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Original Article

Efficacy of bilevel ventilatory support in the treatment of stable patients with obesity hypoventilation syndrome: systematic review and meta-analysis☆

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ABSTRACT

Objective: To systematically review the effects of bilevel ventilatory support (BVS) in patients with Obesity Hypoventilation Syndrome (OHS).
Methods: A search of databases (MEDLINE accessed by PubMed, Cochrane CENTRAL, EMBASE and LILACS) was conducted from inception to June 2018. Randomized trials comparing BVS to other therapeutic modalities such as lifestyle counseling, continuous positive airway pressure (PAP) or BVS with average volume assured pressure support for the treatment of patients with OHS were included. The primary outcome was a change in daytime arterial carbon dioxide levels ($PaCO_2$). Secondary outcome measures included arterial partial pressure of oxygen (PaO_2), blood bicarbonate (HCO_3), percentage of total sleep time (TST) with oxygen saturation <90%, transcutaneous pressure of carbon dioxide ($PtcCO_2$), Epworth Sleepiness Scale (ESS), Medical Outcome Survey Short Form (SF36), Functional Outcomes of Sleep Questionnaire (FOSQ), Severe Respiratory Insufficiency Questionnaire (SRI), compliance with treatment, and weight loss.
Results: Of 176 articles identified, seven studies were included. When BVS was compared to lifestyle counseling, the intervention was superior in improving $PaCO_2$ (−2.90 mmHg; 95%CI −4.28 to −1.52), PaO_2 (2.89 mmHg; 95%CI 0.33 to 5.46), HCO_3 (−2.55 mmol/L; 95%CI −3.28 to −1.81), percentage of TST<90% (−30.55%; 95%CI −37.98 to −23.12), ESS (−2.52; 95%CI −4.16 to −0.88) and FOSQ (6.33; 95%CI 1.78 to 10.88). However, when BVS was compared to other PAP modalities, there was no difference in any of the outcomes evaluated.
Conclusions: Treatment using BVS therapy is superior to lifestyle counseling. Different PAP modalities appear to be equally effective in improving outcomes. CRD42017065326.

1. Introduction

The estimated prevalence of obesity hypoventilation syndrome (OHS) in the general adult population is around 0.3% [1–4]. However, in patients with a body mass index greater than 35 an incidence of over 30% has been reported [5]. Around 80–90% of OHS patients have concomitantly obstructive sleep apnea (OSA), in which recurrent upper airway obstruction results in apneas, hypopneas and oxygen desaturation [1]. The symptoms of OHS are usually more severe and the cardiovascular consequences more dangerous than those of OSA, with a greater risk of hospitalization and death [6–11].

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The pathogenesis of OHS is multifactorial and complex, and currently it is not fully understood. It is believed that several mechanisms are involved, such as changes in respiratory mechanics secondary to obesity, acute hypercapnia due to obstructive events during sleep and central hypoventilation secondary both to leptin resistance and to an altered compensatory response to chronic sleep hypoventilation [12–16].

Early and appropriate treatment of these patients is crucial in reducing the significant morbidity and mortality associated with OHS. Positive airway pressure (PAP) therapy for OHS can significantly improve health-related quality of life, healthcare costs, and even mortality [17]. Although in the recent there has been an increase in the number of randomized controlled trials (RCTs) and reviews assessing this disorder, optimal therapy for these patients remains unclear. Currently, there are eight RCTs addressing the efficacy of different PAP modalities in patients with OHS. Some of these studies approach the treatment comparing bilevel ventilatory support (BVS) to lifestyle counseling [6,18,19] and are extremely important since they establish the essential role of PAP treatment in OHS patients. Some RCTs compare BVS to continuous positive airway pressure (CPAP) [6,20,21] and aim to demonstrate the superiority of one PAP mode over another. Others RCTs compare different BVS modalities [22–24] showing the function of new technologies in OHS treatment. However, there is no meta-analysis approaching this important question.

Therefore, we report a systematic review with meta-analysis of RCTs comparing BVS to other therapeutic modalities (lifestyle counseling and other PAP modalities such as CPAP and BVS with AVAPS [average volume assured pressure support]) regarding respiratory failure, sleep quality and daily sleepiness in patients with OHS.

2. Methods

This systematic review and meta-analysis followed the recommendations proposed by the Cochrane Collaboration [25] and the PRISMA Statement [26]. The study protocol was registered at PROSPERO: CRD42017065326.

2.1. Eligibility criteria

This review included RCTs that compared patients with OHS treated with BVS to patients treated with lifestyle counseling or other PAP modalities, such as CPAP and BVS with AVAPS. Outcomes evaluated were change in $PaCO_2$ (daytime arterial carbon dioxide level), PaO_2 (arterial partial pressure of oxygen), blood bicarbonate (HCO_3), percentage of total sleep time (TST) with oxygen saturation <90%, transcutaneous pressure of carbon dioxide ($PtcCO_2$), Epworth Sleepiness Scale (ESS), Medical Outcome Survey Short Form (SF36), Functional Outcomes of Sleep Questionnaire (FOSQ), Severe Respiratory Insufficiency Questionnaire (SRI), compliance to treatment, and weight loss. In case of a study with multiple publications (or substudies), the study was included only once. Eligible studies included OHS patients with stable hypercapnic respiratory failure. Exclusion criteria were as follows: [1] inclusion of subjects with other causes for chronic respiratory failure than OHS [2]; relevant chronic obstructive pulmonary disease [3]; follow-up shorter than four weeks; and [4] lack of control group data description.

2.2. Search strategy

A paired, independent search was carried out in the following electronic databases (from inception to June 2018): MEDLINE (accessed by PubMed), Cochrane Central Register of Controlled Trials (Cochrane CENTRAL), EMBASE and LILACS. In addition, a search in the references of the published studies was performed. The search comprised the following terms: “Obesity Hypoventilation Syndrome,” “Positive-Pressure Respiration,” “Noninvasive Ventilation,” “Continuous Positive Airway Pressure” combined with a high sensitivity combination of words used in the search for RCTs [27]. There were no language or publication status restrictions. The complete search strategy used in PubMed is shown in Appendix. Details for the other used strategies are available on request.

2.3. Study selection

Two investigators independently evaluated titles and abstracts of all articles identified by the search strategy. All abstracts that did not provide sufficient information regarding the inclusion and exclusion criteria were selected for full-text evaluation. In the second phase, the same reviewers independently evaluated the full-text articles and performed their selection according to the eligibility criteria. Disagreements between reviewers were resolved by consensus.

2.4. Data extraction

Using standardized forms, the same two reviewers independently conducted data extraction regarding the methodological characteristics of the studies, interventions, and outcomes. Differences between reviewers were resolved by consensus or by a third reviewer. The primary outcome analyzed was $PaCO_2$; secondary outcomes were PaO_2, HCO_3, the percentage of TST with oxygen saturation <90%, $PtcCO_2$, ESS, SF36, FOSQ, SRI, compliance to treatment, and weight loss.

2.5. Assessment of bias risk

Study quality assessment was performed using the Cochrane Risk of Bias Tool. It included adequate sequence generation, allocation concealment, blinding of patients, blinding of outcome assessors, use of intention-to-treat analysis, and description of losses and exclusions. Studies without a clear description of these features were considered unclear. Use of intention-to-treat analysis was considered as confirmation on study assessment that the number of participants randomized and the number analyzed were identical. The same two reviewers independently performed studies quality assessment.

