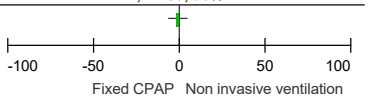
Heterogeneity: Chi² = 0.23, df = 1 (P = 0.63); I² = 0%

Test for overall effect: Z = 1.51 (P = 0.13)



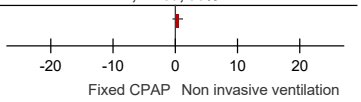

## Figure 22: Quality of life (Functional Outcome of Sleep Questionnaire) (5-20, higher is better)

| Study or Subgroup | Non invasive ventilation Mean | SD | Total | Fixed CPAP Mean | SD | Total | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|
| Masa 2015 | 4.3 | 17 | 71 | 5.1 | 16 | 80 | -0.80 [-6.08, 4.48] |

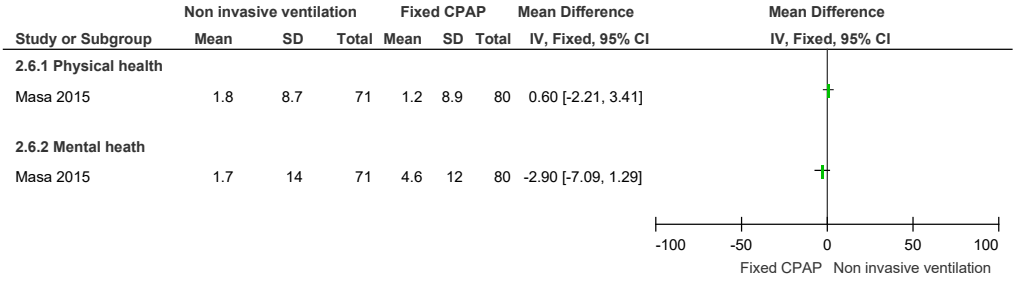



## Figure 23: Quality of life (Sleep Association Quality of Life Index) (1-7, higher is better

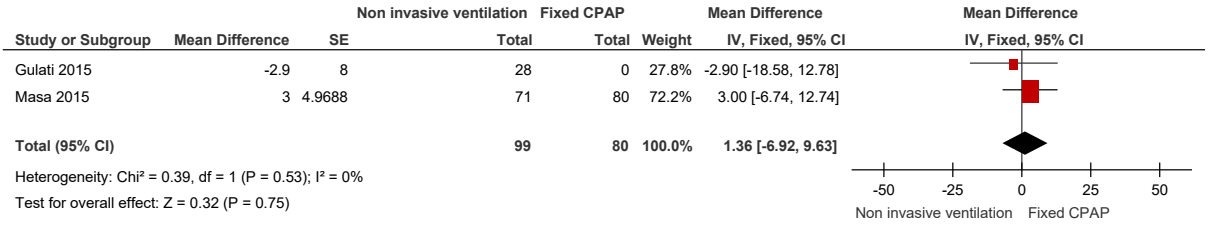
| Study or Subgroup | Mean Difference | SE | Non invasive ventilation Total | Fixed CPAP Total | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|
| Gulati 2015 | 0.4 | 0.38 | 28 | 0 | 0.40 [-0.34, 1.14] |



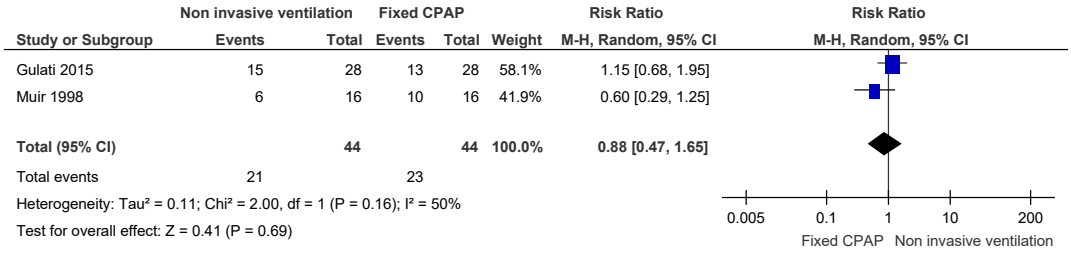
## Figure 24: Quality of life (SF-36 questionnaire) (0-100, higher is better)




## Figure 25: Apnoea Hypopnoea Index (events/hr) (lower is better)




## Figure 26: Patient preference – Non-invasive ventilation/no preference or CPAP




## Figure 27: Tolerability outcomes (lower is better)

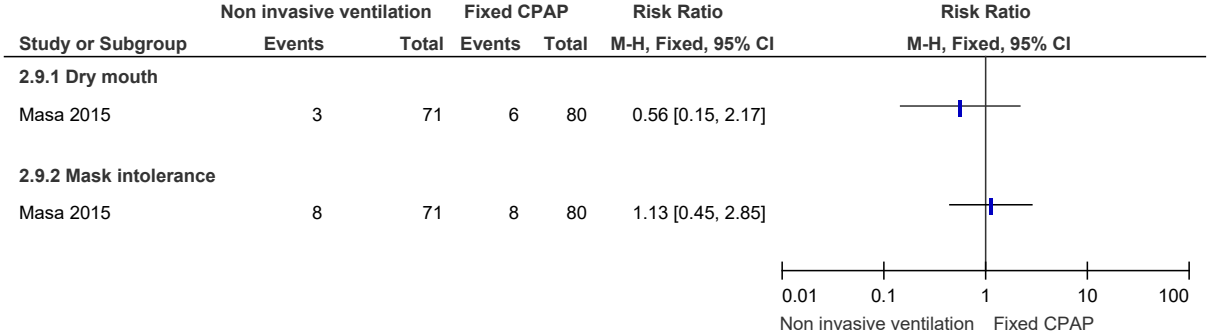
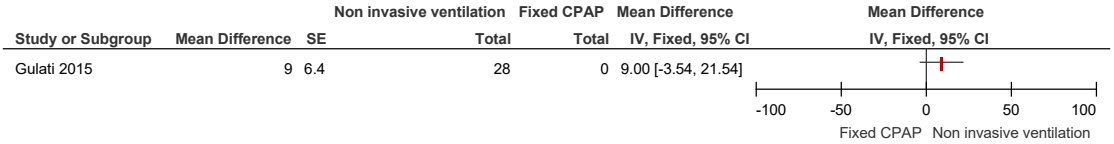


**Figure 28: Treatment comfort score**




# E.3 Heated humidification + fixed level CPAP versus fixed level CPAP alone- severe OSAHS

**Figure 29: Machine usage (hours/night) (higher is better)**

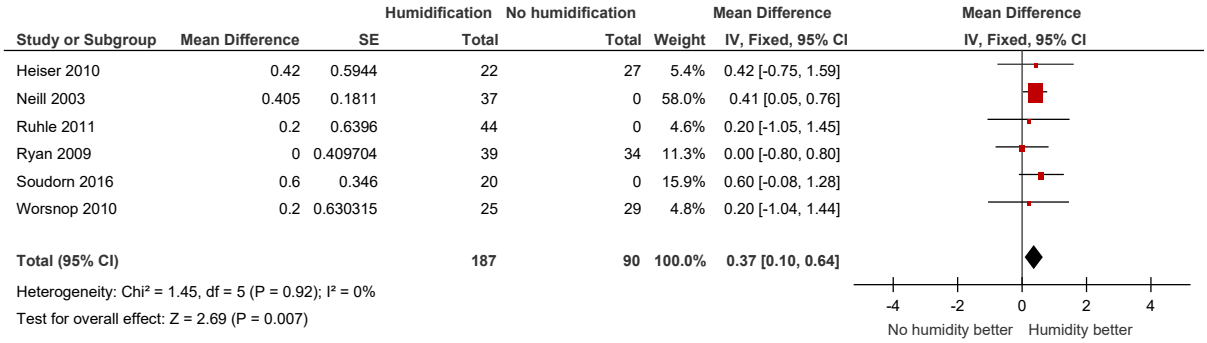
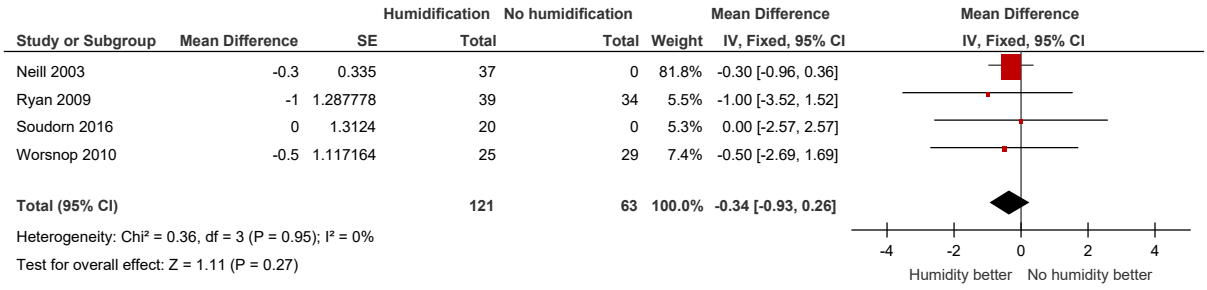
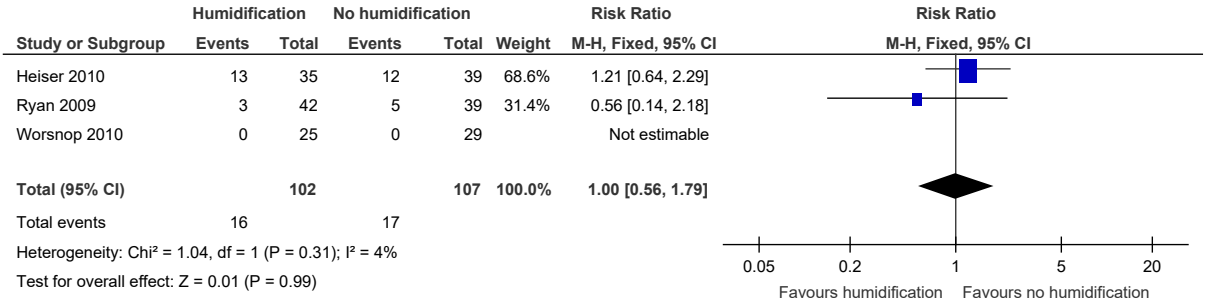


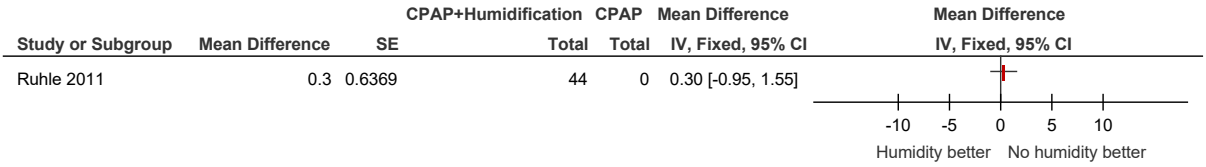

**Figure 30: Symptoms (Epworth Sleepiness Scale) (0 to 24, higher is worse)**



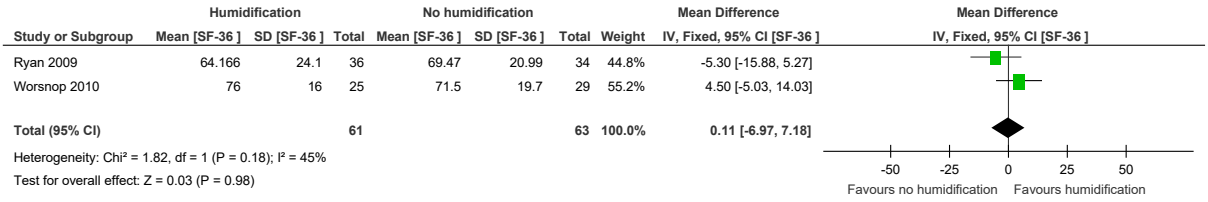
## Figure 31: Withdrawals (parallel group trials/first arm cross-over trials)



