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# Efficacy of bilevel positive airway pressure and continuous positive airway pressure therapy in patients with obesity hypoventilation syndrome: protocol for systematic review and meta-analysis

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## ABSTRACT

**Introduction** Obesity hypoventilation syndrome (OHS) is a major respiratory complication caused by severe obesity, being associated with significant morbidity, negative impacts on quality of life and reduced survival if not treated appropriately. Positive airway pressure therapy is the first-line treatment for OHS although the optimal modality remains unclear. The goal of this study is to identify the efficacy of home bilevel positive airway pressure therapy by comparison to continuous positive airway pressure therapy and determine the best strategy for patients with OHS.

**Methods and analysis** This study will be conducted following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 2015 statement. We will search the following databases: PubMed, Web of Science, EMBASE, Cochrane Central Register of Controlled Trials and CINAHL. Ongoing studies will be identified through the ClinicalTrials.gov and WHO International Clinical Trials Registry Platform Search Portal. Grey literature will be recognised through Google Scholar and other search engines. Only randomised controlled trials meeting the eligibility criteria will be included. The risk of bias of the included studies will be evaluated through the Cochrane Collaboration's tool. RevMan V.5.3.5 software will be used for data analysis. The Q statistic and $I^2$ index will be used for investigating heterogeneity, and subgroup analysis or sensitivity analysis will be used to explore the source of heterogeneity. In addition, the Grading of Recommendations Assessment, Development and Evaluation system will be used to inspect the quality of evidence.

**Ethics and dissemination** Ethics approval is not required because this study contains no primary data collected from humans. This systematic review and meta-analysis will be submitted to a peer-reviewed journal for publication.

**PROSPERO registration number** CRD42017078369.

## Strengths and limitations of this study

- The first systematic review and meta-analysis to compare the efficacy of home bilevel positive airway pressure and continuous positive airway pressure therapy in patients with obesity hypoventilation syndrome (OHS).
- This study will help identify the most appropriate home positive airway pressure therapy strategy for patients with OHS.
- Only randomised controlled trials, representing a high quality of evidence, will be included in this study.
- To determine the most appropriate patients to receive bilevel positive airway pressure therapy through subgroup analysis.

## INTRODUCTION

The increasing incidence of obesity has become a major concern worldwide.[1] Obesity hypoventilation syndrome (OHS) is a major respiratory complication caused by obesity and is characterised by a daytime arterial carbon dioxide pressure ($PaCO_2$) >45 mm Hg with body mass index (BMI) >30 kg/m$^2$ and excluding other causes of hypoventilation (such as neuromuscular disorders, chest wall abnormalities or significant lung diseases.).[2] OHS usually appears to be the end consequence of a complex interplay between upper airway obstruction, sleep hypoventilation, decreased lung capacity, increased respiratory muscle load, changing respiratory centre drive and leptin resistance.[3 4] Due to the presence of chronic hypercapnia and hypoxaemia, patients with OHS are at high risk of severe respiratory failure, pulmonary hypertension, chronic cor pulmonale and other cardiovascular complications if not treated appropriately.[5 6] Moreover, this will greatly affect the patient's health-related quality of

life, exercise performance and survival rate, and may become a serious social and economic burden.[7–9]

Treatment of this disorder is aimed at improving the pathophysiologic abnormalities of patients with OHS which commonly includes positive airway pressure (PAP) therapy, lifestyle intervention, surgery and pharmacotherapy. PAP therapy is considered to be the first-line treatment, which can effectively improve gas exchange, sleep disorders and survival in patients with OHS.[10 11] Additionally, Castro-Añón *et al* indicated that even with the introduction of PAP therapy, mortality in OHS remains higher than that seen in eucapnic obstructive sleep apnea (OSA) individuals.[8] PAP therapy may be delivered as either continuous positive airway pressure (CPAP) or bilevel therapy (including spontaneous (S), timed (T), spontaneous/timed (S/T) or volume-assured pressure support (VAPS) mode). CPAP provides a constant positive pressure in the airway, aiming to reduce upper airway resistance and prevent upper airway obstructive events, thereby controlling sleep disordered breathing and improving oxygenation. However, CPAP is not a truly physiologically based ventilation mode. It simply provides a constant pressure to the airway to maintain the upper airway open and increase lung volumes. In contrast, bilevel therapy provides a differential pressure between inspiration and expiration (pressure support level) which acts to increase tidal volume, improve alveolar hypoventilation and relieve respiratory fatigue.[12] Therefore, theoretically bilevel therapy should be more effective in improving oxygenation and reducing arterial carbon dioxide levels than CPAP.