2.6. Data analysis

Pooled-effect estimates were obtained by comparing the mean change from baseline to end of the study for each group and were expressed as the weighted mean difference between groups. Studies in which it was not possible to calculate the standard deviation of the mean change were imputed as directed in Cochrane Handbook for Systematic Reviews of Interventions [25]. Calculations were performed using a random effects method. A P-value $\leq$ 0.05 was considered statistically significant. Statistical heterogeneity of the treatment effects among studies was assessed using the Inconsistency I^2 test, in which values above 25% and 50% were considered indicative of moderate and high heterogeneity, respectively [28]. All analyses were conducted using Review Manager Version 5.3 [29]. To explore heterogeneity between studies we re-ran the meta-analyses removing one paper at a time to check whether some individual study explained heterogeneity.

2.7. Summary of evidence: GRADE-criteria

We presented the overall quality assessment of the evidence using the GRADE approach, as recommended by the Cochrane Handbook for Systematic Reviews of Interventions [25,30] (Table 3). For each specific outcome, the quality of the evidence

was based on five factors: [1] risk of bias [2]; inconsistency [3]; indirectness [4]; imprecision, and [5] other considerations (publication bias). The quality was reduced by one level for each of the lacking factors. The GRADE approach resulted in four levels of evidence quality of evidence: high, moderate, low, and very low.

3. Results

3.1. Description of studies

The search strategy yielded 176 abstracts; of these, 10 studies were considered potentially relevant and retrieved for detailed analysis. Seven of these studies met the eligibility criteria and were included in the systematic review and meta-analysis (n = 500) (Fig. 1). One of the studies compared three groups – BVS, CPAP and lifestyle counseling - and was included in two analysis (BVS versus lifestyle counseling and BVS versus CPAP) [6]. Three studies compared BVS to lifestyle counseling (total n = 264, of which 130 patients with BVS were considered) [6,18,19]. Three trials compared BVS to CPAP (total n = 247, of which 118 with BVS were considered) [6,20,21]. Two trials compared BVS to BVS with AVAPS [22,23] and one of them was a crossover study [23] (total n = 60, of which 35 with BVS were studied) (Table 1).

3.2. Risk of bias

All studies included in the systematic review described losses to follow-up and exclusions; 71.4% presented an adequate sequence generation, characterizing low bias risk for these items. 42.9% reported allocation concealment, presented blinded assessment of outcomes, and used the intention-to-treat principle for statistical analyses, evidencing a moderate risk of bias; only 28.6% included blinded patients (high risk of bias) (Table 2).

3.3. Effects of interventions

3.3.1. Daytime arterial carbon dioxide level

All included studies evaluated $PaCO_2$. BVS was compared to lifestyle counseling in three studies [6,18,19], all of them evidencing superiority of BVS when compared to lifestyle counseling (−2.90 mm Hg; 95% CI −4.28 to − 1.52; I^2 = 0%). Three studies compared BVS to CPAP [6,20,21] (−1.16 mm Hg; 95% CI −2.93 to 0.61; I^2 = 0%) and two studies compared BVS to BVS with AVAPS [22,23] (1.96 mm Hg; 95% CI −1.87 to 5.78; I^2 = 35%), showing no difference inter-groups (Fig. 2). Based on the GRADE approach, the quality of the evidence for this outcome was considered high to BVS versus lifestyle counseling, moderate to BVS versus CPAP, and very low to BVS versus BVS with AVAPS (Table 3).

3.3.2. Arterial partial pressure of oxygen

All articles included in this meta-analysis evaluated PaO_2. Three studies compared BVS to lifestyle counseling [6,18,19], showing a significant improvement in PaO_2 in the BVS group (2.89 mm Hg; 95% CI 0.33 to 5.46; I^2 = 0%). Three studies compared BVS to CPAP [6,20,21] (−0.26 mm Hg; 95% CI −3.40 to 2.88; I^2 = 0%) and two studies compared BVS to BVS with AVAPS [22,23] (2.60 mm Hg; 95% CI −3.22 to 8.43; I^2 = 0%), evidencing no difference between groups (Fig. 3). Based on the GRADE approach, the quality of the evidence for this outcome was considered moderate compared to BVS versus lifestyle counseling and to BVS versus CPAP and very low to BVS versus BVS with AVAPS (Table 3).

3.3.3. Bicarbonate

All studies evaluated HCO_3. Three articles compared BVS to lifestyle counseling [6,18,19], with a significant improvement in the BVS group (−2.55 mmol/L; 95% CI −3.28 to −1.81, I^2 = 0%). Three studies compared BVS to CPAP [6,20,21] (−0.18 mmol/L; 95% CI −1.15 to 0.79; I^2 = 0%) and two studies compared BVS to BVS with AVAPS [22,23] (0.68 mmol/L; 95% CI −0.68 to 2.03; I^2 = 0%), without any difference between groups (Fig. 4). Based on the GRADE approach, the quality of the evidence for this outcome was considered high compared to BVS versus lifestyle counseling, and moderate compared to BVS versus CPAP and BVS versus BVS with AVAPS (Table 3).

3.3.4. Percentage of total sleep time with oxygen saturation <90%

Three studies comparing BVS to lifestyle counseling measured the percentage of TST with oxygen saturation <90% [6,18,19], showing an inter-group difference (−30.55%; 95% CI −37.98 to −23.12; I^2 = 0%) (Fig. 5). Based on the GRADE approach, the quality of the evidence for this outcome was considered low (Table 3).

3.3.5. transcutaneous pressure of carbon dioxide

Two studies comparing BVS to BVS with AVAPS measured $PtcCO_2$ [22,23], without any inter-group differences (2.06 mm Hg; 95% CI −3.02 to 7.14; I^2 = 12%) (Fig. 6). Based on the GRADE approach, the quality of the evidence for this outcome was considered very low (Table 3).

3.3.6. Epworth Sleepiness Scale

Five studies assessed ESS. Three articles compared BVS to lifestyle counseling [6,18,19], evidencing a significant improvement in this outcome in the BVS group (−2.52; 95% CI −4.16 to −0.88; I^2 = 51%). The high statistical heterogeneity is due to the inclusion of the study by Masa et al. [6], which showed a greater improvement in this outcome in BVS group compared to the other studies, possibly due to OSA severity and the large apnea-hypopnea index reduction, with consequent reduction of the arousal index. Removing this study from the meta-analysis, we no longer observed this heterogeneity (−1.63; 95% CI −3.08 to −0.19; I^2 = 0%). In three studies that compared BVS to CPAP [6,20,21] there was no difference between the groups (−0.74; 95% CI −2.13 to 0.66; I^2 = 0%) (Fig. 7). Based on the GRADE approach, the quality of the evidence for this outcome was considered very low to BVS versus lifestyle counseling, and low to BVS versus CPAP (Table 3).