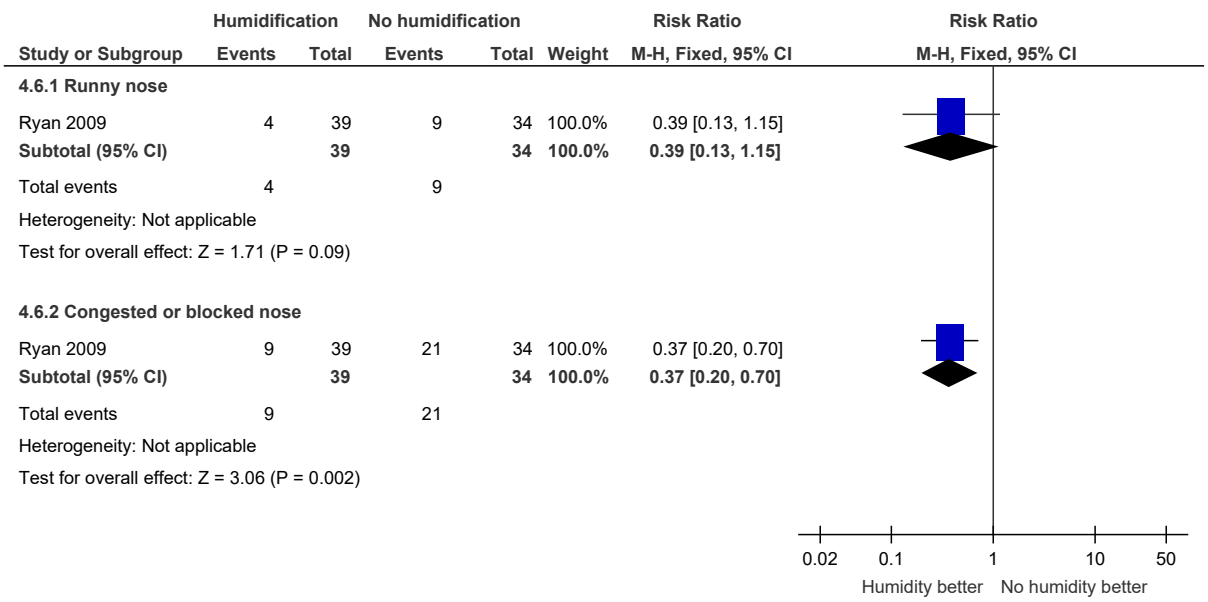

## Figure 32: Apnoea Hypopnoea Index (events/hr) (lower is better)



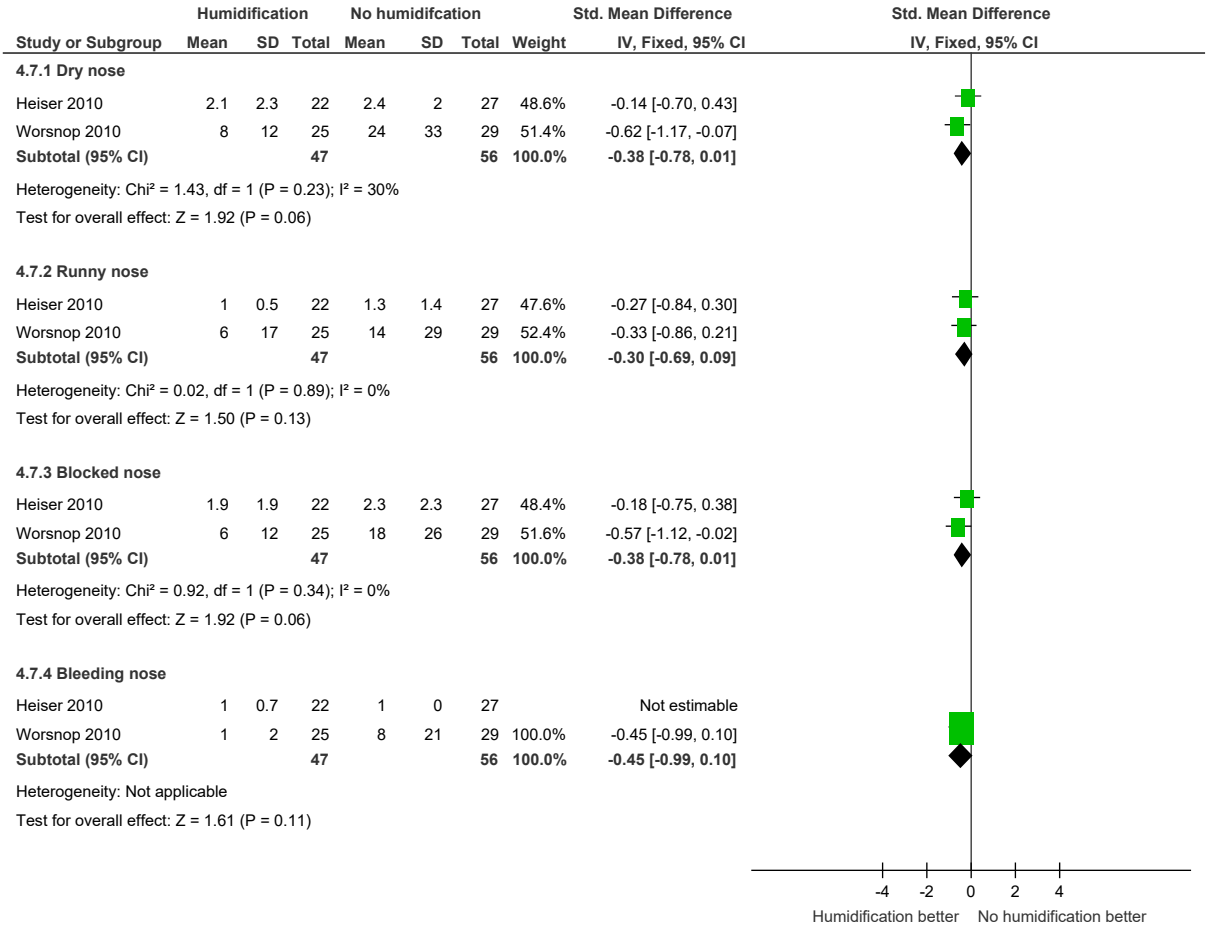

## Figure 33: Quality of life (SF-36 questionnaire) [SF-36 ] (0-100 , higher is better)



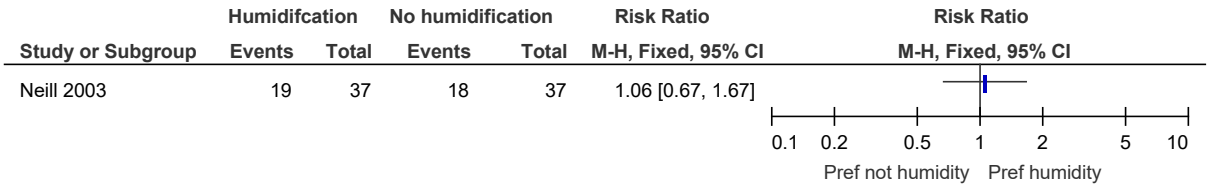
## Figure 34: Nasal symptoms (parallel group trials) – dichotomous



## Figure 35: Nasal symptoms (parallel group trials) – number of days (continuous)



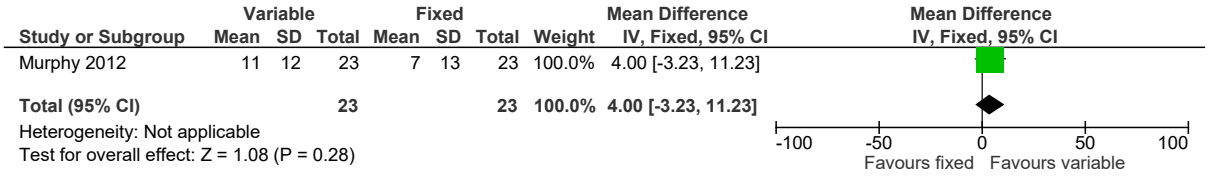

## Figure 36: Preference



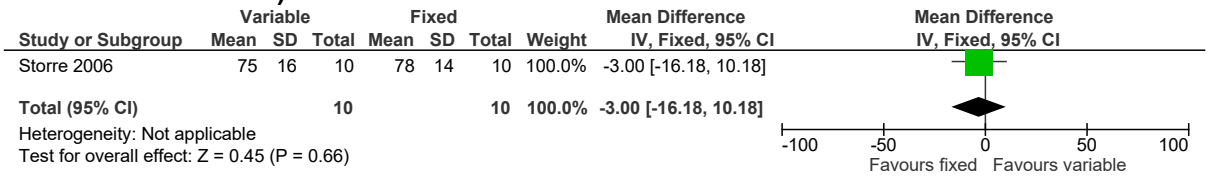

# OHS

# E.4 Volume assured non-invasive ventilation (NIV) vs fixed non-invasive ventilation (NIV)

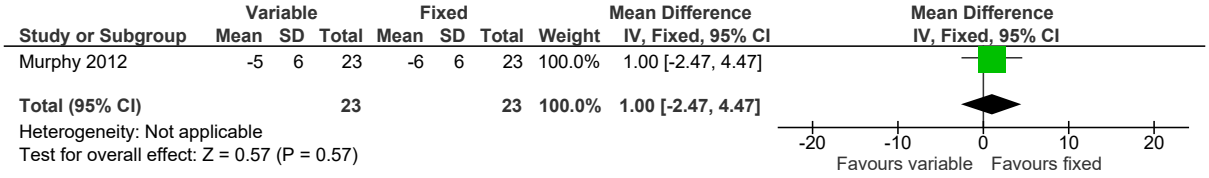
## Figure 37: Disease specific QoL (SRI, 0-100, higher is better, change score from parallel trial)



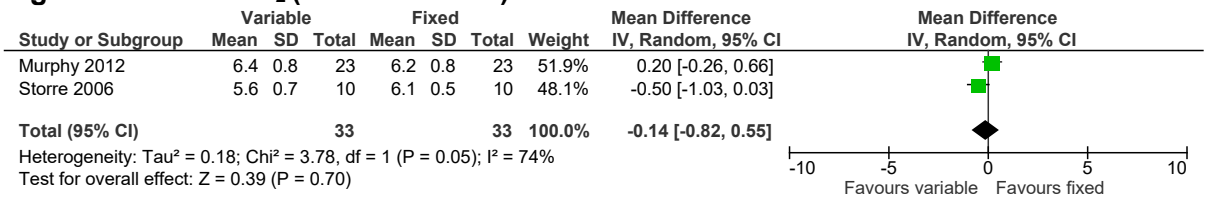

## Figure 38: Disease specific QoL (SRI, 0-100, higher is better, final value from crossover)




## Figure 39: Change in ESS (0-24, higher is worse)




## Figure 40: $PaCO_2$ (lower is better)




## Figure 41: Adherence (hrs/night)

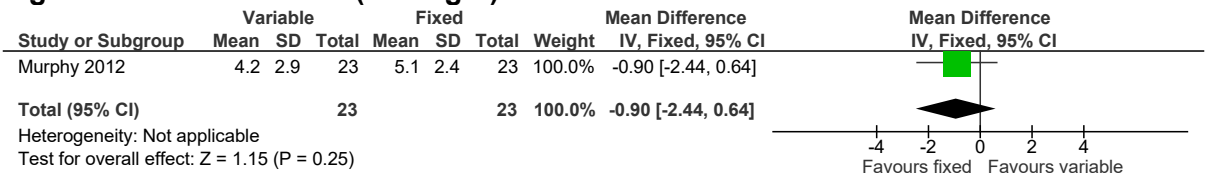


**Figure 42: AHI (lower is better)**

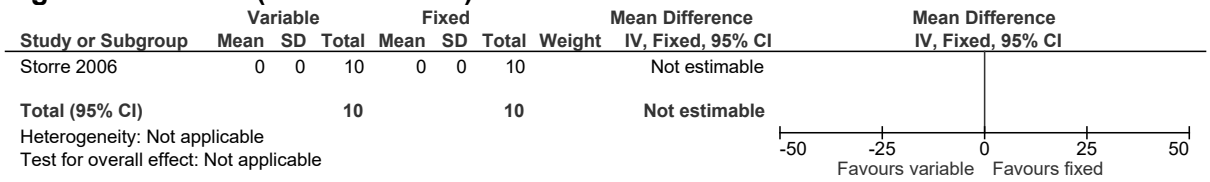



**Figure 43: ODI (lower is better)**

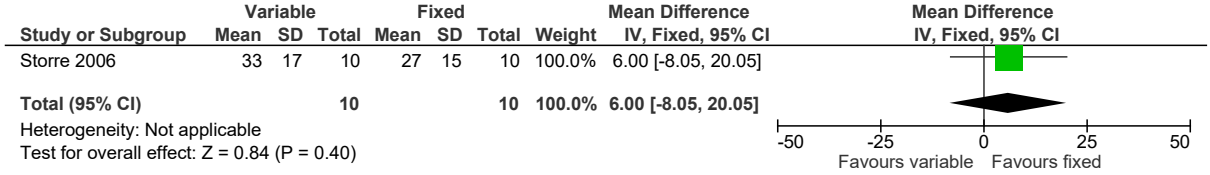
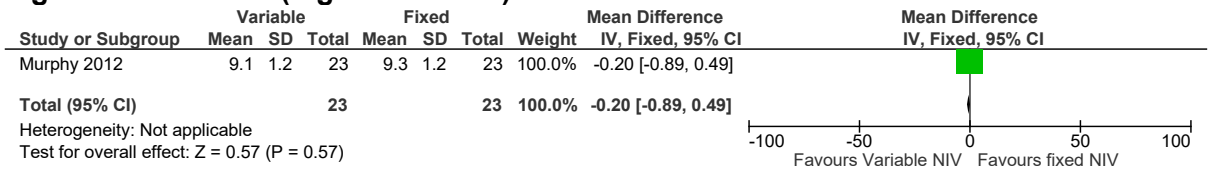



**Figure 44: PaO2 (higher is better)**




# E.5 Non-invasive ventilation (NIV) vs lifestyle

**Figure 45: Change in $PaCO_2$ at 2 months (lower is better)**

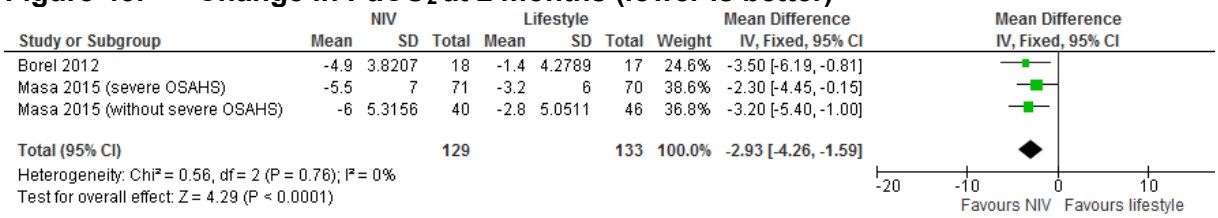
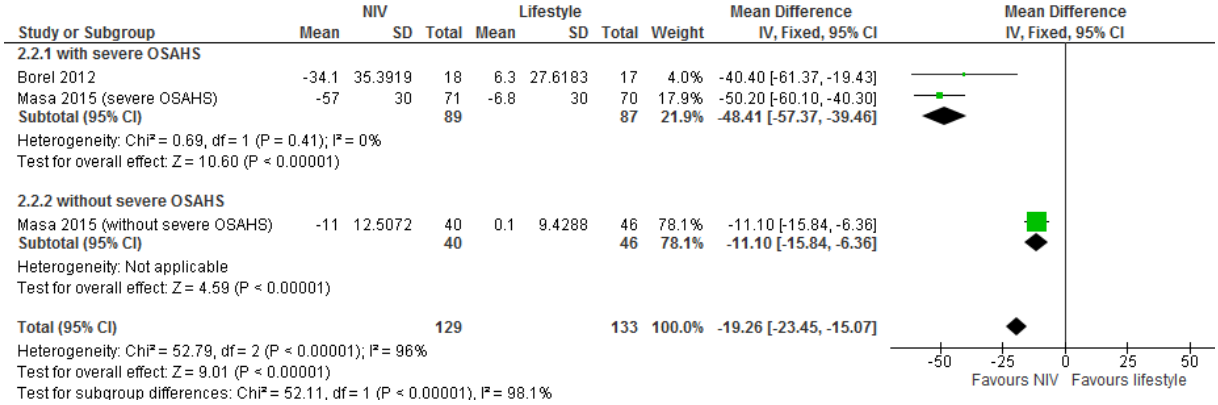
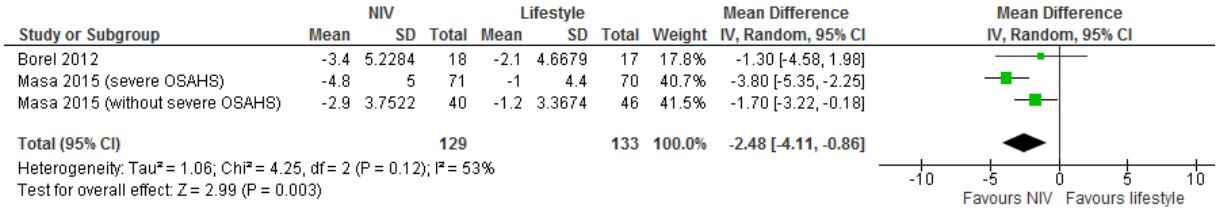


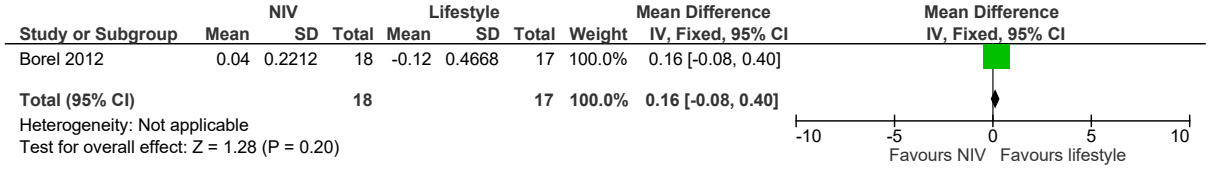

**Figure 46: Change in AHI at 2 months (lower is better)**



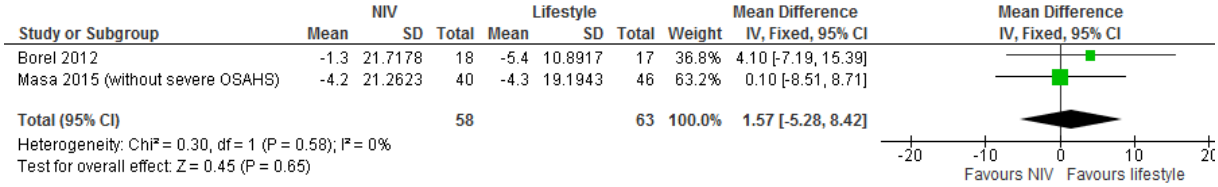
## Figure 47: Change in Epworth at 2 months (0-24, higher is worse)