Currently, the optimal mode of home PAP therapy for patients with OHS has not been determined. Only a few randomised controlled trials (RCT)[13–15] but no systematic reviews or meta-analyses have compared the efficacy of domiciliary bilevel versus CPAP therapy in patients with OHS. The main objective of this study is to determine whether bilevel therapy is more effective than CPAP therapy in treating OHS and to identify the best PAP setting for patients with OHS as the first-line treatment.

## OBJECTIVE

The goal of this systematic literature review and meta-analysis is to determine the effect of the home bilevel therapy by comparison to CPAP therapy in patients with OHS. Specifically, what is the difference of treatment effect between home bilevel and CPAP therapy in patients with OHS as reported in the research published from January 1980 through November 2017?

## METHODS

This manuscript follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 2015 statement.[16]

### Eligibility criteria

#### Study design

Only RCTs will be included. We will include RCTs comparing the efficiency of domiciliary bilevel and CPAP therapy in patients with OHS.

#### Participants

Only subjects diagnosed with OHS (ie, BMI >30 kg/m$^2$ and daytime $PaCO_2$ >45 mm Hg) with exclusion of other conditions that might lead to hypoventilation including neuromuscular disorders, chest abnormalities or chronic obstructive pulmonary disease will be included in this analysis.[2]

#### Interventions

Bilevel therapy, providing a differential pressure between inspiration and expiration, which can increase tidal volume, improve alveolar hypoventilation and relieve respiratory fatigue; CPAP therapy provides a constant positive pressure in the airway, which can reduce upper airway resistance and prevent upper airway obstruction events.[12]

#### Outcomes

- Primary outcome: Daytime $PaCO_2$
- Secondary outcomes:
  - adherence (whether average PAP therapy use of ≥4 hours per night)[17 18]
  - health-related quality of life (the Medical Outcomes Study 36-Item Short-Form Health Survey,[19] Epworth Sleepiness Scale,[20] Severe Respiratory Insufficiency Questionnaire[21])
  - mortality
  - the incidence of hospital readmissions
  - lung function[22]
  - physical activity (6 min walk test[23]).

### Information sources and search strategy

#### Electronic searches

We will search the following databases: PubMed, Web of Science, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, and CINAHL. The searching period will be from January 1980 to November 2017. Literature retrieved will be limited to human subjects and language or publication status will not be limited. The searches will be reworked before the final analyses, and further studies will also be reviewed for the inclusion. The detailed search strategy of PubMed is presented in online supplementary file 1.

#### Searching other resources

Ongoing studies will be identified through the ClinicalTrials.gov (November 2017) and WHO International Clinical Trials Registry Platform Search Portal (http://apps.who.int/trialsearch/). We will contact the authors to get further information on ongoing or unpublished studies, if necessary. In order to ensure that the search is comprehensive, we will look through the bibliography of the included studies or reviews to identify the relevant

reports. Grey literature (including reports and conference presentations) will be searched through Google Scholar and other relevant websites.

## Study records

### Data management

All previously searched literature will be imported into EndNote V.X8 software (Clarivate Analytics, Philadelphia, PA, USA), and duplicates will be removed. The titles and abstracts obtained from the previous searches will be inspected independently by two investigators (WL and XY). If the article meets the eligibility criteria, or if there is any uncertainty about including a particular study, the report will be downloaded.

### Selection process

The imported articles will be screened by two independent investigators (WL and XY) to determine whether they meet the criteria for inclusion. We will ask the authors for additional information when necessary. Reasons for excluding studies will be recorded. The two investigators will resolve any disagreements through discussion, and the third investigator (LQ) will offer advice when agreement cannot be reached.