3.3.7. Medical Outcome Survey Short Form

Five articles assessed SF36, two of which compared BVS to lifestyle counseling [6,19] and three of which compared BVS to CPAP [6,20,21]. Regarding the physical component, BVS was compared to lifestyle counseling (1.77; 95% CI −0.42 to 3.96; I^2 = 0%) and to CPAP (1.06; 95% CI −3.88 to 5.99; I^2 = 41%), with no difference between groups (Fig. 8). Based on the GRADE approach, the quality of the evidence for this outcome was considered low compared to BVS versus lifestyle counseling and very low compared to BVS versus CPAP (Table 3). Regarding the mental component, BVS was compared to lifestyle counseling (2.46; 95% CI −1.91 to 6.84; I^2 = 49%) and to CPAP (1.58; 95% CI −5.56 to 8.72; I^2 = 60%), also showing no difference between groups (Fig. 9). Based on the GRADE approach, the quality of the evidence for this outcome was considered very low compared to BVS versus lifestyle counseling and BVS versus CPAP (Table 3). Statistical heterogeneity in the BVS and CPAP comparison was due to the inclusion of the study of Piper et al. [20], which was more favorable to BVS group in this outcome compared to the other studies. Removing this paper from meta-analysis, there was an absence of heterogeneity for both the physical (0.23; 95% CI −2.38 to 2.84; I^2 = 0%) and the mental component (−2.16; 95% CI −6.02 to 1.70; I^2 = 0%).

Table 1
Characteristics of included studies.

Study, year	N (I/C)	Age (I/C)	Patients	Parameters	Follow-up	Assessed Outcomes	Conclusion
BVS vs. Lifestyle Counseling							
Borel, 2012	19/18	58(11)/54(6)	Patients with OHS	I- BVS ST IPAP 18 ± 3 cm H_2O EPAP11 ± 2 cm H_2O C- Lifestyle counseling	One month	$PaCO_2$, PaO_2, HCO_3, TST<90% and ESS.	When compared with lifestyle counseling, BVS was effective in significantly reducing $PaCO_2$, HCO_3 and TST<90%. Compared to baseline, a significant improvement in ESS was seen with BVS, although the difference between lifestyle counseling and BVS groups was nonsignificant. There was no difference in PaO_2.
Masa, 2015	71/70	64(11)/60(13)	Patients with OHS and severe OSA	I- BVS ST AVAPS IPAP 20 ± 3 EPAP 7 ± 2 cm H_2O C-Lifestyle counseling	Two months	$PaCO_2$, PaO_2, HCO_3, TST <90%, ESS, SF36, FOSQ and weight loss.	$PaCO_2$ improved in both groups, although the improvement was greater in the BVS group, with a significant difference relative to the control group. HCO_3, TST<90%, ESS and FOSQ improved only in BVS group, with statistical significance compared with the control group. PaO_2 improved only with BVS, without significant difference compared to the control group. Weight decreased significantly in BVS and control groups, with no significant differences between the groups. There was no improvement in SF36 in both groups.
Masa, 2016	40/46	67(12)/69(15)	Patients with OHS without severe OSA	I- BVS ST AVAPS IPAP 18.2 ± 3.4 EPAP 7.1 ± 1.8 C- Lifestyle counseling	Two months	$PaCO_2$, PaO_2, HCO_3, TST <90%, ESS, SF36, FOSQ, and weight loss.	$PaCO_2$, HCO_3, and ESS improved in both groups although the improvements were significantly greater in BVS group. PaO_2 improved only in BVS group without reaching inter-group statistical significance. TST<90% improved just in BVS group, with statistical difference between groups. Significant improvement was observed in SF36 mental component for BVS group in intra-group and inter-group comparisons. Changes in SF36 physical component and FOSQ were not statistically significant in both groups. Weight loss was statistically significant only in the control group.
BVS vs. CPAP							
Howard, 2017	29/31	53.2(10.7)/52.9(10)	Newly diagnosed OHS patients, including all severities	I- BVS ST IPAP 19.3 ± 2.8cmH_2O EPAP 11.9 ± 2.3 cm H_2O C- CPAP P 15.2 ± 2.8 cm H_2O	Three months	$PaCO_2$, PaO_2, HCO_3, ESS, SF36, weight loss, and compliance	BVS and CPAP resulted in similar improvements in $PaCO_2$, PaO_2, and HCO_3. ESS and SF36 improved on treatment, without any between-group difference. Body weight was reduced in both groups. Compliance was similar in both groups.
Masa, 2015	71/80	64(11)/57(13)	Patients with OHS and severe OSA	I- BVS ST AVAPS IPAP 20 ± 3 cm H_2O EPAP 7.8 ± 1.8 cm H_2O C- CPAP P 11 ± 2 cm H_2O	Two months	$PaCO_2$, PaO_2, HCO_3, ESS, SF36, weight loss, and compliance	$PaCO_2$, PaO_2, HCO_3, ESS, and FOSQ improved in BVS and CPAP treatments, without significant differences between the groups. SF36 mental component improved only in the CPAP group. There was no statistical significance in the different groups for the outcome SF36 physical component. Only in the BVS group, was there a significant weight loss. Compliance was the same for both treatments.
Piper, 2008	18/18	47(13)/52(17)	Patients with OHS without severe nocturnal hypoxemia	I- BVS S IPAP 16 ± 2 cm H_2O EPAP 10 ± 2 cm H_2O C- CPAP P 14 ± 3 cm H_2O	Three months	$PaCO_2$, HCO_3, ESS, SF36, weight loss, compliance	$PaCO_2$, HCO_3, ESS and weight loss improved in both groups, with no difference between groups. There was no difference in SF36 between the two groups. There was no difference in compliance for both treatments.

BVS vs. AVAPS							
Murphy, 2012	25/25	56(11)/53(9)	Super obese patients with OHS	I- BVS ST (standard) IPAP 25 ± 3 cm H_2O EPAP 10 ± 2 cm H_2O C- BVS ST AVAPS Vte 657 ± 96 ml EPAP 9 ± 1 cm H_2O	Three months	$PaCO_2$, PaO_2, HCO_3, $PtcCO_2$, and SRI	Improvements in $PaCO_2$, HCO_3, and SRI were observed in both groups, but without a between-group difference. There was no significant change in PaO_2 in both groups. There was no inter-group difference in $PtcCO_2$.
Storre, 2006	10/10 (crossover trial)	53.5(11.7)/53.5 (11.7)	Patients with OHS and OSA who failed to CPAP therapy.	I- BVS ST (standard) IPAP 15 ± 2 cm H_2O EPAP 6 ± 1 cm H_2O C - BVS ST AVAPS Vte: 608 ± 134 ml IPAP 16 ± 4 cm H_2O EPAP 6 ± 1 cm H_2O	Six weeks	$PaCO_2$, PaO_2, HCO_3, $PtcCO_2$, and SRI	$PaCO_2$ and HCO_3 decreased in BVS with AVAPS group only (compared with baseline), but without statistical significance when compared to the BVS group. BVS with AVAPS mode provided a more efficient reduction in $PtcCO_2$ than BVS; however, this reduction did not provide further clinical benefits regarding sleep quality and SRI compared to standard BVS. There was no significant change in PaO_2 in both groups. SRI improved in both groups.

Age and Parameters are presented as mean (SD). AVAPS, average volume-assured pressure support; HCO_3, blood bicarbonate; BVS, bilevel ventilatory support; C, comparator; CPAP, continuous positive airway pressure; EPAP, expiratory positive airway pressure; ESS, Epworth Sleepiness Scale; FOSQ, Functional Outcomes of Sleep Questionnaire; I, Intervention; IPAP, inspiratory positive airway pressure; N, number; OHS, obesity hypoventilation syndrome; OSA, obstructive sleep apnea; P, pressure; $PaCO_2$, arterial partial pressure of carbon dioxide; PaO_2, arterial partial pressure of oxygen; $PtcCO_2$, transcutaneous pressure of carbon dioxide; S, spontaneous mode; SF 36, Medical Outcome Survey Short Form 36; SRI, severe respiratory insufficiency questionnaire; ST, spontaneous timed mode; TST < 90%, total sleep time with oxygen saturation < 90%; Vte, estimated tidal volume.