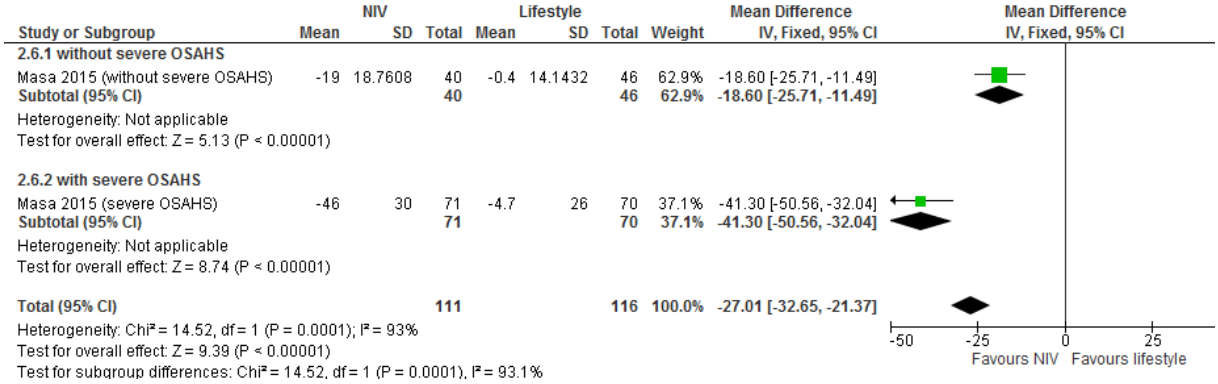

## Figure 48: Change in HbA1c at 2 months (lower is better)



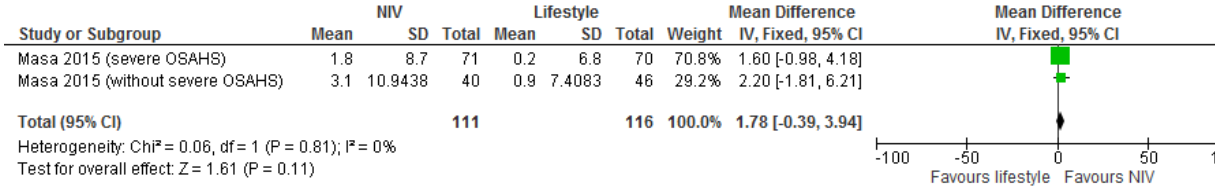

## Figure 49: Change in SBP at 2 months (lower is better)



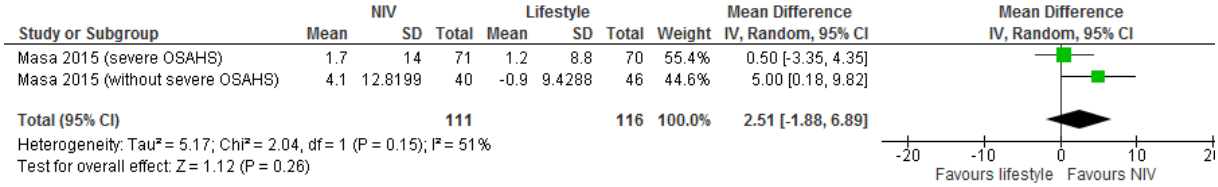

## Figure 50: Change in ODI at 2 months (lower is better)



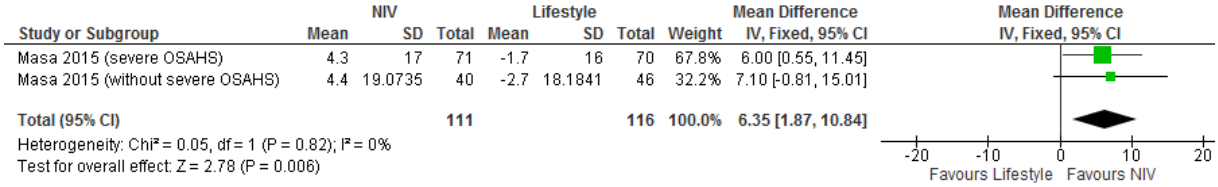

## Figure 51: Change in SF-36 physical summary at 2 months (0-100, higher is better)



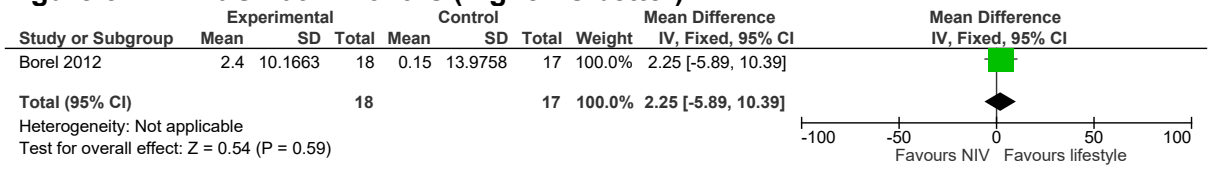
## Figure 52: Change in SF-36 mental summary at 2 months (0-100, higher is better)



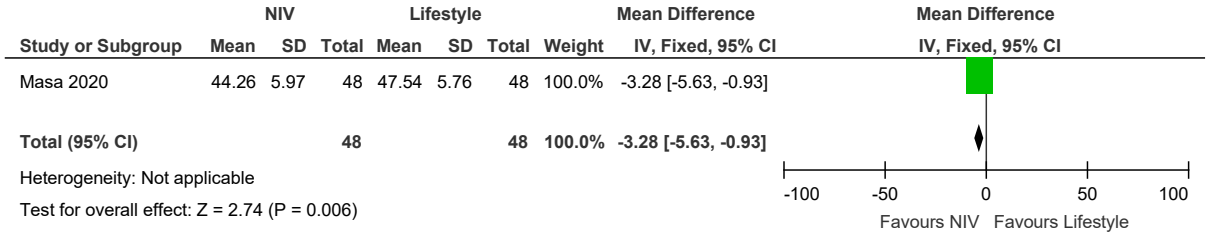

## Figure 53: Change in FOSQ at 2 months (5-20, higher is better)




## Figure 54: PaO2 at 2 months (higher is better)




## Figure 55: PaCO2 at 3 years (without severe OSA) (lower is better)




## Figure 56: ESS at at 3 years (without severe OSA) (0-24, higher is worse)

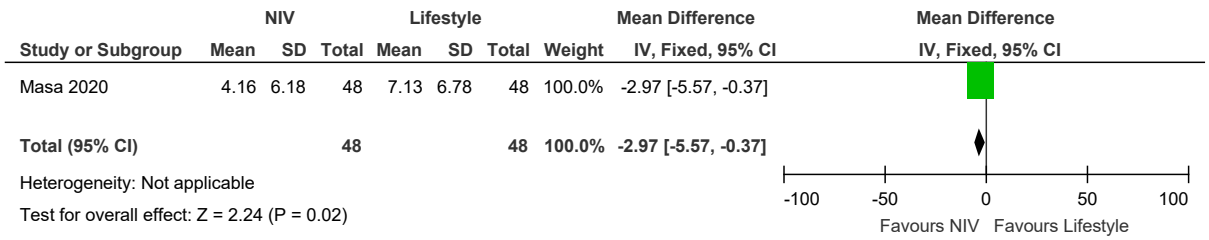


**Figure 57: FOSQ at at 3 years (without severe OSA) (5-20, higher is better)**

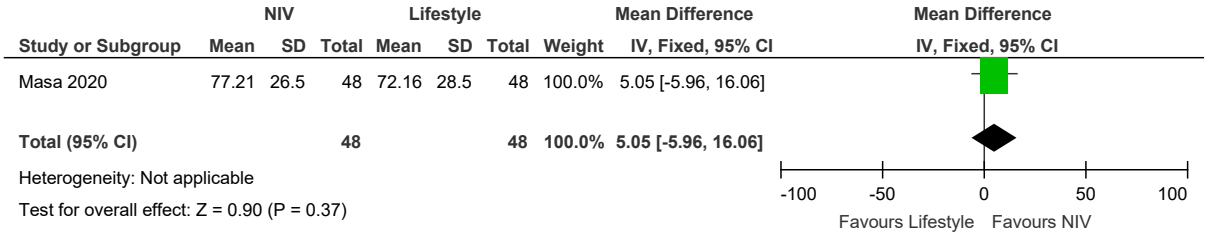



**Figure 58: SF-36 Physical at at 3 years (without severe OSA) (0-100, higher is better)**

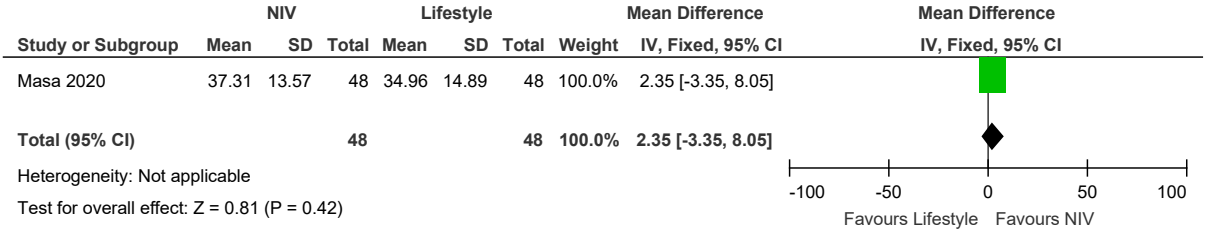



Figure 59: **SF-36 Mental at 3 years (without severe OSA) (0-100, higher is better)**

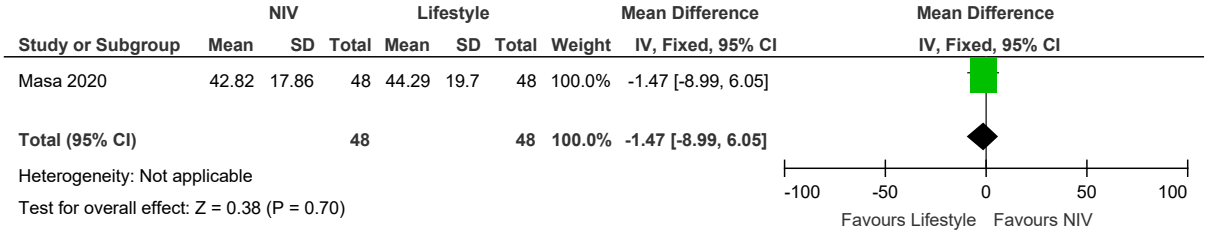



Figure 60: **Mortality at 3 years (without severe OSA)**

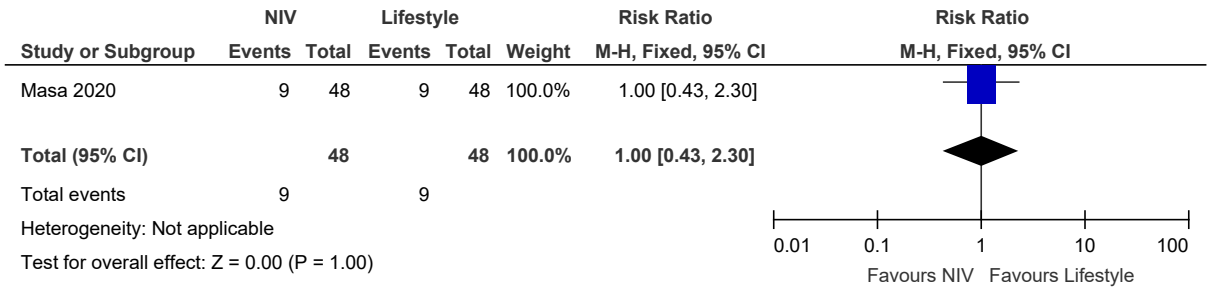



**Figure 61: Cardiovascular events at at 3 years (without severe OSA)**

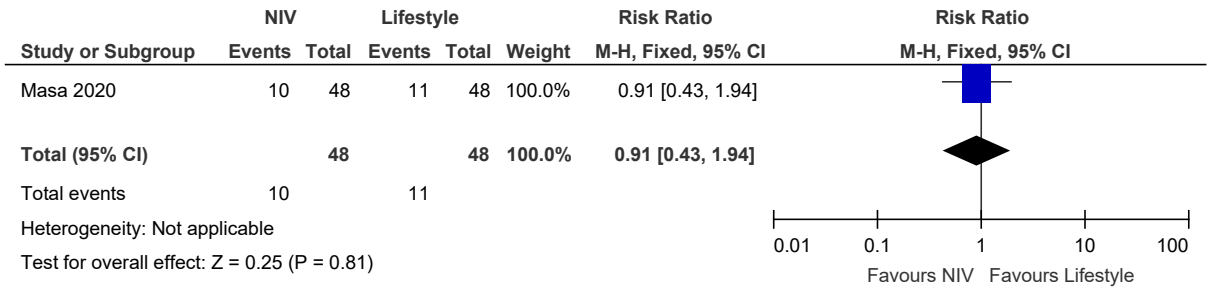



**Figure 62: Systolic blood pressure at 3 years (without severe OSA)**

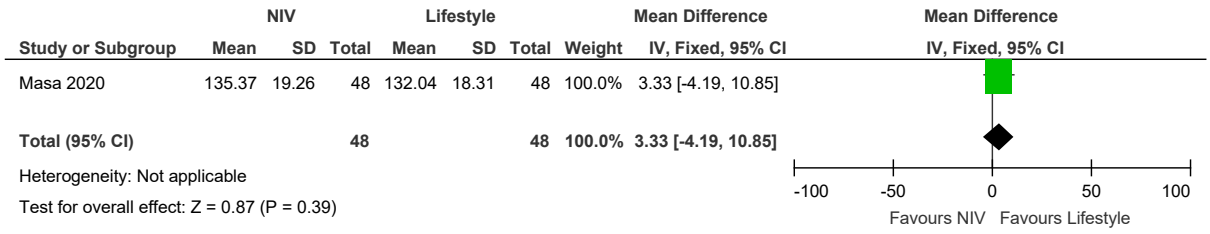
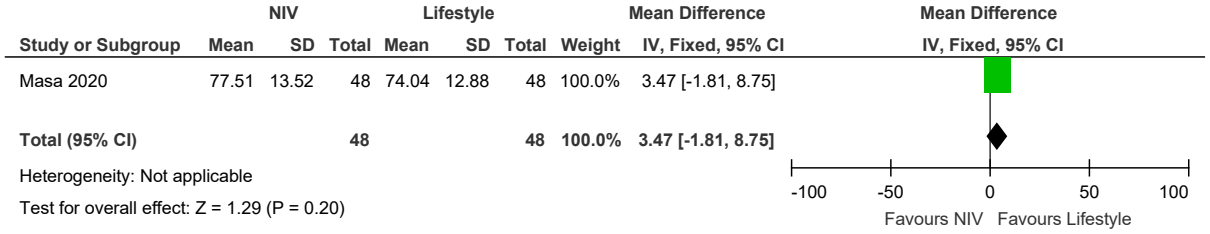
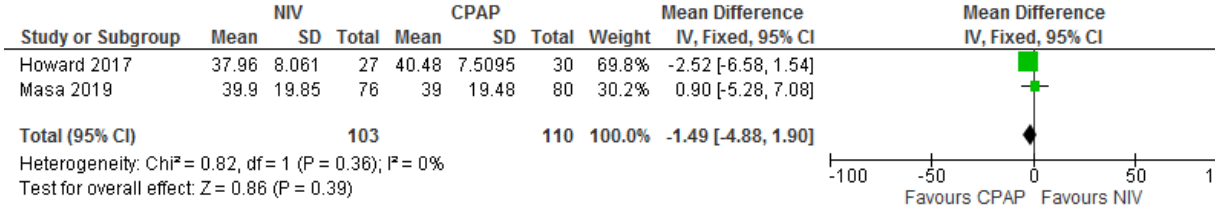



**Figure 63: Diastolic blood pressure at 3 years (without severe OSA)**

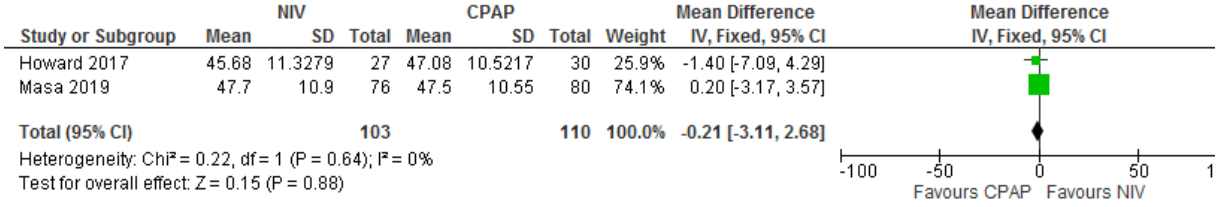


# E.6 Non-invasive ventilation (NIV) vs CPAP

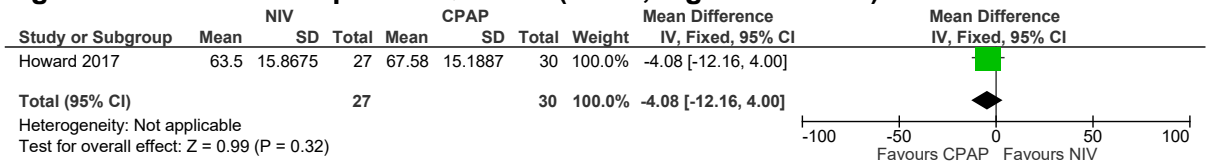
## Figure 64: SF-36 physical (0-100, higher is better)