### Data collection process

Two investigators (BP and YT) will independently extract data using a standardised data collection form. The extracted data will include: (1) study characteristics such as first author, journal, year and study design; (2) patients' characteristics including the number of patients in each group, age, sex, BMI and severity of OHS; (3) intervention characteristics (type of PAP therapy, mode of bilevel therapy, inspiratory PAP, expiratory PAP and back-up rate), mean daily use of ventilation and treatment duration; and (4) primary and secondary outcomes as described above. For crossover trials, we will only extract the data from the first phase, primarily because of the carry-over effect. When the extraction process is complete, we will merge the two collections into one for further analysis. Should there be any disagreements at this stage, the two investigators will reach an agreement through discussion. If agreement cannot be reached, the third investigator (LQ) will participate in the discussion to reach a final conclusion.

## Risk of bias in individual studies

Two investigators (YQ and JW) will use the Cochrane Collaboration's tool to assess the risk of bias of the included studies.[24 25] Six domains will be assessed: selection bias, performance bias, detection bias, attrition bias, reporting bias and 'other' bias. Each domain will be judged as 'low risk', 'unclear risk' or 'high risk'. The support for these judgements will be clarified in a risk of bias table. Divergences will be discussed first by the two investigators, and if an agreement cannot be reached, the third investigator (LQ) will provide a suggestion.

## Data synthesis

Analyses will be done using RevMan V.5.3.5 software (Cochrane, London, UK).

### Measures of treatment effect

For continuous outcomes such as $PaCO_2$, 6 min walk distance, and so on, the weighted mean difference or standardised mean difference with 95% CIs will be used. Dichotomous outcomes such as patient mortality and the incidence of hospital readmission will be described using the risk ratio with 95% CIs.

### Dealing with missing data

When data are missing or inapplicable, we will contact the original authors by email or use a formula to convert them into available data.[24 26 27] If the missing data cannot be obtained, we will follow the recommendations of the Cochrane Handbook for Systematic Reviews of Intervention[24]: (1) make precise the hypothesis of any methods used to handle the missing data; (2) sensitivity analyses will be used to assess how sensitive results are to reasonable changes in the assumptions that are made; (3) consider the potential effect of the missing data as limitations in our study.

### Assessment of heterogeneity

We will investigate statistical heterogeneity among the included studies using the Q statistic and $I^2$ index. A p value of ≤0.10 for the Q statistic will be considered to be statistically significant heterogeneity. $I^2$ values <25%, 25%–50% or >50% represent low, moderate or high heterogeneity, respectively. We will apply a fixed effects model if no heterogeneity exists. When substantial heterogeneity ($I^2$>50% or p≤0.1) is detected, we will try to identify the source of heterogeneity by subgroup analysis, sensitivity analysis or using a random effects model. If substantial heterogeneity cannot be well explained, we will not proceed with the meta-analysis and a descriptive, qualitative summary will be made.[24]

### Additional analyses

Possible sources of heterogeneity will be determined through carrying out subgroup analysis based on gender, BMI, the baseline presentation of the patient (acute decompensation or during clinical stability), the severity of the OHS (mild ($PaCO_2$ 46–60 mm Hg), moderate ($PaCO_2$ 60–80 mm Hg) or severe ($PaCO_2$ ≥80 mm Hg)),[28] whether combined with obstructive sleep apnoea, the mode of bilevel therapy, the mean daily home use of the ventilator and the duration of the follow-up periods (short term (<3 months) or long term (≥3 months)). Sensitivity analysis will also be performed to detect the source of heterogeneity. When substantial heterogeneity exists, we will exclude the study and compare its impact on the pooled estimate. If we find the source of heterogeneity, we will review the literature again to evaluate its quality and bias and decide whether the particular study is to be retained or excluded. If the study is excluded, the reasons for its removal will be explained in the discussion. If the quantitative synthesis is not appropriate, a

narrative method will be used. This approach will present the information in a text or table in order to interpret and summarise the features and outcomes among the included studies.

### Metabiases

Publication bias will be assessed through the funnel plot if the number of the included studies is ≥10. In addition, in order to assess the reporting bias, we will search the database of the registered protocols mentioned above to confirm whether the study's prespecified outcomes have not been reported.