3.3.8. Functional Outcomes of Sleep Questionnaire

Two studies comparing BVS to lifestyle counseling assessed FOSQ [6,19], evidencing an improvement in the BVS group when compared to lifestyle counseling (6.33; 95% CI 1.78 to 10.88; $I^2 = 0\%$) (Fig. 10). Based on the GRADE approach, the quality of the evidence for this outcome was considered low (Table 3).

3.3.9. Severe respiratory insufficiency questionnaire

Two studies comparing BVS to BVS with AVAPS assessed SRI [22,23], without any difference between groups (−3.15; 95% CI −9.64 to 3.35; $I^2 = 0\%$) (Fig. 11). Based on the GRADE approach, the quality of the evidence for this outcome was considered very low (Table 3).

3.3.10. Treatment compliance

Compliance was evaluated in three studies comparing BVS to CPAP [6,20,21], showing no inter-group difference (0.11; 95% CI −0.46 to 0.67; $I^2 = 0\%$) (Fig. 12). Based on the GRADE approach, the quality of the evidence for this outcome was considered moderate (Table 3).

3.3.11. Weight loss

Four studies assessed this outcome. In two studies comparing BVS to lifestyle counseling [6,19] (0.39; 95% CI −2.56 to 3.35; $I^2 = 57\%$) and in three studies comparing BVS to CPAP [6,20,21] (−0.72; 95% CI −2.38 to 0.95; $I^2 = 0\%$), there were no inter-group differences (Fig. 13). Based on the GRADE approach, the quality of the evidence for this outcome was considered low compared to BVS versus lifestyle counseling and moderate compared to BVS versus CPAP (Table 3).

4. Discussion

In this systematic review, we found that BVS was associated with significant improvement in $PaCO_2$, PaO_2, HCO_3, the percentage of TST<90%, ESS and FOSQ when compared to lifestyle counseling in patients with OHS. However, when BVS was compared to other PAP modalities, there was no evidence of the superiority of one over the other in the analyzed outcomes.

Our study is the first meta-analysis comparing different treatment modalities in patients with OHS. The findings of this research are of great clinical value since they reinforce the need for treating sleep disorders in patients with OHS. An important limitation that should be considered when evaluating the results of this meta-analysis is the heterogeneity of the included patients; some patients presented mild OSA associated with OHS [19] while others presented severe OSA. Moreover, in Masa et al. [6,19], all patients received an orientation about lifestyle modification: 1000 calorie diet, regular sleep habits, exercise, and avoiding sedatives, stimulants, alcohol, and smoking tobacco; on the other hand, in Borel et al. [18], only the lifestyle counseling group received these orientations: exposure about diet, exercises and modification of lifestyle in general.

An individual analysis of the study's limitations may help one to understand some findings of this meta-analysis. The results of Piper et al. [20], for example, cannot be applied to all patients with OHS, since the trial excluded OHS patients with severe persistent hypoventilation during initial CPAP titration. Consequently, it is not possible to determine if these severe patients would have a complete response to CPAP therapy [31]. Another limitation is the ventilation mode employed since S mode permits inspiratory trigger failure or central apneas. Although ST mode can induce some patient-ventilator asynchronies, the backup rate reduced the number of central and mixed respiratory events compared to spontaneous ventilation in a randomized study [32]. It cannot be asserted that the fact that our study did not demonstrate differences between PAP modes could not be due to the use of S mode.

Table 2
Risk of bias of included studies.

	Adequate sequence generation	Allocation concealment	Blinding of patients	Blinding of outcome assessors	Description of losses and exclusions	Intention-to-treat analysis
BVS *versus* Lifestyle counseling						
Borel, 2012	Yes	Yes	No	Yes	Yes	No
Masa, 2015	Yes	No	No	No	Yes	Yes
Masa, 2016	Yes	No	No	No	Yes	Yes
BVS *versus* CPAP						
Howard, 2017	Yes	Yes	Yes	Yes	Yes	No
Masa, 2015	Yes	No	No	No	Yes	Yes
Piper, 2008	Yes	Yes	No	Yes	Yes	Yes
BVS *versus* AVAPS						
Murphy, 2012	No	No	Yes	No	Yes	No
Storre, 2006	No	No	No	No	Yes	No

Table 3
Quality of evidence using The GRADE approach.

Certainty assessment					N		Absolute	Certainty
N (RCTs)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Intervention	Comparation	(95% CI)	
$PaCO_2$ - BVS vs Lifestyle counseling								
3	Not Serious	Not Serious	Not Serious	Not Serious	130	134	2.9 (95% CI 4.28–1.52)	HIGH
$PaCO_2$ - BVS vs CPAP								
3	Not Serious	Not Serious	Not Serious	Serious[a]	118	129	1.16 (95% CI 2.93–0.61)	MODERATE
$PaCO_2$ - BVS vs AVAPS								
2	Serious[b]	Serious[c]	Not Serious	Serious[a]	35	35	1.96 (95% CI 1.87–5.78)	VERY LOW
PaO_2 - BVS vs Lifestyle counseling								
3	Not Serious	Not Serious	Not Serious	Serious[a]	130	134	2.89 (95% CI 0.33–5.46)	MODERATE
PaO_2 - BVS vs CPAP								
2	Not Serious	Not Serious	Not Serious	Serious[a]	100	111	0.26 (95% CI 3.4–2.88)	MODERATE
PaO_2 - BVS vs AVAPS								
2	Serious[b]	Not Serious	Not Serious	Very Serious[a]	35	35	2.6 (95% CI 3.22–8.43)	VERY LOW
HCO_3 - BVS vs Lifestyle counseling								
3	Not Serious	Not Serious	Not Serious	Not Serious	130	134	2.55 (95% CI 3.28–1.81)	HIGH
HCO_3 - BVS vs CPAP								
3	Not Serious	Not Serious	Not Serious	Serious[a]	118	129	0.18 (95% CI 1.15–0.79)	MODERATE
HCO_3 - BVS vs AVAPS								
2	Serious[b]	Not Serious	Not Serious	Not Serious	35	35	0.68 (95% CI 0.68–2.03)	MODERATE
% TST < 90% - BVS vs Lifestyle Counseling								
3	Not Serious	Not Serious	Not Serious	Very Serious[a]	130	134	30.35 (95% CI 37.98–23.12)	LOW
$PtCO_2$ - BVS vs. AVAPS								
2	Serious[b]	Not Serious	Not Serious	Very Serious[a]	35	35	2.06 (95% CI 3.02–7.14)	VERY LOW
ESS - BVS vs. Lifestyle counseling								
3	Serious[b]	Serious[d]	Not Serious	Serious[a]	130	134	2.52 (95%CI 4.16–0.88)	VERY LOW
ESS - BVS vs. CPAP								
3	Serious[b]	Not Serious	Not Serious	Serious[a]	118	129	0.74 (95% CI 2.13–0.66)	LOW
SF-36 physical - BVS vs. Lifestyle counseling								
2	Serious[b]	Not Serious	Not Serious	Serious[a]	111	116	1.77 (95% CI 0.42–3.96)	LOW
SF-36 physical - BVS vs. CPAP								
3	Serious[b]	Very Serious[c]	Not Serious	Serious[a]	118	129	1.06 (95% CI 3.88–5.99)	VERY LOW
SF-36 mental - BVS vs lifestyle counseling								
2	Serious[b]	Serious[c]	Not Serious	Very Serious[a]	111	116	2.46 (95% CI 1.91–6.84)	VERY LOW
SF-36 mental - BVS vs. CPAP								
2	Serious[b]	Serious[d]	Not Serious	Very Serious[a]	100	111	2.16 (95% CI 6.02–1.7)	VERY LOW
FOSQ - BVS vs. Lifestyle counseling								
2	Serious[b]	Not Serious	Not Serious	Serious[a]	111	116	6.33 (95% CI 1.78–10.88)	LOW
SRI - BVS vs. AVAPS								
2	Very Serious[b]	Not Serious	Not Serious	Serious[a]	35	35	3.15 (95% CI 9.64–3.35)	VERY LOW
Compliance - BVS vs. CPAP								
3	Not Serious	Not Serious	Not Serious	Serious[a]	118	129	0.11 (95% CI 0.46–0.67)	MODERATE
Weight loss - BVS vs. Lifestyle counseling								
2	Not Serious	Serious[d]	Not Serious	Serious[a]	111	116	0.39 (95% CI 2.56–3.35)	LOW
Weight loss - BVS vs. CPAP								
3	Not Serious	Not Serious	Not Serious	Serious[a]	118	129	0.72 (95% CI 2.38–0.95)	MODERATE