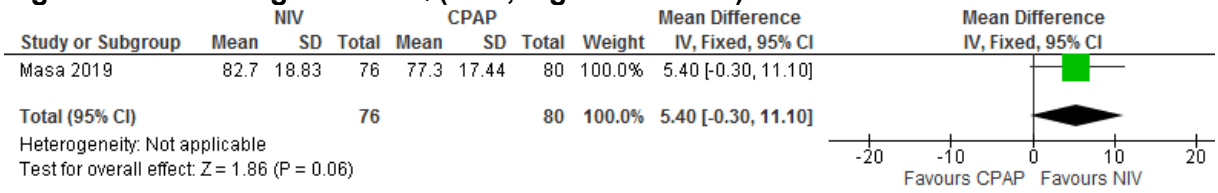

## Figure 65: SF-36 mental (0-100, higher is better)



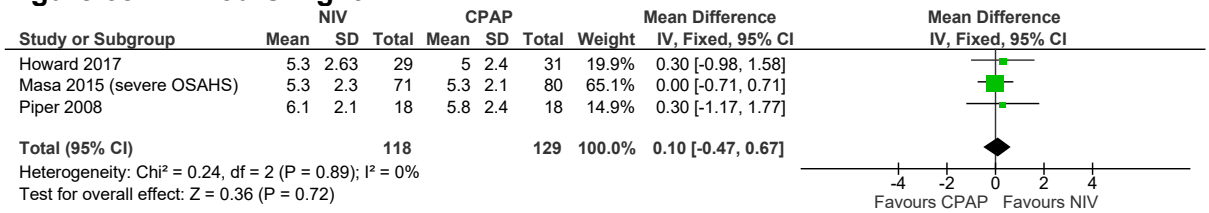

## Figure 66: Disease specific QoL SRI (0-100, higher is better)



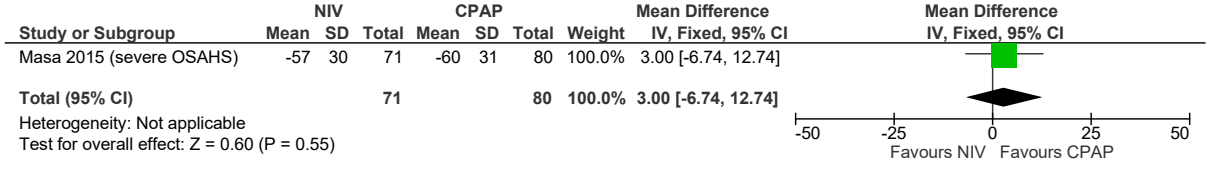

## Figure 67: Change in FOSQ (5-20, higher is better)



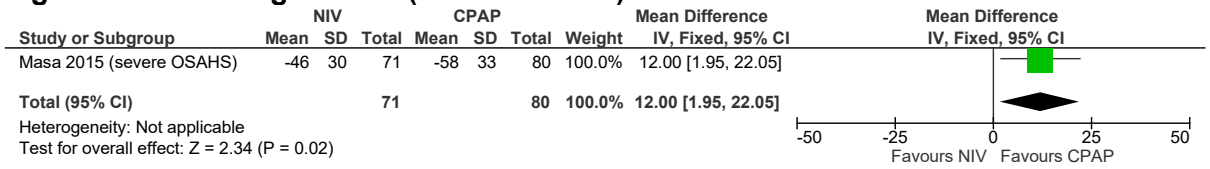

## Figure 68: Hours/night



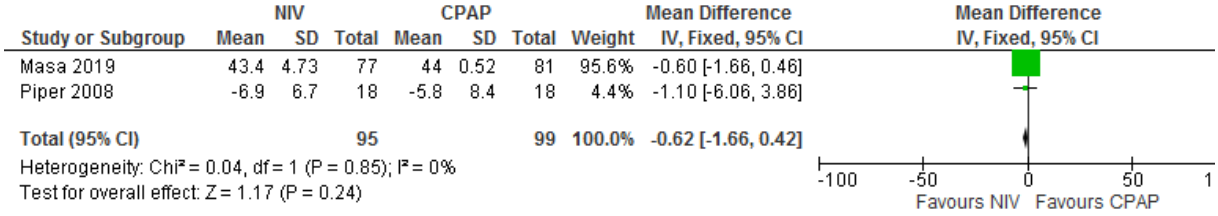

## Figure 69: Change in AHI (lower is better)



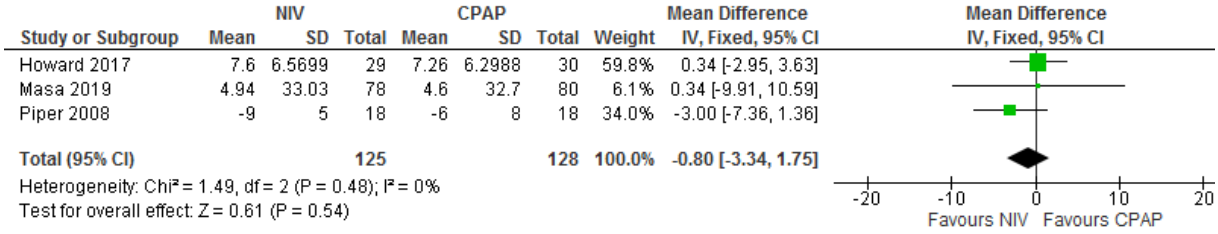
## Figure 70: Change in ODI (lower is better)



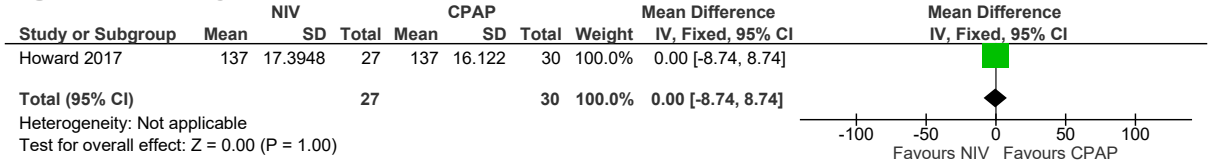

## Figure 71: Change in $PaCO_2$ (lower is better)



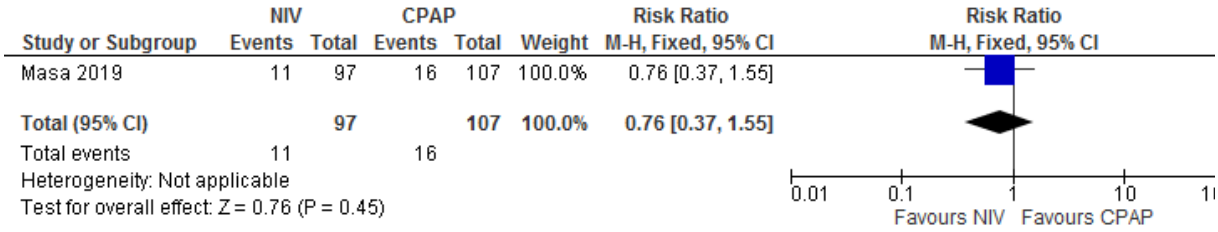

## Figure 72: ESS (FV/CS, 0-24, higher is worse)



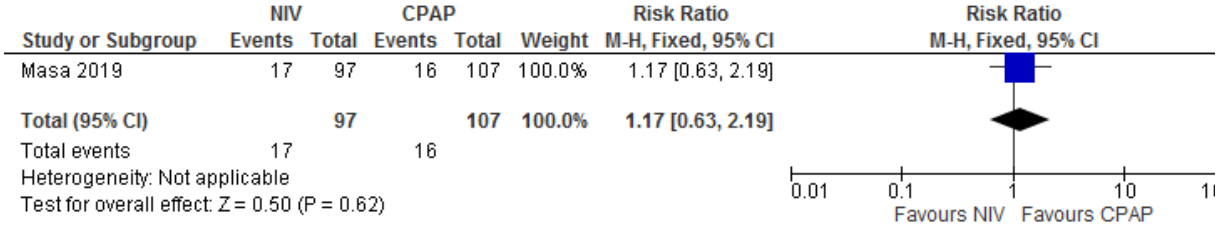

## Figure 73: Systolic BP (lower is better)



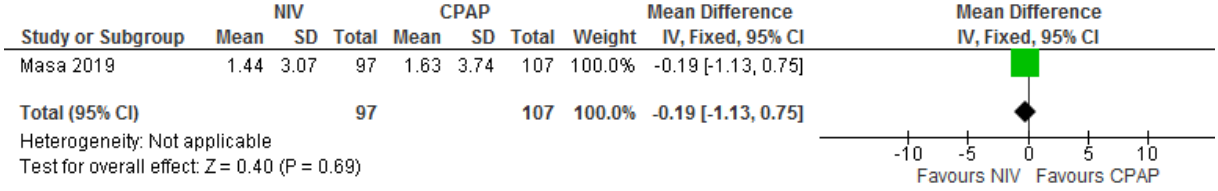
### Figure 74: Mortality




### Figure 75: Cardiovascular events

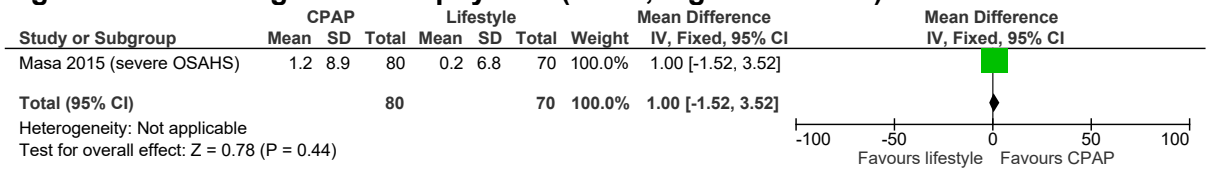



### Figure 76: hospitalisation per year per patient

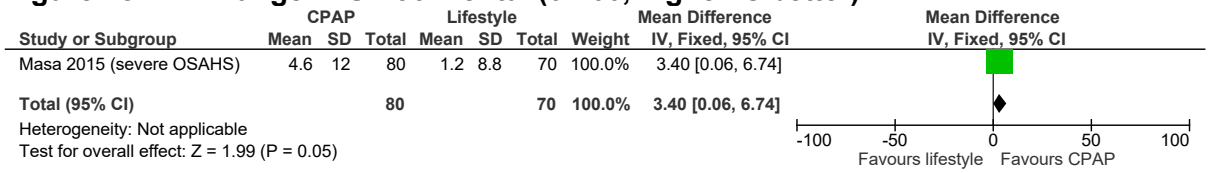



# E.7 CPAP vs lifestyle

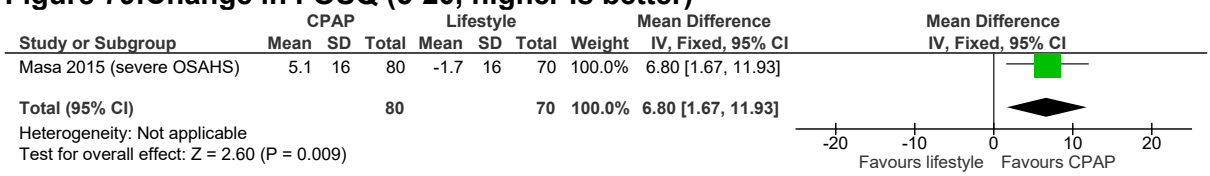
### Figure 77: Change in SF-36 physical (0-100, higher is better)




### Figure 78: Change in SF-36 mental (0-100, higher is better)

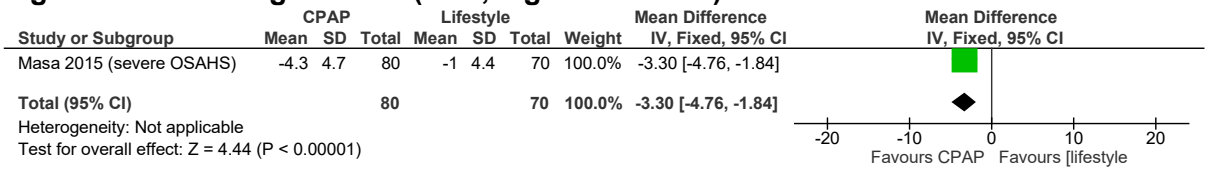



### Figure 79:Change in FOSQ (5-20, higher is better)

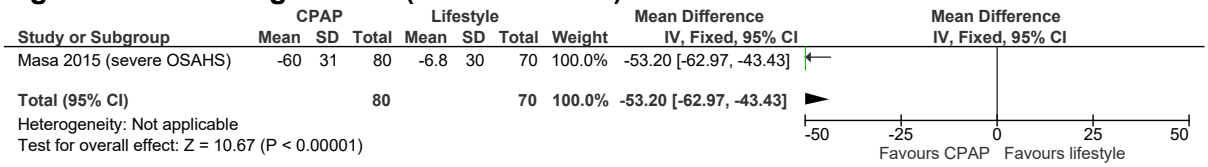


*<Insert Note here>*

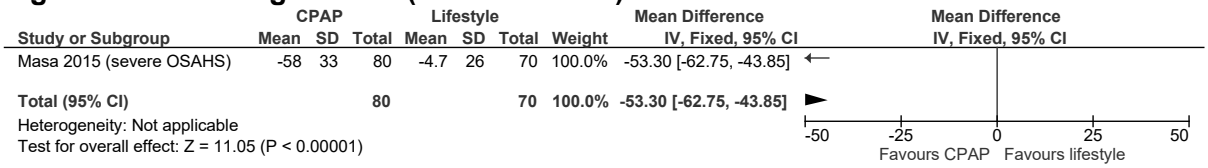
## Figure 80: Change in ESS (0-24, higher is worse)



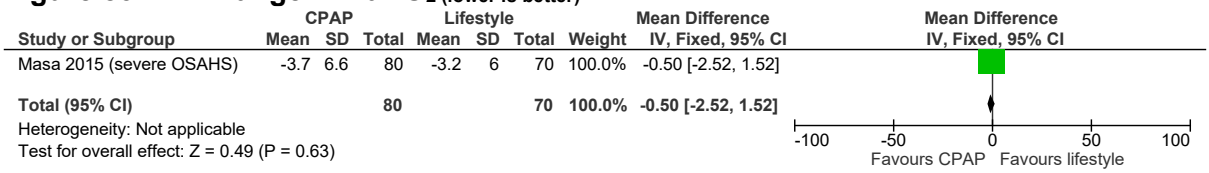

## Figure 81: Change in AHI (lower is better)




## Figure 82: Change in ODI (lower is better)




## Figure 83: Change in $PaCO_2$ (lower is better)



# Appendix F: GRADE tables

# OSAHS

**Table 22: Clinical evidence profile: Auto-CPAP versus fixed level CPAP for improving usage of continuous positive airway pressure machines in adults with OSAHS- severe OSAHS**