### Confidence in cumulative estimate

The Grading of Recommendations Assessment, Development and Evaluation system will be used for rating the quality of evidence for all outcomes of the included studies. The quality of evidence will be classified into four levels of quality (high, moderate, low and very low). Because RCTs are considered to be high quality, the quality of the evidence may be downgraded when study limitations, inconsistency of results, indirectness of evidence, imprecision or reporting bias occurs.[29 30]

### Patient and public involvement statement

Patients and public were not involved in this manuscript.

## DISCUSSION

PAP therapy is considered as the first-line treatment for patients with OHS. However, the optimal mode of PAP therapy is still not clear. To the best of our knowledge, this is the first systematic review and meta-analysis to undertake a comparison between domiciliary bilevel and CPAP therapy for patients with OHS. Therefore, the findings will aid clinicians in choosing the most appropriate long-term home therapy for these individuals.

Bilevel therapy can be delivered as S, T, S/T or VAPS mode.[31] In S mode, ventilator will only be triggered when it detects a pressure or flow change by the inspiratory effort of the patient. In this mode, inspiratory trigger failure may occur due to excessive leakage or from the emergence of central apnoea, leading to poor nocturnal gas exchange and sleep quality.[32 33] With the T mode, all breaths are triggered by the ventilator only which can produce patient/ventilator asynchrony and patient discomfort. The S/T mode allows the patient to trigger the device to initiate inspiratory support, but if the patient's spontaneous respiratory rate drops below the back-up rate set by the clinician, then the ventilator will trigger the breath. This may reduce the rate of patient/ventilator asynchrony, relieve inspiratory effort and provide better gas exchange if the back-up rate is set high enough.[32] VAPS mode, a mixed mode of bilevel therapy, automatically adjusts the inspiratory pressure level within a preset pressure range in order to maintain a clinician-set target tidal volume. With the VAPS mode, it can adapt to variations in ventilatory need created by changes in body position, sleep stage or lung mechanics.[34 35] Hence, subgroup analysis will be performed to find out which modes of bilevel therapy provide better outcomes for patients with OHS.

### Ethics and dissemination

Our findings will be submitted to a peer-reviewed journal for publication.

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**Contributors** LL, RC and LQ contributed to the conception and design of the study, drafting the submitted article and revising the draft critically for important intellectual content. LL and YT contributed to the search strategy. Data management and selection process were proceeded by WL and XY. BP and YT were responsible for the data collection. YQ, FF and JW contributed to the risk of bias assessment. All authors contributed to data analysis, amending the paper, being responsible for all aspects of the work and approving the final version of the manuscript.

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**Competing interests** None declared.

**Patient consent** Not required.

**Ethics approval** Ethics approval is not required because this is a protocol for a systematic review and meta-analysis in which no primary human data will be collected.

**Provenance and peer review** Not commissioned; externally peer reviewed.



## REFERENCES

1. Ng M, Fleming T, Robinson M, *et al*. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2014;384:766–81.
2. Anon. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. *Sleep* 1999;22:667–89.
3. Shetty S, Parthasarathy S. Obesity hypoventilation syndrome. *Curr Pulmonol Rep* 2015;4:42–55.
4. Piper A. Obesity hypoventilation syndrome: weighing in on therapy options. *Chest* 2016;149:856–68.
5. Jennum P, Ibsen R, Kjellberg J. Morbidity prior to a diagnosis of sleep-disordered breathing: a controlled national study. *J Clin Sleep Med* 2013;9:103–8.
6. Borel JC, Burel B, Tamisier R, *et al*. Comorbidities and mortality in hypercapnic obese under domiciliary noninvasive ventilation. *PLoS One* 2013;8:e52006–8.