AVAPS, average volume-assured pressure support; BVS, bilevel ventilatory support; CI, Confidence Interval; CPAP, continuous positive airway pressure; ESS, Epworth Sleepiness Scale; FOSQ, Functional Outcomes of Sleep Questionnaire; N, number; PaCO2, arterial partial pressure of carbon dioxide; PaO2, arterial partial pressure of oxygen; PtcCO2, transcutaneous pressure of carbon dioxide; RCT, Randomized Clinical Trial; SF 36, Medical Outcome Survey Short Form 36; SRI, severe respiratory insufficiency questionnaire; vs., versus.
Explanations: a. Large confidence interval (CI); b. Some studies do not report whether there was allocation concealment, whether there was blinding of patients and outcome assessors and whether the analysis was performed by intention to treat; c. Moderate heterogeneity (30–50%); d. High heterogeneity (over 50%).

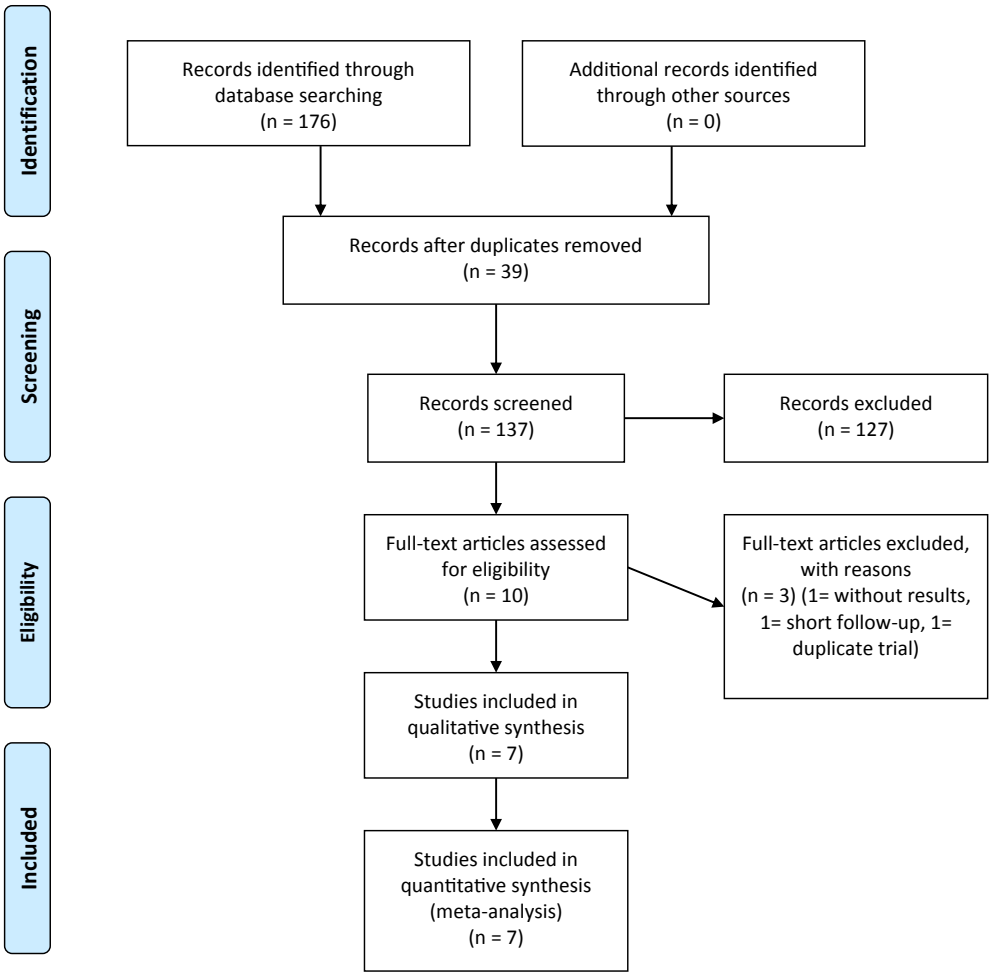

Fig. 1. Flow diagram of included studies.
From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta- *A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097, **For more information, visit www.prisma-statement.org.**

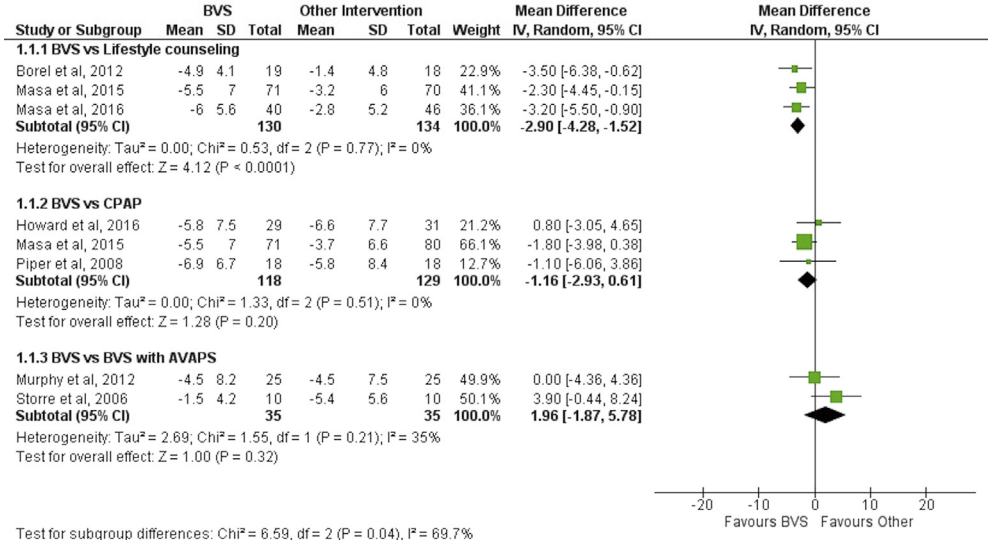

Fig. 2. Comparison between Bilevel Ventilatory Support (BVS) *versus* lifestyle counseling and BVS *versus* other Positive Airway Pressure (PAP) modalities regarding $PaCO_2$.