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Auto-CPAP versus fixed CPAP | Control | Relative (95% CI) | Absolute | | |
| **Machine usage (hours/night) (Better indicated by higher values)** | | | | | | | | | | | | |
| 31 | randomised trials | serious[1] | no serious inconsistency | serious indirectness[5] | no serious imprecision | None | 1075 | 377 | - | MD 0.21 higher (0.11 to 0.31 higher) | ⊕⊕OO LOW | IMPORTANT |
| **Number of participants who used CPAP therapy > 4 hours per night** | | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | no serious inconsistency | serious indirectness[5] | no serious imprecision | None | 113/173 (65.3%) | 44.8% | RR 1.06 (0.9 to 1.24) | 27 more per 1000 (from 45 fewer to 108 more) | ⊕⊕OO LOW | IMPORTANT |
| **Symptoms (Epworth Sleepiness Scale) (Better indicated by lower values)** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 25 | randomised trials | serious[1] | no serious inconsistency | serious indirectness[5] | no serious imprecision | None | 957 | 328 | - | MD 0.44 lower (0.72 to 0.16 lower) | ⊕⊕OO LOW | IMPORTANT |
| **Withdrawals (parallel group trials/first arm crossover trials)** | | | | | | | | | | | | |
| 13 | randomised trials | serious[1] | no serious inconsistency | serious indirectness[5] | serious[2] | None | 79/668 (11.8%) | 8% | RR 0.91 (0.67 to 1.24) | 7 fewer per 1000 (from 26 fewer to 19 more) | ⊕OOO VERY LOW | IMPORTANT |
| **Quality of life (Functional Outcome of Sleep Questionnaire) (Better indicated by higher values)** | | | | | | | | | | | | |
| 3 | randomised trials | serious[1] | no serious inconsistency | serious indirectness[5] | no serious imprecision | none | 193 | 159 | - | MD 0.12 higher (0.21 lower to 0.46 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Quality of life (Sleep Association Quality of Life Index) (Better indicated by higher values) (scale 1-7)** | | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | no serious inconsistency | serious indirectness[5] | no serious imprecision | None | 67 | 30 | - | MD 0.14 lower (0.54 lower to 0.27 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Quality of life (SF-36 questionnaire) - Physical functioning (Better indicated by higher values)** | | | | | | | | | | | | |
| 3 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | None | 30 | 30 | - | MD 0.76 higher (3.5 lower to 5.01 higher) | ⊕⊕OO LOW | CRITICAL |
| **Quality of life (SF-36 questionnaire) - Role physical (Better indicated by higher values)** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | None | 30 | 30 | - | MD 3.73 lower (13.46 lower to 6.01 higher) | ⊕⊕OO LOW | CRITICAL |
| **Quality of life (SF-36 questionnaire) - Bodily pain (Better indicated by higher values)** | | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | None | 30 | 30 | - | MD 4.21 higher (4.23 lower to 12.64 higher) | ⊕⊕OO LOW | CRITICAL |
| **Quality of life (SF-36 questionnaire) - General health (Better indicated by higher values)** | | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | None | 30 | 30 | - | MD 2.49 higher (4.99 lower to 9.97 higher) | ⊕⊕OO LOW | CRITICAL |
| **Quality of life (SF-36 questionnaire) - Vitality (Better indicated by higher values)** | | | | | | | | | | | | |
| 6 | randomised trials | serious[1] | no serious inconsistency | serious indirectness[5] | serious[2] | None | 149 | 149 | - | MD 1.32 higher (1.25 lower to 3.88 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Quality of life (SF-36 questionnaire) - Social functioning (Better indicated by higher values)** | | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | None | 30 | 30 | - | MD 3.31 higher (4.29 lower to 10.92 higher) | ⊕⊕OO LOW | CRITICAL |
| **Quality of life (SF-36 questionnaire) - Role emotional (Better indicated by higher values)** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | None | 30 | 30 | - | MD 0.7 higher (4.19 lower to 5.59 higher) | ⊕⊕OO LOW | CRITICAL |
| **Quality of life (SF-36 questionnaire) - Mental health (Better indicated by higher values)** | | | | | | | | | | | | |
| 3 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | None | 30 | 30 | - | MD 0.2 higher (1.88 lower to 2.27 higher) | ⊕⊕OO LOW | CRITICAL |
| **Apnoea Hypopnoea Index (events/hr) (Better indicated by lower values)** | | | | | | | | | | | | |
| 26 | randomised trials | serious[1] | no serious inconsistency | serious indirectness[5] | no serious imprecision | None | 886 | 370 | - | MD 0.48 higher (0.16 to 0.8 higher) | ⊕⊕OO LOW | IMPORTANT |
| **Arousals (events/hr) (Better indicated by lower values)** | | | | | | | | | | | | |
| 4 | randomised trials | serious[1] | no serious inconsistency | serious indirectness[5] | no serious imprecision | None | 99 | 37 | - | MD 0.66 lower (2.9 lower to 1.58 higher) | ⊕⊕OO LOW | IMPORTANT |
| **Pressure of CPAP treatment (cm H2O) (Better indicated by lower values)** | | | | | | | | | | | | |
| 24 | randomised trials | serious[1] | very serious[4] | serious indirectness[5] | no serious imprecision | None | 883 | 288 | - | MD 1.49 lower (2.12 to 0.85 lower) | ⊕OOO VERY LOW | IMPORTANT |
| **Systolic blood pressure (Better indicated by lower values)** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | None | 176 | 177 | - | MD 1.87 higher (1.08 lower to 4.82 higher) | ⊕⊕OO LOW | IMPORTANT |
| **Diastolic blood pressure (Better indicated by lower values)** | | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | very serious[4] | no serious indirectness | serious[2] | None | 176 | 177 | - | MD 4.01 higher (1.46 lower to 9.49 higher) | ⊕OOO VERY LOW | IMPORTANT |
| **24 hour mean BP (Better indicated by lower values)** | | | | | | | | | | | | |
| 2 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | None | 274 | 256 | - | MD 0.59 higher (1.05 lower to 2.22 higher) | ⊕⊕⊕⊕ HIGH | IMPORTANT |
| **24 hour systolic BP (Better indicated by lower values)** | | | | | | | | | | | | |
| 2 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | None | 274 | 256 | - | MD 0.15 lower (2.21 lower to 1.91 higher) | ⊕⊕⊕⊕ HIGH | IMPORTANT |
| **24 hour diastolic BP (Better indicated by lower values)** | | | | | | | | | | | | |
| 2 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | None | 274 | 256 | - | MD 0.9 higher (0.65 lower to 2.44 higher) | ⊕⊕⊕⊕ HIGH | IMPORTANT |
| **Tolerability outcomes - Intolerable treatment pressure** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[2] | None | 42/91 (46.2%) | 51.3% | RR 0.9 (0.66 to 1.23) | 51 fewer per 1000 (from 174 fewer to 118 more) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Tolerability outcomes - Mask Leak** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[2] | None | 34/91 (37.4%) | 33.8% | RR 1.11 (0.74 to 1.66) | 37 more per 1000 (from 88 fewer to 223 more) | ⊕⊕OO LOW | IMPORTANT |
| **Tolerability outcomes - Dry mouth** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[2] | None | 42/91 (46.2%) | 56.3% | RR 0.82 (0.61 to 1.1) | 101 fewer per 1000 (from 220 fewer to 56 more) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Tolerability outcomes - Stuffy nose** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[2] | None | 28/91 (30.8%) | 31.3% | RR 0.98 (0.63 to 1.54) | 6 fewer per 1000 (from 116 fewer to 169 more) | ⊕⊕OO LOW | IMPORTANT |
| **Patient preference (auto-CPAP/not auto-CPAP)** | | | | | | | | | | | | |
| 14 | randomised trials | serious[1] | very serious[4] | serious indirectness[5] | serious[2] | None | 255/541 (47.1%) | 47.5% | RR 0.99 (0.64 to 1.56) | 5 fewer per 1000 (from 171 fewer to 266 more) | ⊕OOO VERY LOW | IMPORTANT |
| **Mortality** | | | | | | | | | | | | |
| Outcome not reported | | | | | | | | | | | | |

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by one increment if the confidence interval crossed one MID and downgraded by two increments if the confidence interval crossed both MIDs . Established MIDs for SF-36 physical/mental- 2/3; ESS- 2.5; EQ5D- 0.03; FOSQ- 2; GRADE default MID(0.5XSD) used for all other continuous outcomes.
[3] Imprecision could not be assessed as control group SD not available
[4] Downgraded by 1 or 2 increments for heterogeneity, . Random effect analysis used.

[5]Downgraded by 1 or 2 increments because: The majority of the evidence included an indirect population (downgrade by one increment) or a very indirect population (downgrade by two increments). The population was deemed to be indirect when the outcome included evidence from studies with different severity OSAHS populations or when the study did not report the AHI of the population included

## Table 23: Clinical evidence profile: Non-invasive ventilation (NIV) versus fixed level CPAP for improving usage of continuous positive airway pressure machines in adults with OSAHS- severe OSAHS

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Bi-level PAP versus fixed CPAP | Control | Relative (95% CI) | Absolute | | |
| **Machine usage (hours/night) (Better indicated by lower values)** | | | | | | | | | | | | |
| 4 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | None | 137 | 131 | - | MD 0.14 higher (0.17 lower to 0.45 higher) | ⊕⊕OO LOW | IMPORTANT |
| **Symptoms (Epworth Sleepiness Scale) (Better indicated by lower values)** | | | | | | | | | | | | |
| 4 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | None | 121 | 105 | - | MD 0.49 lower (1.46 lower to 0.48 higher) | ⊕⊕OO LOW | IMPORTANT |
| **Withdrawals (parallel group trials/first arm cross-over trials)** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | None | 12/117 (10.3%) | 13.8% | RR 0.61 (0.33 to 1.15) | 54 fewer per 1000 (from 92 fewer to 21 more) | ⊕OOO VERY LOW | IMPORTANT |
| **Quality of life (Functional Outcome of Sleep Questionnaire) (Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 71 | 80 | - | MD 0.8 lower (6.08 lower to 4.48 higher) | ⊕⊕OO LOW | CRITICAL |
| **Quality of life (Sleep Association Quality of Life Index) (Better indicated by higher values) scale 1-7** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | None | 28 | - | - | MD 0.4 higher (0.34 lower to 1.14 higher) | ⊕⊕⊕O MODERATE | CRITICAL |
| **Quality of life (SF-36 questionnaire) - Physical health (Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | None | 71 | 80 | - | MD 0.6 higher (2.21 lower to 3.41 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Quality of life (SF-36 questionnaire) - Mental health (Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | None | 71 | 80 | - | MD 2.9 lower (7.09 lower to 1.29 higher) | ⊕⊕OO LOW | CRITICAL |
| **Apnoea Hypopnoea Index (events/hr) (Better indicated by lower values)** | | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | None | 99 | 80 | - | MD 1.36 higher (6.92 lower to 9.63 higher) | ⊕OOO VERY LOW | IMPORTANT |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Patient preference - BiPAP/no preference or CPAP** | | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | Serious[3] | no serious indirectness | very serious[2] | None | 21/44 (47.7%) | 54.5% | RR 0.88 (0.47 to 1.65) | 65 fewer per 1000 (from 289 fewer to 354 more) | ⊕OOO VERY LOW | IMPORTANT |
| **Tolerability outcomes - Dry mouth** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | None | 3/71 (4.2%) | 7.5% | RR 0.56 (0.15 to 2.17) | 33 fewer per 1000 (from 64 fewer to 88 more) | ⊕OOO VERY LOW | IMPORTANT |
| **Tolerability outcomes - Mask intolerance** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | None | 8/71 (11.3%) | 10% | RR 1.13 (0.45 to 2.85) | 13 more per 1000 (from 55 fewer to 185 more) | ⊕OOO VERY LOW | IMPORTANT |
| **Treatment comfort score (Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious imprecision[2] | None | 28 | - | - | MD 9 higher (3.54 lower to 21.54 higher) | ⊕⊕⊕⊕ LOW | IMPORTANT |
| **Mortality** | | | | | | | | | | | | |
| Outcome not reported | | | | | | | | | | | | |

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by one increment if the confidence interval crossed one MID and downgraded by two increments if the confidence interval crossed both MIDs . Established MIDs for SF-36 physical/mental- 2/3; ESS- 2.5; EQ5D- 0.03; FOSQ- 2;. GRADE default MID (0.5XSD) used for all other continuous outcomes..

[3] Downgraded by 1 or 2 increments for heterogeneity, . Random effect analysis used.

**Table 24: Clinical evidence profile: Heated humidification + fixed level CPAP versus fixed level CPAP alone for improving usage of continuous positive airway pressure machines in adults with OSAHS- severe OSAHS**

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Heated humidification + fixed pressure CPAP versus fixed pressure CPAP alone | Control | Relative (95% CI) | Absolute | | |
| **Machine usage (hours/night) (Better indicated by lower values)** | | | | | | | | | | | | |
| 6 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | None | 187 | 90 | - | MD 0.37 higher (0.1 to 0.64 higher) | ⊕⊕OO LOW | IMPORTANT |
| **Symptoms (Epworth Sleepiness Scale) (Better indicated by lower values)** | | | | | | | | | | | | |
| 4 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | None | 121 | 63 | - | MD 0.34 lower (0.93 lower to 0.26 higher) | ⊕⊕OO LOW | IMPORTANT |
| **Withdrawals (parallel group trials/first arm cross-over trials)** | | | | | | | | | | | | |
| 3 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | None | 16/102 (15.7%) | 12.8% | RR 1 (0.56 to 1.79) | 0 fewer per 1000 (from 56 fewer to 101 more) | ⊕OOO VERY LOW | IMPORTANT |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Apnoea Hypopnoea Index (events/hr) (Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | None | 44 | - | - | MD 0.3 higher (0.95 lower to 1.55 higher) | ⊕OOO VERY LOW | IMPORTANT |
| **Quality of life (SF-36 questionnaire) (Better indicated by higher values)** | | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | None | 61 | 63 | - | MD 0.11 higher (6.97 lower to 7.18 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Nasal symptoms (parallel group trials) - Runny nose** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[2] | None | 4/39 (10.3%) | 26.5% | RR 0.39 (0.13 to 1.15) | 162 fewer per 1000 (from 231 fewer to 40 more) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Nasal symptoms (parallel group trials) - Congested or blocked nose** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | None | 9/39 (23.1%) | 61.8% | RR 0.37 (0.2 to 0.7) | 389 fewer per 1000 (from 185 fewer to 494 fewer) | ⊕⊕⊕⊕ HIGH | IMPORTANT |
| **Nasal symptoms (parallel group trials) - Dry nose (Better indicated by lower values)** | | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | None | 47 | 56 | - | SMD 0.38 lower (0.78 lower to 0.01 higher) | ⊕⊕⊕O MODERATE | IMPORTANT |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Nasal symptoms (parallel group trials) - Runny nose (Better indicated by lower values)** | | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | None | 47 | 56 | - | SMD 0.3 lower (0.69 lower to 0.09 higher) | ⊕⊕⊕O MODERATE | |
| **Nasal symptoms (parallel group trials) - Blocked nose (Better indicated by lower values)** | | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | None | 47 | 56 | - | SMD 0.38 lower (0.78 lower to 0.01 higher) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Nasal symptoms (parallel group trials) - Bleeding nose (Better indicated by lower values)** | | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | None | 47 | 56 | - | SMD 0.45 lower (0.99 lower to 0.1 higher) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Preference** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | None | 19/37 (51.4%) | 48.7% | RR 1.06 (0.67 to 1.67) | 29 more per 1000 (from 161 fewer to 326 more) | ⊕OOO VERY LOW | IMPORTANT |
| **Mortality** | | | | | | | | | | | | |
| Outcome not reported | | | | | | | | | | | | |

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by one increment if the confidence interval crossed one MID and downgraded by two increments if the confidence interval crossed both MIDs Established MIDs for SF-36 physical/mental- 2/3; ESS- 2.5; EQ5D- 0.03; FOSQ- 2;. GRADE default MID (0.5XSD) used for all other continuous outcomes.

# OHS

**Table 25: Clinical evidence profile: Variable non-invasive ventilation (NIV) vs fixed non-invasive ventilation (NIV)**

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Variable NIV | Fixed NIV | Relative (95% CI) | Absolute | | |
| **Change in disease specific QoL (follow-up 3 months; measured with: SRI-SS (parallel trial); range of scores: 0-100; Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[1] | None | 23 | 23 | - | MD 4 higher (3.23 lower to 11.23 higher) | ⊕⊕⊕O MODERATE | CRITICAL |
| **Disease specific QoL (follow-up 1.5 months; measured with: SRI-SS (crossover trial); range of scores: 0-100; Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[2] | no serious inconsistency | no serious indirectness | very serious[1] | none | 10 | 10 | - | MD 3 lower (16.18 lower to 10.18 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Change in ESS (follow-up 3 months; range of scores: 0-24; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[1] | none | 23 | 23 | - | MD 1 higher (2.47 lower to 4.47 higher) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **PaCO2 (follow-up 1.5-3 months; measured with: kPa; Better indicated by lower values)** | | | | | | | | | | | | |
| 2 | randomised trials | no serious risk of bias | serious[3] | no serious indirectness | very serious[1] | none | 33 | 33 | - | MD 0.14 lower (0.82 lower to 0.55 higher) | ⊕OOO VERY LOW | IMPORTANT |
| **Adherence (hours per night) (follow-up 3 months; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[1] | none | 23 | 23 | - | MD 0.9 lower (2.44 lower to 0.64 higher) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **AHI (follow-up 1.5 months; Better indicated by lower values)** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomised trials | serious[2] | no serious inconsistency | no serious indirectness | serious[4] | none | 10 | 10 | - | not pooled | ⊕⊕OO LOW | IMPORTANT |
| **ODI (follow-up 1.5 months; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[2] | no serious inconsistency | no serious indirectness | very serious[1] | none | 10 | 10 | - | MD 6 higher (8.05 lower to 20.05 higher) | ⊕OOO VERY LOW | IMPORTANT |
| **Pao2 (Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[1] | none | 23 | 23 | - | MD 0.2 higher (0.89 lower to 0.49 higher) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Mortality** | | | | | | | | | | | | |
| Outcome not reported | | | | | | | | | | | | |

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. Established MIDs for SF-36 physical/mental- 2/3; ESS- 2.5; EQ5D- 0.03; FOSQ- 2; GRADE default MID (0.5XSD) used for all other continuous outcomes.
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[3], Downgraded by 1 or 2 increments for heterogenity, unexplained by subgroup analysis. Random effect analysis used.
[4] The mean and SD in both arms was 0