7. Hida W. Quality of life in obesity hypoventilation syndrome. *Sleep Breath* 2003;7:1–2.
8. Castro-Añón O, Pérez de Llano LA, De la Fuente Sánchez S, *et al*. Obesity-hypoventilation syndrome: increased risk of death over sleep apnea syndrome. *PLoS One* 2015;10:e0117808.
9. Jennum P, Ibsen R, Kjellberg J. Social consequences of sleep disordered breathing on patients and their partners: a controlled national study. *Eur Respir J* 2014;43:134–44.
10. Priou P, Hamel JF, Person C, *et al*. Long-term outcome of noninvasive positive pressure ventilation for obesity hypoventilation syndrome. *Chest* 2010;138:84–90.
11. Pérez de Llano LA, Golpe R, Ortiz Piquer M, *et al*. Short-term and long-term effects of nasal intermittent positive pressure ventilation in patients with obesity-hypoventilation syndrome. *Chest* 2005;128:587–94.
12. Mehta S, Hill NS. Noninvasive ventilation. *Am J Respir Crit Care Med* 2001;163:540–77.
13. Piper AJ, Wang D, Yee BJ, *et al*. Randomised trial of CPAP vs bilevel support in the treatment of obesity hypoventilation syndrome without severe nocturnal desaturation. *Thorax* 2008;63:395–401.
14. Masa JF, Corral J, Alonso ML, *et al*. Spanish Sleep Network. Efficacy of Different Treatment Alternatives for Obesity Hypoventilation Syndrome. Pickwick Study. *Am J Respir Crit Care Med* 2015;192:86–95.
15. Howard ME, Piper AJ, Stevens B, *et al*. A randomised controlled trial of CPAP versus non-invasive ventilation for initial treatment of obesity hypoventilation syndrome. *Thorax* 2017;72:437–44.
16. Moher D, Shamseer L, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
17. Mokhlesi B, Tulaimat A, Evans AT, *et al*. Impact of adherence with positive airway pressure therapy on hypercapnia in obstructive sleep apnea. *J Clin Sleep Med* 2006;2:57–62.
18. Murphy PB, Davidson C, Hind MD, *et al*. Volume targeted versus pressure support non-invasive ventilation in patients with super obesity and chronic respiratory failure: a randomised controlled trial. *Thorax* 2012;67:727–34.
19. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473–83.
20. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991;14:540–5.
21. Windisch W, Freidel K, Schucher B, *et al*. The Severe Respiratory Insufficiency (SRI) Questionnaire: a specific measure of health-related quality of life in patients receiving home mechanical ventilation. *J Clin Epidemiol* 2003;56:752–9.
22. Miller MR, Hankinson J, Brusasco V, *et al*. Standardisation of spirometry. *Eur Respir J* 2005;26:319–38.
23. Holland AE, Spruit MA, Troosters T, *et al*. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. *Eur Respir J* 2014;44:1428–46.
24. In: JPT H, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*. London, UK: The Cochrane Collaboration, 2011.
25. Higgins JP, Altman DG, Gøtzsche PC, *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
26. Liberati A, Altman DG, Tetzlaff J, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med* 2009;6:e1000100.
27. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol* 2005;5:13.
28. Cabrera Lacalzada C, Díaz-Lobato S. Grading obesity hypoventilation syndrome severity. *Eur Respir J* 2008;32:817–8.
29. Guyatt GH, Oxman AD, Vist GE, *et al*. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–6.
30. Guyatt G, Oxman AD, Akl EA, *et al*. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011;64:383–94.
31. Johnson KG, Johnson DC. Treatment of sleep-disordered breathing with positive airway pressure devices: technology update. *Med Devices* 2015;8:425.
32. Contal O, Adler D, Borel JC, *et al*. Impact of different backup respiratory rates on the efficacy of noninvasive positive pressure ventilation in obesity hypoventilation syndrome: a randomized trial. *Chest* 2013;143:37–46.
33. Fanfulla F, Taurino AE, Lupo ND, *et al*. Effect of sleep on patient/ventilator asynchrony in patients undergoing chronic non-invasive mechanical ventilation. *Respir Med* 2007;101:1702–7.
34. Pluym M, Kabir AW, Gohar A. The use of volume-assured pressure support noninvasive ventilation in acute and chronic respiratory failure: a practical guide and literature review. *Hosp Pract* 2015;43:299–307.
35. Nilius G, Katamadze N, Domanski U, *et al*. Non-invasive ventilation with intelligent volume-assured pressure support versus pressure-controlled ventilation: effects on the respiratory event rate and sleep quality in COPD with chronic hypercapnia. *Int J Chron Obstruct Pulmon Dis* 2017;12:1039–45.