Masa et al. [6] is a very noteworthy study since it had a larger sample size than the other randomized trials and did not exclude patients with CPAP-resistant hypoxemia. Their study also shows that nocturnal efficacy was similar in BVS and CPAP groups, even regarding oxygen level, suggesting that the mechanisms underlying CPAP-resistant hypoxemia also apply to BVS treatment. The results

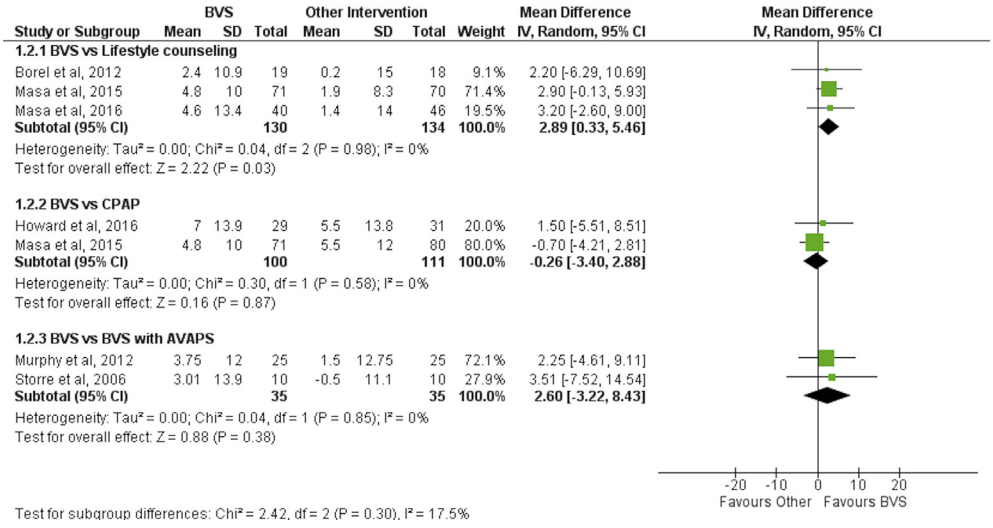

Fig. 3. Comparison between Bilevel Ventilatory Support (BVS) *versus* lifestyle counseling and BVS *versus* other Positive Airway Pressure (PAP) modalities regarding PaO_2.

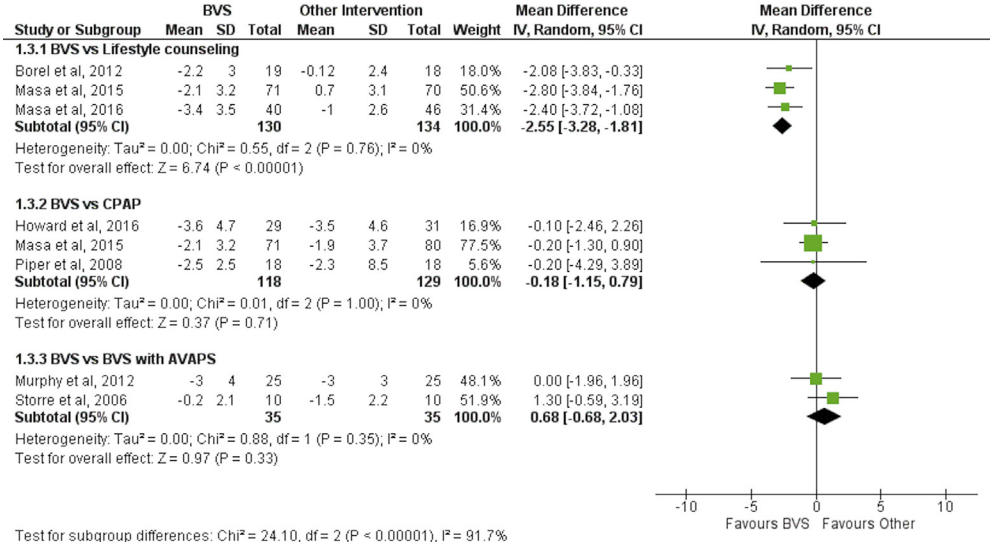

Fig. 4. Comparison between Bilevel Ventilatory Support (BVS) *versus* lifestyle counseling and BVS *versus* other Positive Airway Pressure (PAP) modalities regarding HCO_3.

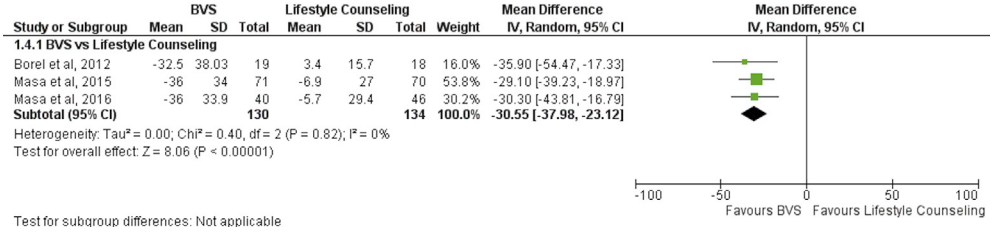

Fig. 5. Comparison between Bilevel Ventilatory Support (BVS) *versus* lifestyle counseling regarding Total Sleep Time with Oxygen Saturation <90%.

of Howard et al. [21] help to clarify pending issues in the Piper study [20]. These authors suggest that CPAP can be safely used to treat all OHS stages following initial stabilization, with careful monitoring, since it is similar to BVS in improving ventilatory parameters and symptoms after three months of treatment (regardless of the employed mode, S or ST). However, it should be noted that the majority of the included population had severe OSA. Thus, it is possible that patients with OHS and milder OSA may respond differently to CPAP in comparison to BVS since recent trials have shown that those with severe OSA would have a better response to CPAP than patients with mild-to-moderate OSA.

New ventilatory modes have been presented with the aim of optimizing the treatment of patients with ventilatory dysfunction. The concept that the use of AVAPS mode would be more effective in OHS patients is based on the fact that, conceptually, BVS is not able to maintain adequate ventilation during the changes in pulmonary

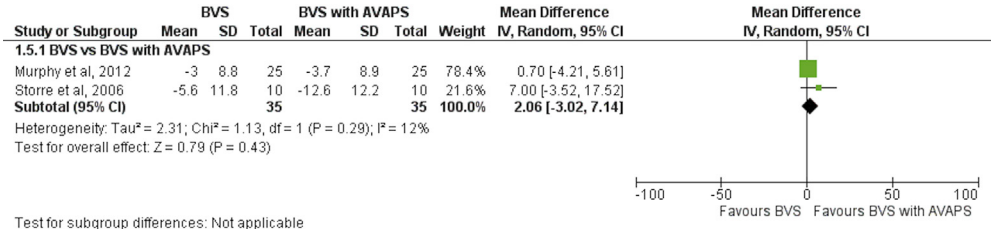

Fig. 6. Comparison between Bilevel Ventilatory Support (BVS) *versus* BVS with Average Volume Assured Pressure Support (AVAPS) regarding Transcutaneous Pressure of Carbon Dioxide ($PtcCO_2$).