## Table 26: Clinical evidence profile: non-invasive ventilation (NIV) vs lifestyle

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **NIV** | **Lifestyle** | **Relative (95% CI)** | **Absolute** | | |
| **Change in PaCO2 (follow-up 1-2 months; Better indicated by lower values)** | | | | | | | | | | | | |
| 3 | randomised trials | no serious risk of bias | no serious inconsistency | No serious indirectness | serious[1] | none | 129 | 133 | - | MD 2.93 lower (4.26 to 1.59 lower) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **PaCO2 at 3 years (without severe OSA) (Better indicated by lower values)** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[1] | none | 48 | 48 | - | MD 3.28 lower (5.63 to 0.93 lower) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Change in AHI (people with severe OSAHS) (follow-up 1-2 months; Better indicated by lower values)** | | | | | | | | | | | | |
| 2 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 89 | 87 | - | MD 48.41 lower (57.37 to 39.46 lower) | ⊕⊕⊕⊕ HIGH | IMPORTANT |
| **Change in AHI (people without severe OSAHS) (follow-up 2 months; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 40 | 46 | - | MD 11.10 lower (15.84 to 6.36 lower) | ⊕⊕⊕⊕ HIGH | IMPORTANT |
| **Change in ESS (follow-up 1-2 months; range of scores: 0-24; Better indicated by lower values)** | | | | | | | | | | | | |
| 3 | randomised trials | serious[2] | Serious inconsistency[3] | no serious indirectness | serious[1] | none | 129 | 133 | - | MD 2.48 lower (4.11 to 0.86 lower) | ⊕OOO VERY LOW | IMPORTANT |
| **ESS at 3 years (without severe OSA) (Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[2] | no serious inconsistency | no serious indirectness | serious[1] | none | 48 | 48 | - | MD 2.97 lower (5.57 to 0.37 lower) | ⊕⊕OO LOW | IMPORTANT |
| **Change in HbA1c (follow-up 1 months; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[1] | none | 18 | 17 | - | MD 0.16 higher (0.08 lower to 0.4 higher) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Change in SBP (follow-up 1-2 months; Better indicated by lower values)** | | | | | | | | | | | | |
| 2 | randomised trials | no serious risk of bias | no serious inconsistency | No serious indirectness | serious[1] | none | 58 | 63 | - | MD 1.57 higher (5.28 lower to 8.42 higher) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Systolic blood pressure at 3 years (without severe OSA) (Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[1] | none | 48 | 48 | - | MD 3.33 higher (4.19 lower to 10.85 higher) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Diastolic blood pressure at 3 years (without severe OSA) (Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[1] | none | 48 | 48 | - | MD 3.47 higher (1.81 lower to 8.75 higher) | ⊕⊕⊕O MODERATE | IMPORTANT |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Change in ODI (people with severe OSAHS) (follow-up 2 months; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 71 | 70 | - | MD 41.30 lower (50.56 to 32.04 lower) | ⊕⊕⊕⊕ HIGH | IMPORTANT |
| **Change in ODI (people without severe OSAHS) (follow-up 2 months; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 40 | 46 | - | MD 18.60 lower (25.71 to 11.49 lower) | ⊕⊕⊕⊕ HIGH | IMPORTANT |
| **Change in SF-36 physical summary (follow-up 2 months; range of scores: 0-100; Better indicated by higher values)** | | | | | | | | | | | | |
| 2 | randomised trials | serious[2] | no serious inconsistency | No serious indirectness | serious[1] | none | 111 | 116 | - | MD 1.78 higher (0.39 lower to 3.94 higher) | ⊕⊕OO LOW | CRITICAL |
| **SF-36 physical at 3 years (without severe OSA) (Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[2] | no serious inconsistency | no serious indirectness | very serious[2] | none | 48 | 48 | - | MD 2.35 higher (3.35 lower to 8.05 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Change in SF-36 mental summary (follow-up 2 months; range of scores: 0-100; Better indicated by higher values)** | | | | | | | | | | | | |
| 2 | randomised trials | serious[2] | Serious inconsistency[3] | serious indirectness[4] | serious[1] | none | 111 | 116 | - | MD 2.51 higher (1.88 lower to 6.89 higher | ⊕OOO VERY LOW | CRITICAL |
| **SF 36 mental at 3 years (without severe OSA) (Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[2] | no serious inconsistency | no serious indirectness | very serious[1] | none | 48 | 48 | - | MD 1.47 lower (8.99 lower to 6.05 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Change in FOSQ (follow-up 2 months; range of scores: 5-30; Better indicated by higher values)** | | | | | | | | | | | | |
| 2 | randomised trials | serious[2] | no serious inconsistency | no serious indirectness | serious[1] | none | 111 | 116 | - | MD 6.35 higher (1.87 to 10.84 higher) | ⊕⊕OO LOW | CRITICAL |
| **FOSQ at 3 years (without severe OSA) (Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[2] | no serious inconsistency | no serious indirectness | very serious[1] | none | 48 | 48 | - | MD 5.05 higher (5.96 lower to 16.06 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Pa02 (Better indicated by lower values)** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[1] | none | 19 | 20 | - | MD 2.25 higher (5.89 lower to 10.39 higher) | ⊕⊕OO LOW | IMPORTANT |
| **Mortality at 3 years (without severe OSA)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[1] | none | 9/48 (18.8%) | 18.8% | RR 1 (0.43 to 2.3) | 0 fewer per 1000 (from 107 fewer to 244 more) | ⊕⊕OO LOW | CRITICAL |
| **Cardiovascular events at 3 years (without severe OSA)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[1] | none | 10/48 (20.8%) | 22.9% | RR 0.91 (0.43 to 1.94) | 21 fewer per 1000 (from 131 fewer to 215 more) | ⊕⊕OO LOW | IMPORTANT |

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. Established MIDs for SF-36 physical/mental- 2/3; ESS- 2.5; EQ5D- 0.03; FOSQ- 2; AHI- different severity groups, likely true MCID will vary, qualitatively considered in decision making throughout. GRADE default MID (0.5XSD) used for all other continuous outcomes.

[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

[3]Downgraded by 1 or 2 increments for heterogeneity, unexplained by sub-group analysis.Random effects analysis used.

## Table 27: Clinical evidence profile: Non-invasive ventilation (NIV) vs CPAP

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **NIV** | **CPAP** | **Relative (95% CI)** | **Absolute** | | |
| **Change in SF-36 physical (follow-up 2-3 months to 3 years; range of scores: 0-100; Better indicated by higher values)** | | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | None | 103 | 110 | - | MD 1.49 lower (4.88 lower to 1.9 higher) | ⊕⊕OO LOW | CRITICAL |
| **Change in SF-36 mental (follow-up 2-3 months to 3 years; range of scores: 0-100; Better indicated by higher values)** | | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | None | 103 | 110 | - | MD 0.21 higher (3.11 lower to 2.38 higher) | ⊕⊕OO LOW | CRITICAL |
| **SRI (follow-up 3 months; range of scores: 0-100; Better indicated by higher values)** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[2] | None | 27 | 30 | - | MD 4.08 lower (12.16 lower to 4 higher) | ⊕⊕⊕O MODERATE | CRITICAL |
| **Change in FOSQ (follow-up 3 years; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | None | 76 | 80 | - | MD 5.4 higher (0.3 lower to 11.1 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Hours/night (follow-up 2-3 months; Better indicated by lower values)** | | | | | | | | | | | | |
| 3 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | None | 118 | 129 | - | MD 0.1 higher (0.47 lower to 0.67 higher) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Change in AHI (follow-up 2 months; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[2] | None | 71 | 80 | - | MD 3 higher (6.74 lower to 12.74 higher) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Change in ODI (follow-up 2 months; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[2] | None | 71 | 80 | - | MD 12 higher (1.95 to 22.05 higher) | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Change in PaCO2 (follow-up 2-3 months to 3 years; Better indicated by lower values)** | | | | | | | | | | | | |
| 2 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision[2] | None | 95 | 99 | - | MD 0.62 lower (1.66 lower to 0.42 higher) | ⊕⊕⊕⊕ HIGH | IMPORTANT |
| **ESS (follow-up 2-3 months to 3 years; range of scores: 0-24; Better indicated by higher values)** | | | | | | | | | | | | |
| 3 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | None | 125 | 128 | - | MD 0.8 lower (3.34 lower to 1.75 higher) | ⊕⊕OO LOW | IMPORTANT |
| **Systolic BP (follow-up 3 months; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[2] | None | 27 | 30 | - | MD 0 higher (8.74 lower to 8.74 higher) | ⊕⊕OO LOW | IMPORTANT |
| **Mortality** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[2] | None | 11/97 (11.3%) | 15% | RR 0.76 (0.37 to 1.55) | 36 fewer per 1000 (from 95 fewer to 82 more) | ⊕⊕OO LOW | CRITICAL |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Cardiovascular events** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[2] | None | 17/97 (17.5%) | 15% | RR 1.17 (0.63 to 2.19) | 25 more per 1000 (from 56 fewer to 179 more) | ⊕⊕OO LOW | IMPORTANT |
| **hospitalisation per patient per year (Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | None | 97 | 107 | - | MD 0.19 lower (1.13 lower to 0.75 higher) | ⊕⊕⊕⊕ HIGH | IMPORTANT |

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. Established MIDs for SF-36 physical/mental- 2/3; ESS- 2.5; EQ5D- 0.03; FOSQ- 2. GRADE default MID(0.5XSD) used for all other continuous outcomes.

## Table 28: Clinical evidence profile: CPAP (fixed) vs lifestyle

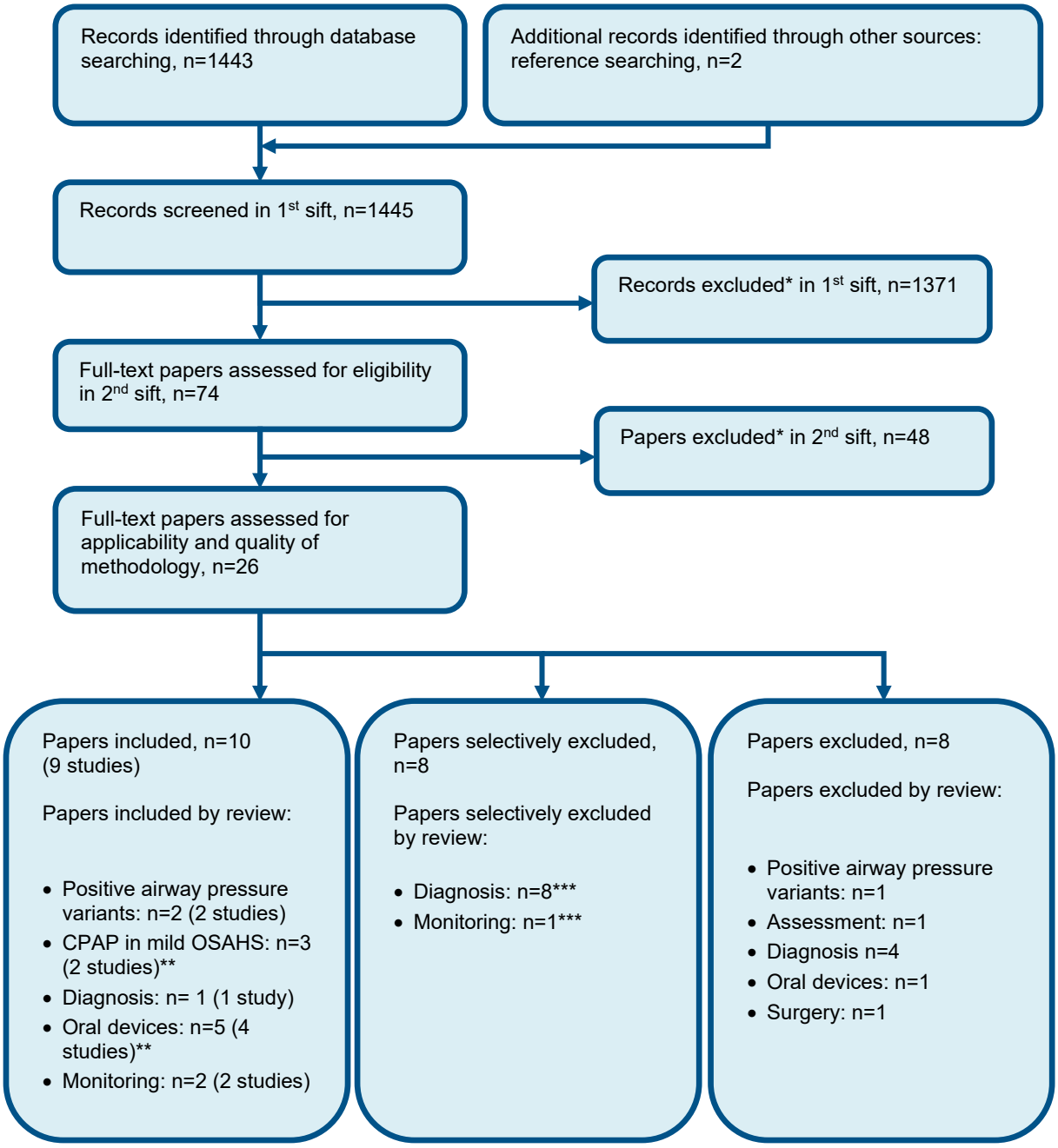
| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **CPAP (fixed)** | **Lifestyle** | **Relative (95% CI)** | **Absolute** | | |
| **Change in SF-36 physical (follow-up 2 months; range of scores: 0-100; Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 80 | 70 | - | MD 1 higher (1.52 lower to 3.52 higher) | ⊕⊕OO LOW | CRITICAL |
| **Change in SF-36 mental (follow-up 2 months; range of scores: 0-100; Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 80 | 70 | - | MD 3.4 higher (0.06 to 6.74 higher) | ⊕⊕OO LOW | CRITICAL |
| **Change in FOSQ (follow-up 2 months; range of scores: 5-20; Better indicated by higher values)** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 80 | 70 | - | MD 6.8 higher (1.67 to 11.93 higher) | ⊕⊕OO LOW | CRITICAL |
| **Change in ESS (follow-up 2 months; range of scores: 0-24; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 80 | 70 | - | MD 3.3 lower (4.76 to 1.84 lower) | ⊕⊕OO LOW | IMPORTANT |
| **Change in AHI (follow-up 2 months; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 80 | 70 | - | MD 53.2 lower (62.97 to 43.43 lower) | ⊕⊕⊕⊕ HIGH | IMPORTANT |
| **Change in ODI (follow-up 2 months; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 80 | 70 | - | MD 53.3 lower (62.75 to 43.85 lower) | ⊕⊕⊕⊕ HIGH | IMPORTANT |
| **Change in PaCO2 (follow-up 2 months; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 80 | 70 | - | MD 0.5 lower (2.52 lower to 1.52 higher) | ⊕⊕⊕⊕ HIGH | IMPORTANT |
| **Mortality** | | | | | | | | | | | | |
| Outcome not reported | | | | | | | | | | | | |

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. Established MIDs for SF-36 physical/mental- 2/3; ESS- 2.5; EQ5D- 0.03; FOSQ- 2.GRADE default MID(0.5XSD) used for all other continuous outcomes.

# Appendix G: Health economic evidence selection

**Figure 84: Flow chart of health economic study selection for the guideline**




* Non-relevant population, intervention, comparison, design or setting; non-English language
** Two studies (in three papers) were included for two different questions
*** One study was considered for two different questions

# Appendix H: Health economic evidence tables

| | Bloch 2018[23] | | | |
|---|---|---|---|---|
| **Study details** | **Population & interventions** | **Costs** | **Health outcomes** | **Cost effectiveness** |
| **Economic analysis:** Cost-consequences analysis<br><br>**Study design:** Multicentre **r**andomised controlled trial<br><br>**Perspective:** Switzerland third party payer<br>**Follow-up** 2 years<br>**Discounting:** Costs: ; NR Outcomes: NR | **Population:**<br>208 adults with OSAHS and excessive sleepiness. Patients then used autoCPAP (pressure 5–15 mbar) at home during a 2–4-week adaptation period. Participants using autoCPAP during adaptation for ≥2 hours/night and wishing to continue CPAP therapy were randomised.<br><br>Median age: 55.5<br>Male:87%<br><br>**Intervention 1:**<br>Fixed-level CPAP with pressure set at the 90th percentile applied by the autoCPAP device during adaptation. Philips Respironics RemStar<br>**Intervention 2:**<br>Automatic CPAP (pressure 5–15 mbar). ResMed AutoSet device | **OSAHS costs over 2 years (median per patient):**<br>Intervention 1: 5070<br>Intervention 2: 5250<br>Incremental (2−1): 180<br>(95% CI: NR; p=NR)<br><br>**Total costs over 2 years (median per patient):**<br>Intervention 1: 11440<br>Intervention 2: 11380<br>Incremental (2−1): -60<br>(95% CI: NR; p=NR)<br><br>**Currency & cost year:**<br>Swiss francs, year NR so assumed to be 2017 (presented here as 2017 UK pounds[(b)])]<br>**Cost components incorporated:**<br>Hospital and physician bills. | **SF-6D change, Baseline to 2 years (mean per patient):**<br>Intervention 1:+0.03<br>Intervention 2:+0.00<br>Incremental (2−1):-0.03<br>(95% CI: -0.06, 0.00; p=0.069)<br>**QALYs over 2 years** calculated by NGC assuming linear change in SF-6D over 2 years:<br>Incremental (2−1):-0.03<br><br>**ESS change, Baseline to 2 years (mean per patient):**<br>Intervention 1:-6.7<br>Intervention 2: -7.3<br>Incremental (2−1): -0.6<br>(95% CI: -1.5, 0.4; p=0.161)<br>**Unscheduled OSAHS visits over 2 years (mean per patient):**<br>Intervention 1: 0.18<br>Intervention 2: 0<br>Incremental (2−1): -0.18<br>(95% CI: NR; p=NR) | Using OSAHS costs and QALYs calculated by NGC:<br>Fixed-level pressure dominates<br><br>Using all health care costs and QALYs calculated by NGC:<br>Fixed-level cost £2000 per additional QALY gained.<br><br>**Analysis of uncertainty:**<br>Outcomes were reported as intention to treat in addition to per protocol analyses (which were very similar) |
| **Data sources** | | | | |

| | |
|---|---|
| **Health outcomes:** Randomised controlled trial reported in the same paper. **Quality-of-life weights:** SF-6D **Cost sources:** Healthcare costs were obtained from a third party perspective by collecting health insurance, physician's office and hospital bills. | |
| **Comments** | |
| **Source of funding:** Swiss National Science Foundation, the Lung Leagues of Zurich, St. Gallen and Thurgau and by unconditional grants from the Respironics Foundation and ResMed Switzerland. **Limitations:** QALYs not calculated and quality of life measured by SF-6D not EQ-5D. Switzerland cost perspective. Costs were medians not means. Based on a single trial not a systematic review. Not double-blinded. Funding from manufacturers. **Other:** | |
| **Overall applicability:**(c) Partially applicable | **Overall quality:**(d) Potentially serious limitations |

*Abbreviations: 95% CI= 95% confidence interval; CPAP=Continuous positive airway pressure; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; NR= not reported; pa= probabilistic analysis; QALYs= quality-adjusted life years; SF-6D=short form – 6 dimensions*
*(a) Converted using 2017 purchasing power parities[190]*
*(b) Directly applicable / Partially applicable / Not applicable*
*(c) Minor limitations / Potentially serious limitations / Very serious limitations*

| **Study** | **Masa 2020** [141] | | | |
|---|---|---|---|---|
| **Study details** | **Population & interventions** | **Costs** | **Health outcomes** | **Cost effectiveness** |
| **Economic analysis:** Cost-effectiveness analysis<br><br>**Study design:** Two parallel multicentre randomized controlled trials (16 clinical sites)<br><br>**Approach to analysis:** Within-trial CEA<br><br>**Perspective:** Spanish healthcare system<br><br>**Follow-up:** 3 years | **Population:** Stable ambulatory patients with OHS and concomitant severe OSA (AHI ≥30)<br><br>**CPAP trial population characteristics:**<br>Patient N: 107<br>Mean age: 60<br>Male: 50%<br><br>**NIV trial population characteristics:**<br>Patient N: 97<br>Mean age: 65<br>Male: 37% | **Total cost (including hospitalisation)/year:**<br>Intervention 1: £2787<br>Intervention 2: £1984<br>Incremental (2−1): Saves £830<br>(95% CI: 252, 1347; p=0.995)<br><br>**Currency & cost year:**<br>2018 Spanish Euros (presented here as 2019 UK pounds(a))<br>**Cost components incorporated:**<br>The cost of hospitalisation days plus other hospital | **Hospitalisation days/year:**<br>Intervention 1: 1.89<br>Intervention 2: 2.13<br>Incremental (2−1): 0.24<br>(95% CI:-1.94, 2.30; p=0.378)<br><br>**Probability of hospitalisation:**<br>Intervention 1: 35.1%<br>Intervention 2: 35.5%<br>Incremental (2−1): 0.4%<br>(95% CI: NR; p=0.945) | **Incremental cost per hospital day averted: 1 vs 2:** £3736<br><br>Treatment with CPAP led to sufficiently lower healthcare costs to overcome the cost of longer hospital stay compared with NIV.<br><br>**Analysis of uncertainty:**<br>The effect of a higher proportion of treatment dropouts in the CPAP group was explored in sensitivity analysis. |

| | | | | |
|---|---|---|---|---|
| **Discounting:**<br>Costs: NR<br>Outcomes: NR | **Intervention 1:**<br>Non-invasive ventilation set at a bilevel PAP with assured volume<br><br>**Intervention 2:**<br>Fixed pressure CPAP set based on a conventional CPAP titration study | resources, including: ICU days and ED visits; non-annual, baseline and annual clinic visits; NIV daytime adjustment and tests; medication for comorbid conditions; home care for PAP therapy | | |
| **Data sources** | | | | |
| **Health outcomes:** Masa 2015 and the current trial were the source for health outcomes values used in this study. **Quality-of-life weights:** SF-36 data was collected within the trial but was not reported by this study or used to inform this analysis. **Cost sources:** Hospital resource utilisation and costs were collected on 11 occasions over 3 years: after the first and second months, and every 3 months until completing 2 years, then every 6 months until completing 3 years of follow-up; additional details not reported. | | | | |
| **Comments** | | | | |
| **Source of funding:** Instituto de Salud Carlos III (Fondo de Investigaciones Sanitarias, Ministerio de Sanidad y Consumo) PI050402, Spanish Respiratory Foundation 2005 (FEPAR) and Air Liquide Spain. **Limitations:** Spanish healthcare system; QALYs and clinical outcomes not included; no discounting; Within RCT cost-effectiveness analysis so does not cover entire evidence base; details regarding resource and cost source not reported. **Other:** None. | | | | |
| **Overall applicability:** Partially applicable[(b)] **Overall quality:** Minor limitations[(c)] | | | | |

*Abbreviations: CEA= cost-effectiveness analysis; 95% CI= 95% confidence interval; NR= not reported; NS = not significant;*
*(a) Converted using 2018 purchasing power parities[190]*
*(b) Directly applicable / Partially applicable / Not applicable*
*(c) Minor limitations / Potentially serious limitations / Very serious limitations*

# Appendix I: Excluded studies

## I.1 Excluded clinical studies

**Table 29: Studies excluded from the clinical review- OSAHS**

| Study | Exclusion reason |
|---|---|
| Afshar 2020[1] | Systematic review. Screened for relevant references. |
| Al Zuheibi 2013[2] | Randomised trial comparing effects of APAP alone (autoadjusting CPAP), to APAP with C-Flex (expiratory pressure relief) and to APAP with A-Flex (pressure relief at end of inspiration and onset of expiration) on comfort, compliance, AHI and treatment pressures<br>- no fixed CPAP arm |
| Almasri 2007[3] | Study of different humidifying units plus CPAP |
| Aloia 2001[6] | CBT |
| Aloia 2004[5] | Review article |
| Aloia 2005[7] | CPAP or C-flex given in a sequential, non-randomised order |
| Aloia 2005a[4] | Not randomised |
| Anderson 2003[8] | Study assessing oral versus nasal interface of CPAP |
| Bachour 2004[9] | Study assessing chinstrap over a 2-night laboratory titration study |
| Ball 2011[12] | Randomised, double-blind cross-over trial comparing effects of auto-titrating BiPAP versus standard BiPAP on AHI and treatment pressure<br>- no fixed CPAP arm / study duration 2 days |
| Ballard 2007[13] | Inappropriate intervention - Bi-level PAP (multimodality) |
| Bakker 2010[11] | Inappropriate intervention -CPAP with expiratory pressure relief |
| Bardwell 2007[14] | Placebo-controlled trial |
| Bastos 2013[15] | Comparison of effects of high span versus low span autoadjusting CPAP on compliance, AHI and treatment pressure |

| Study | Exclusion reason |
|---|---|
| | - no fixed CPAP arm |
| Becker 1991[16] | Non randomised study of treatment failure in central sleep apnoea |
| Becker 1998[17] | Review article |
| Berry 2002[18] | Review article |
| Berthon-Jones 1996[19] | Non randomised study of APAP for OSA treatment |
| Bielicke 2008[20] | Comparison of effects of auto-titrating CPAP (APAP) versus auto-titrating CPAP with expiratory pressure relief (A-Flex) on AHI<br>- no fixed CPAP arm, study duration 2 nights |
| Blau 2009[21] | Comparison of AutoCPAP with A-Flex (AutoCPAP with pressure relief during expiration) |
| Blau 2012[22] | Inappropriate intervention - Bi-level PAP (multimodality) |
| Boudewyns 1999[26] | Non randomised study of CPAP treatment |
| Boyer 2019[27] | Device no longer used- the ICON+ auto CPAP machine was discontinued on 31/8/18 (information from eu-pap.co.uk) |
| Bradshaw 2004[28] | Effect of nose drops |
| Brammer 1999[29] | Not randomised |
| Buyse 2003[30, 31] | Different algorithms of 2 auto-CPAP compared to each other. |
| Canisius 2007[32] | Inadequate duration |
| Chan 2004[35] | Study assessing interface chamber of CPAP |
| Chervin 1997[37] | Educational/psychosocial intervention |
| Chihara 2012[38, 39] | Randomised trial comparing effects of APAP (autoadjusting PAP), APAP with C-Flex (expiratory pressure relief) or APAP with A-Flex (pressure relief at end inspiration and start of exhalation) on compliance, ESS, QoL<br>- no fixed CPAP arm |
| Colrain 2007[41] | Inadequate duration |

| Study | Exclusion reason |
|---|---|
| Constantinidis 2000[42] | Non randomised study of nasal mucosal tissue changes with CPAP treatment |
| Coughlin 2004[46] | CPAP versus sub-therapeutic pressure of CPAP |
| Cross 2005[48] | Study assessing efficacy of CPAP |
| Cumin 2011[49] | Randomised, cross-over trial comparing effect of fixed CPAP versus CPAP SensAwake on overnight PSG parameters<br>- overnight study only |
| Damjanovic 2005[52] | Educational/psychosocial support |
| Delwiche 2003[53] | Comparison between different auto-CPAP devices |
| Dolan 2008[54] | Inappropriate intervention -CPAP with expiratory pressure relief |
| Dungan 2010[55] | Comparison of effects of conventional autoadjusting CPAP versus new autoCPAP device (SensAwake - pressure reduction during awakenings) on overnight PSG parameters<br>- overnight study only / no fixed CPAP arm |
| Duntley 2005[56] | One-night study |
| Duoung 2005[57] | One-night study |
| Engleman 1993[58] | Non randomised study of objective compliance measure of CPAP use |
| Engleman 1994[59] | Non-randomised study of CPAP compliance |
| Epstein 2000[60] | Educational/psychosocial intervention |
| Feenstra 2005[61] | Assessment of nose drops on CPAP machine usage |
| Ficker 1997[64] | Laboratory-based study |
| Ficker 1998[65] | Laboratory-based study |
| Ficker 2000[63] | Laboratory-based study |

| Study | Exclusion reason |
|---|---|
| Fletcher 1991[67] | Educational/psychosocial intervention |
| Fleury 1996[68] | Non-randomised study of CPAP compliance |
| Gagnadoux 1999[69] | Non-randomised study on effectiveness of Autoset to determine treatment pressure |
| Galetke 2006[72] | Manual versus auto-titrating study |
| Galetke 2008a[73] | Comparison of CPAP with standard heated humidification versus CPAP with humidification via a heated breathing tube<br>- no fixed CPAP arm |
| Galetke 2016[71] | Control group received humidification in addition to fixed pressure CPAP. |
| Gfüellner 2007[75] | Inappropriate intervention -CPAP with expiratory pressure relief |
| Goncalves 2006[76] | Inadequate duration |
| Greenfield 2003[78] | Placebo control |
| Grote 2000[79] | Non-randomised study on CPAP compliance |
| Gupta 2011[82] | Prospective, randomised, controlled trial comparing effects of standard care versus period of CPAP mask acclimatization period prior to commencing CPAP on CPAP adherence at 4 weeks<br>- not a comparative trial of pressure modification devices in OSA |
| Herold 2007[85] | Participants randomised to receive auto-CPAP as a titration strategy |
| Hertegonne 2003[87] | Laboratory-based titration study |
| Hertegonne 2006[86] | Split-night titration study |
| Horvath 2008[88] | Different levels of Bi-PAP compared |
| Hosselet 1999[89] | Review article |
| Hoster 1996[90] | Laboratory-based study |
| Hostler 2014[91] | Comparison of effects of auto-titrating CPAP (APAP) versus auto-titrating CPAP with expiratory pressure relief (A-Flex) on compliance<br>- no fixed CPAP arm |
| Hoy 1999[96] | Educational/psychosocial intervention |
| Huang 2001[97] | Non-randomised study |

| Study | Exclusion reason |
|---|---|
| Hui 2000[99] | Educational/psychosocial intervention |
| Hui 2001[100] | Non-randomised study of CPAP effectiveness |
| Hui 2006[101] | Different pressure levels of CPAP compared (therapeutic and subtherapeutic) |
| Hukins 2005[103] | Different titration strategies compared |
| Husain 2003[104] | No fixed CPAP control group |
| Juhàsz 2001[109] | Two-night in laboratory titration study |
| Khanna 2003[111] | Comparison outside the focus of the review: oral versus nasal interface |
| Khayat 2007[112] | Participants with significant cardiac comorbidity |
| Kotzian 2019[114] | Inappropriate intervention- telemonitoring |
| Krieger 1992[115] | Non-randomised study on CPAP compliance following simplified diagnostic procedure for OSA |
| Krieger 1999[116] | Review article |
| Kushida 2011[117] | Inappropriate intervention - Autoflex (multimodality) |
| Lai 2017[118] | Study assessed Long-term efficacy of an education programme<br>in improving adherence with continuous positive<br>airway pressure treatment for obstructive sleep apnoea. Study included in adherence review. |
| Lebret 2019[119] | Part of Pepin 2016 #980. Check pepin paper for inclusion. Emailed Emma Dennett for excluded studies list. |
| Leidag 2008[120] | Inappropriate intervention -CPAP with expiratory pressure relief |
| Likar 1997[121] | Non-randomised study of CPAP compliance |
| Liu 2007[122] | Inadequate duration |
| Loberes 2004[123] | Study assessing the effects of daytime CPAP titration |
| Lopez-Martin 2005[124] | Not assessment of pressure modification |
| Loube 2004[125] | Inappropriate intervention -CPAP with expiratory pressure relief |
| Loube 2003[126, 127] | Laboratory based titration study |
| Lugo 2019[128] | Inappropriate comparison. hospital routine (HR) and out-of-hospital Virtual Sleep Unit (VSU). |

| Study | Exclusion reason |
|---|---|
| Mador 2005[129, 130] | Randomisation between immediate provision of humidification and delayed provision of humidification |
| Marshall 2008[134] | Inappropriate intervention -CPAP with expiratory pressure relief |
| Mansfield 2003[131] | Participants randomised to CPAP or inactive control |
| Marshall 2003[133] | Not assessment of pressure modification |
| Masa 2004[140, 144] | Different titration strategies compared |
| Massie 1999[146] | Head to head comparison of active agents (heated versus cold humidification). No control group receiving only fixed pressure CPAP |
| McArdle 2010[148] | Comparison of effects of manual titration versus laboratory APAP titration versus home APAP titration on CPAP compliance<br>- patients switched to fixed CPAP after titration study |
| McNicholas 1997[149] | Editorial |
| Meurice 2009[155] | Inappropriate intervention - Autoflex (multimodality) |
| Meurice 1994[151] | Non-randomised study of CPAP compliance |
| Meurice 1998[154] | Randomised comparison of 2 types of auto-CPAP |
| Meurice 2007a [152] | Study of educational interventions |
| Montserrat 2006[158] | Inadequate duration |
| Modrak 2007[156] | Inappropriate intervention -CPAP with expiratory pressure relief |
| Morley 2001[159] | Journal correspondence |
| Mortimore 1998[160] | Randomised trial comparing nose and face mask CPAP therapy |
| Mulgrew 2005[163] | Different diagnostic strategies compared |
| Mulgrew 2006[162] | Inadequate duration |
| Munoz 2009[164] | Comparing effects of three different autoadjusting CPAP devices on respiratory events<br>- no fixed CPAP arm |