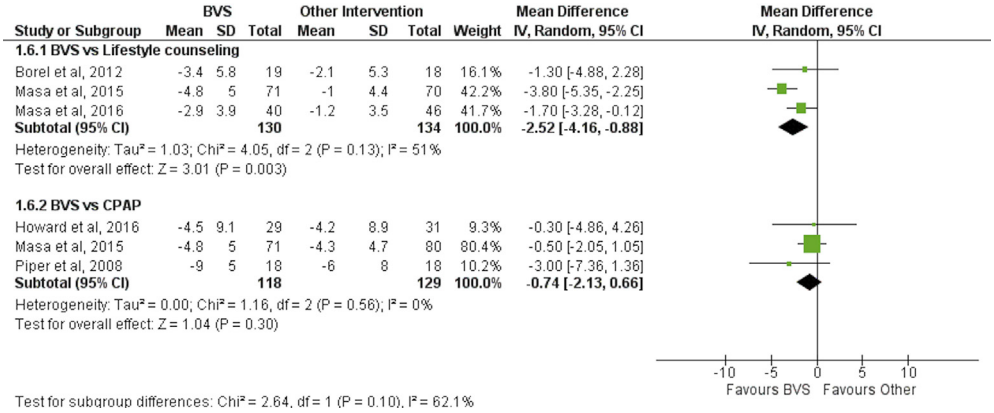

Fig. 7. Comparison between Bilevel Ventilatory Support (BVS) *versus* lifestyle counseling and BVS *versus* Continuous Positive Airway Pressure (CPAP) regarding Epworth Sleepiness Scale (ESS).

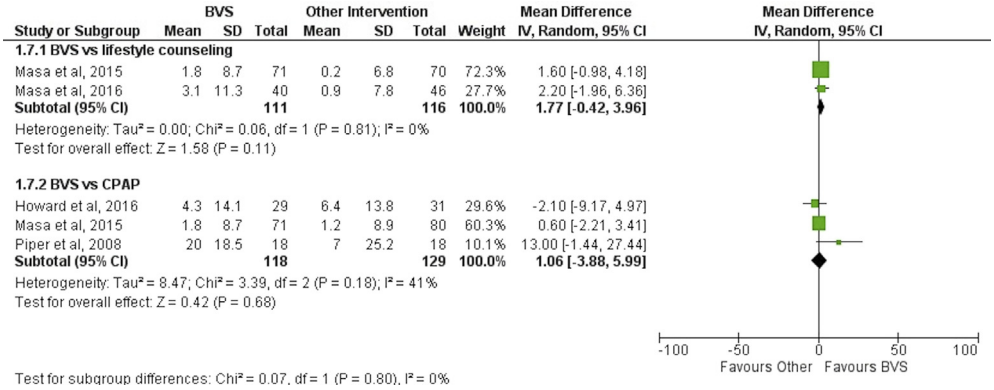

Fig. 8. Comparison between Bilevel Ventilatory Support (BVS) *versus* lifestyle counseling and BVS *versus* Continuous Positive Airway Pressure (CPAP) regarding Medical Outcome Survey Short Form (SF36) – Physical Component.

mechanics that occur throughout sleep. Thus, an auto-titrating hybrid ventilatory mode that targets a pre-set volume might be more effective [22,33]. The data analysis of the two studies included in this meta-analysis that compared standard BVS and BVS with AVAPS found no differences between different modalities of noninvasive ventilation in any of the analyzed outcomes. While, current evidence does not support any significant benefits of AVAPS mode over fixed pressure BVS, it may be useful in selected cases [34].

Previous studies suggest BVS with AVAPS provided enhanced nocturnal ventilatory control with a greater reduction in $PtcCO_2$ during ventilation using AVAPS mode compared to standard BVS [23,24]. These studies used a ventilator setup that favored higher levels of pressure of support delivered in an AVAPS ventilation arm resulting in greater carbon dioxide clearance. In contrast, Murphy et al. [22] did not show this superiority of AVAPS mode, probably because they used a titration protocol to minimize the differences between the groups.

This review and meta-analysis has some limitations. The literature review has revealed just a few RCTs comparing different treatment modalities for OHS patients, reinforcing the need for new studies that should take into account the heterogeneity of this population. The follow-up of included studies ranges between 6 and 12 weeks, which may be a short time in which to evaluate important outcomes. Although data suggests that a four-week period may be sufficient to achieve the full benefits of therapy with regard to changes in blood gases [35,36], outcomes related to sleep quality and quality of life may require a longer period to show full effects. Furthermore, there is heterogeneity between patients included in this study, with a large difference in age and also in OHS and OSA severity. Another significant question is the different

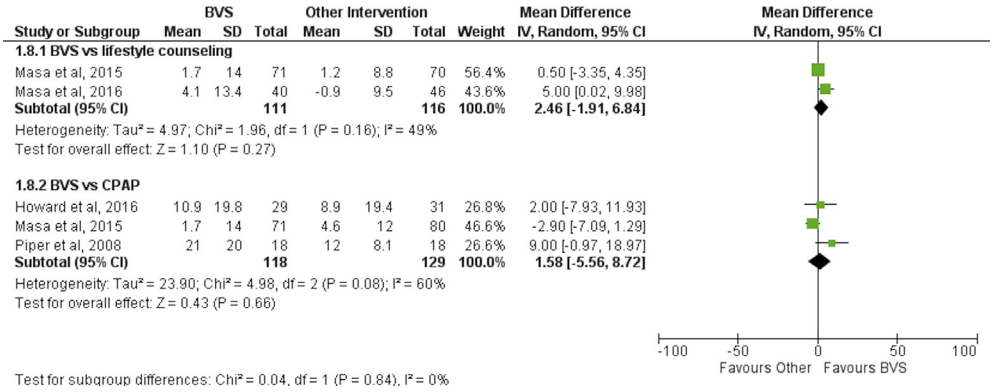

Fig. 9. Comparison between Bilevel Ventilatory Support (BVS) *versus* lifestyle counseling and BVS *versus* other Positive Airway Pressure (PAP) modalities regarding Medical Outcome Survey Short Form (SF36) – Mental Component.

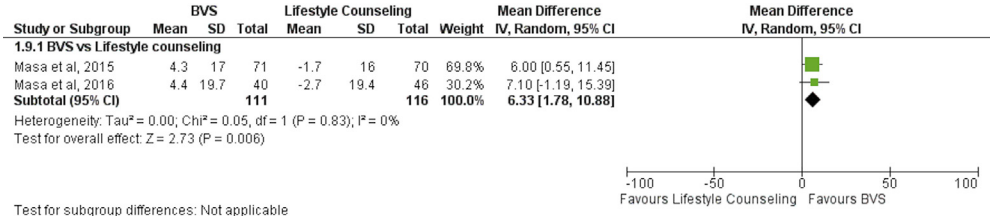

Fig. 10. Comparison between Bilevel Ventilatory Support (BVS) *versus* lifestyle counseling regarding Functional Outcomes of Sleep Questionnaire (FOSQ).