| Study | Exclusion reason |
|---|---|
| Murase 2020[165] | Inappropriate intervention- Telemedicine to improve adherence. Included in adherence review. |
| Murray 2002[169] | Responder analysis |
| Neale 2011[178, 179] | Randomised trial comparing 6 autoadaptingCPAP devices in patients previously treated with fixed CPAP<br><br>- fixed CPAP arm not run concurrently with autoCPAP arms |
| Nilius 2019[184] | Inappropriate intervention- Telemedicine to improve adherence. Included in adherence review. |
| Nolan 2006[186, 187] | Randomisation between different auto-titrating CPAP machines; data from fixed CPAP machines captured from start of trial |
| Nilius 2006[183] | Inappropriate intervention -CPAP with expiratory pressure relief |
| Palasiewicz 1997[191, 244] | Randomised study conducted when participants were awake |
| Peach 2003[194] | Educational/psychosocial intervention |
| Pépin 2009[198] | Inappropriate intervention -CPAP with expiratory pressure relief |
| Pépin 1995[197] | Non-randomised trial on side effects of nasal CPAP therapy |
| Pépin 1999[196] | RCT assessing different ways of measuring compliance with CPAP therapy. No comparison of active interventions. |
| Penzel 2004[195] | Laboratory-based study |
| Pevernagie 2004[200] | No fixed CPAP control |
| Pierce 2005[201, 202] | Different APAP therapies compared |
| Pilz 2000[203] | Laboratory-based study |
| Piper 2008[206] | Participants recruited with obesity hypoventilation syndrome |
| Planès 2003[207] | Randomised trial comparing auto with fixed pressure CPAP. This trial was excluded as an educational intervention administered at baseline was not standardised between the two treatment groups. Titration was also performed in different settings for auto and fixed pressure CPAP. |
| Powell 2014[208] | Comparison of effects of an established auto-titrating CPAP device (REMstar Auto C-flex) with a |

| Study | Exclusion reason |
|---|---|
| | lightweight device (Transcend Auto) on AHI and treatment pressure<br><br>- no fixed CPAP arm |
| Powell 2012[209] | Inappropriate intervention - Bi-level PAP (multimodality) |
| Pradeepan 2017[210] | Study in people with positional OSA. This study population may be present with similar symptoms to OSA, but since onset is related to sleep position, pressure requirement will differ from those with non-positional OSA. |
| Rains 1996[213] | Non-randomised study assessing educational interventions in 4 children with OSA (PsycINFO) |
| Randerath 1999[217] | Randomised comparison of 2 different automatic titrating modes of pressure. Excluded as no randomised comparison made with fixed pressure CPAP was made |
| Randerath 1999b[216] | This study compared different media for informing patients about CPAP. This was excluded as there was no adequate control group, and the intervention was restricted to a sleep laboratory, rather than an assessment of long-term treatment on CPAP usage |
| Randerath 2001a[214] | Laboratory-based study |
| Randerath 2003[215] | Comparison of 2 different active treatments (BiPAP versus auto-CPAP), without a randomised comparison with fixed CPAP |
| Richards 2007[222] | Study of CBT |
| Rosenthal 2001[226] | This study was excluded as participants were prescribed CPAP machines set at different hours of use (< 6.5 hours and > 7.5 hours) |
| Rosenthal 2012[227] | Comparison of effects of auto-titrating PAP (Standard AutoPAP) versus auto-titrating PAP with expiratory pressure relief (SmartFlex™) on overnight pulse oximetry and compliance<br><br>- no fixed CPAP arm |
| Rubio 2015[83] | Inadequate duration. |
| Salgado 2006[232, 233] | Humidification added to APAP. No fixed pressure comparator. |
| Scharf 1996[236] | No attempt to measure compliance |

| Study | Exclusion reason |
|---|---|
| Sharma 1996[241] | RCT efficacy of auto-CPAP versus constant CPAP for overnight titration study. Cross-over study - no long-term assessment of patient acceptance of treatment possible. |
| Signes-Costa 2005[242] | Assessment of different strategies to diagnose and manage OSA |
| Sin 2002[243] | Non-randomised cohort study on the effects of a complex intervention on patient compliance with CPAP therapy |
| Speer 2012[247] | Randomised trial comparing effect of heated humidification with automatically adjustable temperature versus heated humidification with constant temperature on CPAP usage in OSA patients<br><br>- no fixed CPAP only arm |
| Stammnitz 2004[248] | Laboratory-based study |
| Suzuki 2007[250] | Participants randomised to auto-CPAP or no treatment as a means of titration prior to fixed pressure CPAP |
| Taylor 2003[251, 252] | Assessment of telemedicine intervention |
| Torvaldsson 2003[255] | Inadequate duration (2 x 1 week treatment arms) |
| van der Aa 2003[256] | Different titration strategies |
| Walter 2003[258] | Randomised comparison between auto-CPAP and BiLevel PAP |
| Wenzel 2007[259] | Inappropriate intervention -CPAP with expiratory pressure relief |
| Wiese 2005[262] | Educational/behavioural intervention |
| Wiest 1999[264] | Head to head comparison of active agents (heated humidification and oily nose drops). No control group receiving only fixed pressure CPAP |
| Wiest 2002[263] | 2-night titration study |
| Wimms 2013[266] | Comparison of S9 (humidification with autoadjusting CPAP) versus CPAP<br><br>- not a randomised trial |
| Zhu 2018[268] | Meta-analysis- screened for relevant references |

**Table 29: Studies excluded from the clinical review-OHS**

| Study | Exclusion reason |
|---|---|
| Afshar 2020[1] | Systematic review. Screened for relevant references. |
| Bakker 2011[10] | Inappropriate population. Morbidly obese OSA patients. |
| Borel 2010[24] | Conference Abstract |
| Carter 2016[33] | Not RCT |
| Chung 2018[40] | Cochrane protocol |
| Corral 2018[45] | No useful outcomes. |
| Contal 2011[44] | Conference Abstract |
| Contal 2013[43] | Clinical Trials citation only |
| Couillard 2015[47] | Not in English |
| Gonzalez Moro 2005[77] | Conference Abstract |
| Guan 2018[80] | Protocol |
| Howard 2014[93] | Conference Abstract |
| Howard 2015[94] | Conference Abstract |
| Jimenez 2016[108] | Conference Abstract |
| Janssens 2009[106] | Not appropriate comparison. Volume targeting by bi-level positive pressure ventilation (BPPV) |
| Masa 2019[143] | No protocol outcomes. |
| Masa 2001[136] | Inappropriate comparison. People with OHS vs people with kyphoscoliosis |
| Masa 2015[138] | Conference Abstract |
| Meurice 2007 [150] | Included in OSAHS part of the review. |
| Mokhlesi 2020[157] | Inappropriate study design- observational study. |
| Murphy 2010[166] | unobtainable conference abstract |
| Murphy 2011[167] | Conference Abstract |
| Nicolini 2018[182] | Literature review. Screened for relevant references. |
| NCT 2010[177] | Clinical Trials citation only |
| NCT 2012[176] | Clinical Trials citation only |
| Patout 2020[192] | Inappropriate intervention- automated expiratory positive airway pressure versus volume targeted non-invasive ventilation. |
| Pinto 2017[204] | Conference Abstract |
| Piper 2006[205] | Conference Abstract |

| Study | Exclusion reason |
|---|---|
| Quiroga 2018[211] | Conference Abstract |
| Quiroga 2017[212] | Conference Abstract |
| Rautela 2011[218] | Conference Abstract |
| Roche 2018[223] | Conference Abstract |
| Royer 2019[229] | Systematic review. Screened for relevant references. |
| Sanchez Quiroga 2017[234] | Conference Abstract |
| Sanchez Quiroga 2018[235] | Conference Abstract |
| Serrano 2011[240] | Conference Abstract |
| Soghier 2019[245] | Systematic review. Screened for relevant references. |

## I.1 Excluded economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2003 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below:

**Table 30: Studies excluded from the economic evaluation review**

| Study | Exclusion reason |
|---|---|
| **Planès 2003[207]** | Randomised trial comparing auto with fixed pressure CPAP. This trial was excluded as an educational intervention administered at baseline was not standardised between the two treatment groups. Titration was also performed in different settings for auto and fixed pressure CPAP. Also French health care costs were from 1999. |

# Appendix J: Research recommendations

### J.1 Treatment for people with COPD-OSAHS overlap syndrome

**Research question:** What is the optimal treatment for people with COPD-OSAHS overlap syndrome – non-invasive ventilation or CPAP?

**Why this is important:**

In the COPD-OSAHS overlap syndrome, people face the symptom burden of both OSAHS and COPD, and in many cases the combination of these two conditions increases the risk of hypoventilation and acute decompensation. There have been no randomised, controlled trials to determine the tolerability, efficacy and cost effectiveness of CPAP compared to non-invasive

ventilation in ameliorating symptoms, controlling OSAHS and hypercapnia, nor the impact on health care utilisation.

**Criteria for selecting high-priority research recommendations:**

| | |
|---|---|
| **PICO question** | Population: *Inclusion* Adults with COPD-OSAHS overlap syndrome, defined as COPD and OSAHS, with hypercapnia who are stable. *Exclusion*: Adults with COPD-OSAHS overlap syndrome who have decompensated and are acutely unwell<br>Intervention: CPAP, with minimisation by severity of OSAHS, COPD and hypercapnia<br>Comparison: Non-invasive ventilation<br><br>Outcomes:<br>- Patient related outcome measures – Epworth Sleepiness scale and quality of life<br>- Objective measures – Adherence to therapy, residual AHI, control of hypercapnia, blood pressure and cardiovascular events<br>- Health care utilisation – medical contacts and hospital admissions<br>- NHS costs and cost per quality-adjusted life-year.<br>- Pre-specified sub-group analysis by severity of OSAHS, COPD and hypercapnia, types of CPAP (auto CPAP vs fixed CPAP) |
| **Importance to patients or the population** | In COPD-OSAHS overlap syndrome with hypercapnia both CPAP and ventilation are used in clinical practice, with clinicians tending towards ventilation when hypercapnia is more significant. However, it is not known which treatment method is better tolerated by patients and more effective in improving symptoms, controlling OSAHS and hypercapnia or reducing the need for unplanned medical contacts. Theoretically, CPAP may be adequate to ameliorate hypercapnia through control of OSAHS, and it could be better tolerated since no synchronisation of breathing with the device is required. However it may not be as good at controlling hypoventilation. |
| **Relevance to NICE guidance** | Future NICE guidance can give specific recommendations regarding in which scenario CPAP or non-invasive ventilation is preferred for patients with COPD-OSAHS overlap syndrome. |
| **Relevance to the NHS** | A clear recommendation for situations in which CPAP or non-invasive ventilation should be used for patients with hypercapnic COPD-OSAHS overlap syndrome will help ensure best care is provided for patients. If CPAP was demonstrated to be non-inferior compared to ventilation (as has been demonstrated for selected patients with obesity hypoventilation and OSAHS), there are likely to be significant financial savings to the NHS. |
| **National priorities** | • COPD commonly affects older age groups of patients<br>• Optimal treatment may reduce hospital bed use |
| **Current evidence base** | There is no head-to-head randomised controlled trial of CPAP versus non-invasive ventilation in patients with hypercapnic COPD-OSAHS overlap syndrome. Current decision-making is based upon data extrapolated from patients with obesity hypoventilation with OSAHS, and with COPD alone. |
| **Equality** | The recommendation is unlikely to impact on equality issues. |

| | |
|---|---|
| **Study design** | Randomised, controlled single-blind trial with health economic analysis. Minimisation by severity of OSAHS, COPD and hypercapnia to allow sub-group analysis. |
| **Feasibility** | The trial is feasible, carried out as a multi-centre study. Treatments offered are in keeping with those presently used in clinical practice, so no patient would have delay in provision of a recognised treatment. |
| **Other comments** | The trial may attract commercial funding from companies who provide CPAP and non-invasive ventilation. |
| **Importance** | High: the research is essential to inform future updates of key recommendations in the guideline and maximise resource allocation |

## J.2 Auto CPAP vs fixed pressure CPAP for OSAHS

**Research question:** What is the clinical and cost effectiveness of auto CPAP and fixed-level CPAP for managing obstructive sleep apnoea/hypopnoea syndrome (OSAHS)?

**Why this is important:**

Positive airway pressure is an established treatment for OSAHS that can be delivered via a number of devices and through the use of fixed or variable pressure ("auto titration"). All evidence in the review was for people with moderate to severe sleep apnoea; however, the majority of the studies were in people with severe sleep apnoea. The quality of the evidence was predominantly of low or very low quality and was downgraded due to due to risk of bias, inconsistency and imprecision. They showed little difference in outcomes between auto and fixed-level CPAP. Auto CPAP is more adaptable than fixed-level CPAP because it can vary the pressure according to the individual needs. Because patients are only getting the pressure they need, those who have tried both often report that auto-CPAP is more comfortable to use. This in turn may lead to better adherence and fewer visits to the sleep specialist. However, auto-CPAP is generally more expensive than fixed-level, but the difference in cost between the two has decreased over time. Although the advent of telemonitoring is thought to have helped improve adherence with use of fixed-level CPAP, it is still not known which is more cost-effective between auto and fixed-level CPAP. A randomised controlled trial of the clinical and cost-effectiveness using the latest devices would help answer this question. `

**Criteria for selecting high-priority research recommendations:**

| | |
|---|---|
| PICO question | Population:<br><br>Inclusion: People (16 and older) with OSAHS due to start CPAP treatment for the first time.<br><br>Population will be stratified by:<br>severity: Mild, moderate, severe (based on AHI/ODI)<br><br>Exclusion:<br>Children and young adults (under 16 years old)<br><br>Intervention:<br>Auto CPAP with telemonitoring<br>Fixed-level CPAP with telemonitoring |

| | |
|---|---|
| | Comparison:<br>To each other<br><br>Outcomes:<br>Quality of life including EQ-5D and Sleep Apnea Quality of Life Index (SAQLI)<br>Sleepiness scores ( e.g. Epworth)<br>Maintenance of wakefulness test<br>Apnoea-Hypopnoea index<br>Mask leak data<br>Hours of use (adherence measure)<br>Minor adverse effects of treatment<br>Tolerability of the treatment<br>Treatment pressure<br>Number of healthcare appointments<br>NHS costs and cost per Quality-Adjusted Life-Year (QALY)<br><br>Follow up: 1 month and 6 months |
| **Importance to patients or the population** | The research will allow a consistent evidence-based approach to the first choice of treatment of either auto CPAP with telemonitoring or fixed pressure CPAP with telemonitoring for people with OSAHS. The cost of these devices vary across the country. NHS supply chain prices suggests auto-CPAP is more expensive than fixed level CPAP but NHS Trusts arrange local deals with suppliers so auto CPAP can be obtained at a similar cost in some areas of the country. |
| **Relevance to NICE guidance** | This research will enable future guidelines to clearly recommend either auto CPAP with telemonitoring or fixed CPAP with telemonitoring as first choice of treatment. |
| **Relevance to the NHS** | A clear recommendation will offer clinicians clearer guidance on use of auto CPAP and fixed pressure CPAP |
| **National priorities** | No |
| **Current evidence base** | The current evidence is reviewed in Evidence report F of the full guideline. There was evidence from 36 studies comparing auto-CPAP with fixed level CPAP. The evidence showed fixed-level CPAP and auto-CPAP to be equally effective, and auto-CPAP to be more costly. Therefore, the committee agreed to recommend fixed-level CPAP as the first-choice treatment. However, some people, particularly those in whom high pressures are only needed part of the time, find auto-CPAP more comfortable and effective than fixed-level CPAP. For others, telemonitoring may not be possible because of technological constraints such as the lack of availability of internet or poor internet connection. The committee agreed that auto-CPAP should be an option in these cases.<br>There was limited evidence for fixed pressure CPAP with telemonitoring. The committee agreed that there was insufficient evidence to make a clear recommendation for a first-choice treatment just based on clinical effectiveness. |
| **Equality** | The recommendation is unlikely to impact on equality issues. |
| **Study design** | Randomised controlled trial of auto CPAP with telemonitoring vs fixed pressure CPAP with telemonitoring. |
| **Feasibility** | The trial is feasible and should be straightforward to carry out. |
| **Other comments** | - |
| **Importance** | High: the research is essential to inform future updates of key recommendations in the guideline and maximise resource allocation. |