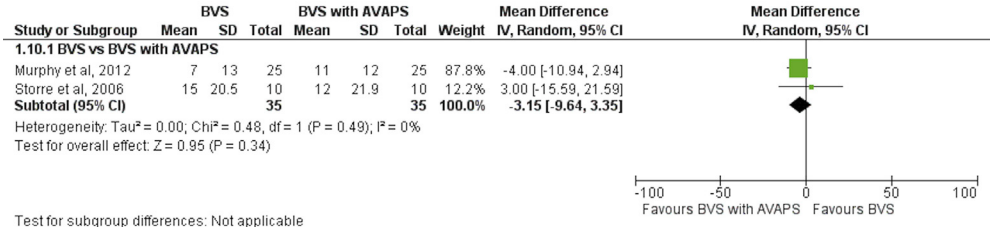

Fig. 11. Comparison between Bilevel Ventilatory Support (BVS) *versus* BVS with Average Volume Assured Pressure Support (AVAPS) regarding Severe Respiratory Insufficiency Questionnaire (SRI).

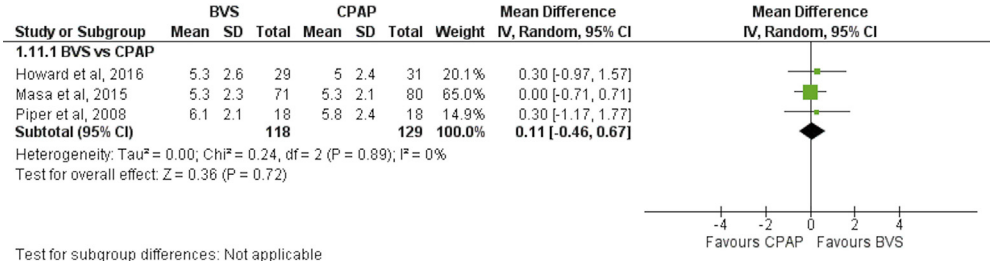

Fig. 12. Comparison between Bilevel Ventilatory Support (BVS) *versus* Continuous Positive Airway Pressure (CPAP) regarding compliance to treatment.

titration models used in the reviewed studies since there is not a single method used to perform a PAP titration.

The big challenge is to know the best form of PAP for a particular patient, since there is a wide heterogeneity of patients with OHS, and each of these patients will require adapted management depending on the severity of his or her disease. The concept supporting BVS as a treatment of OHS comes from open studies [37,38]. However, the majority of patients with OHS appear to respond to CPAP and, in this subgroup, both CPAP and BVS seem to be equally effective in improving the analyzed outcomes. Meanwhile, some patients, especially those with OHS without associated severe OSA, may continue with sleep hypoventilation and diurnal hypercapnia, showing severe oxygen desaturation on CPAP and requiring ventilatory support. This study is the first meta-analysis discussing different modalities of treatment for patients with OHS. Furthermore, this study helps to clarify the best PAP mode for different patients and allows the clinician to initiate a lower cost therapy with safety since there is a strict follow-up. Finally, we do not forget that the success of any treatment is based on a multidisciplinary approach, since the

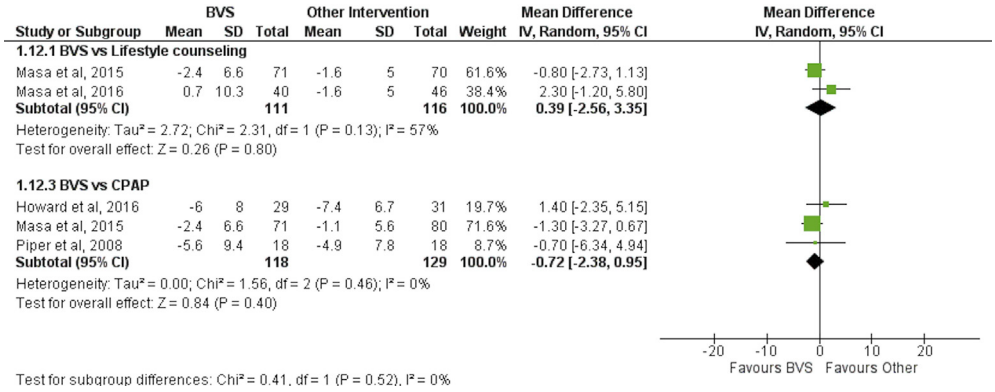

Fig. 13. Comparison between Bilevel Ventilatory Support (BVS) *versus* lifestyle counseling and BVS *versus* Continuous Positive Airway Pressure (CPAP) regarding weight loss.

management of this complex condition includes treating the obesity, encouraging the patients to perform physical activities according to their capacity, and managing the cardiometabolic comorbidities [39–41].

5. Conclusion

This systematic review with meta-analysis suggests that treatment using BVS therapy is superior to lifestyle counseling since it provides improvements in gas exchange, sleepiness, and quality of life. Different PAP modalities appear to be equally effective in improving outcomes. However, larger and long-term comparative studies are necessary to confirm these findings.

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Conflicts of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2018.09.018.

Appendix. Literature search strategy used for the MEDLINE database

#1	Search (“Obesity Hypoventilation Syndrome”[Mesh] OR “Obesity Hypoventilation Syndrome” OR “Hypoventilation Syndrome, Obesity” OR “Syndrome, Obesity Hypoventilation” OR “Pickwickian Syndrome” OR “Syndrome, Pickwickian” OR “Obesity-Hypoventilation Syndrome”)
#2	Search (“Positive-Pressure Respiration”[Mesh] OR “Positive-Pressure Respiration” OR “Positive Pressure Respiration” OR “Positive-Pressure Respirations” OR “Respiration, Positive-Pressure” OR “Respirations, Positive-Pressure” OR “Positive-Pressure Ventilation” OR “Positive Pressure Ventilation” OR “Positive-Pressure Ventilations” OR “Ventilation, Positive-Pressure” OR “Ventilations, Positive-Pressure” OR “Positive End-Expiratory Pressure” OR “End-Expiratory Pressure, Positive” OR “End-Expiratory Pressures, Positive” OR “Positive End Expiratory Pressure” OR “Positive End-Expiratory Pressures” OR “Pressure, Positive End-Expiratory” OR “Pressures, Positive End-Expiratory” OR “Noninvasive Ventilation”[Mesh] OR “Noninvasive Ventilation” OR “Noninvasive Ventilations” OR “Ventilation, Noninvasive” OR “Ventilations, Noninvasive” OR “Non-Invasive Ventilation” OR “Non-Invasive Ventilations” OR “Ventilation, Non-Invasive” OR “Ventilations, Non-Invasive” OR “Non Invasive Ventilation” OR “Non Invasive Ventilations” OR “Ventilation, Non Invasive” OR “Ventilations, Non Invasive” OR “Continuous Positive Airway Pressure”[Mesh] OR “Continuous Positive Airway Pressure” OR “CPAP Ventilation” OR “Ventilation, CPAP” OR “Biphasic Continuous Positive Airway Pressure” OR “Bilevel Continuous Positive Airway Pressure” OR “Nasal Continuous Positive Airway Pressure” OR “nCPAP Ventilation” OR “Ventilation, nCPAP” OR “Airway Pressure Release Ventilation” OR “APRV Ventilation Mode” OR “APRV Ventilation Modes” OR “Ventilation Mode, APRV” OR “Ventilation Modes, APRV”)
#3	Search ((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial [pt] OR clinical trials[mh] OR (“clinical trial”[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR (“latinsquare”[tw]) OR placebos[mh] OR placebo*[tw] OR random* [tw] OR research design[mh:noexp] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control*[tw] OR prospective*[tw] OR volunteer*[tw]) NOT (animal[mh] NOT human [mh]))
#4	Search #1 AND #2 AND #3

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