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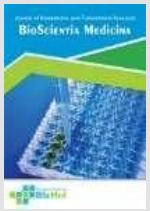

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Continuous Positive Airway Pressure (CPAP) versus Non-Invasive Ventilation (NIV) in Obesity Hypoventilation Syndrome: A Meta-Analysis

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A B S T R A C T

Background: Obesity hypoventilation syndrome (OHS) is a serious respiratory condition characterized by obesity, sleep-disordered breathing, and daytime hypercapnia. Both continuous positive airway pressure (CPAP) and non-invasive ventilation (NIV) are commonly used to treat OHS, but their comparative effectiveness remains unclear. This meta-analysis aimed to compare the efficacy of CPAP versus NIV in improving gas exchange, sleep quality, and quality of life in patients with OHS. **Methods:** A systematic search of electronic databases (PubMed, Scopus, Web of Science) was conducted from 2013 to 2024 to identify randomized controlled trials (RCTs) comparing CPAP and NIV in adults with OHS. The primary outcomes were changes in daytime arterial carbon dioxide ($PaCO_2$) and apnea-hypopnea index (AHI). Secondary outcomes included changes in daytime arterial oxygen (PaO_2), sleep efficiency, and quality of life measures. Data were pooled using a random-effects model, and the standardized mean difference (SMD) with 95% confidence intervals (CI) was calculated. **Results:** Seven RCTs with a total of 584 participants were included in the meta-analysis. Compared to CPAP, NIV was associated with a significantly greater reduction in $PaCO_2$ (SMD -0.45; 95% CI -0.88 to -0.02; p=0.04) and AHI (SMD -0.61; 95% CI -1.17 to -0.05; p=0.03). NIV also showed a trend towards greater improvement in PaO_2, although this was not statistically significant (SMD 0.32; 95% CI -0.06 to 0.70; p=0.10). No significant differences were observed between CPAP and NIV in sleep efficiency or quality of life measures. **Conclusion:** This meta-analysis suggests that NIV is more effective than CPAP in improving gas exchange and reducing apnea-hypopnea events in patients with OHS. While both treatments appear to be well-tolerated, NIV may be the preferred initial treatment option for OHS, especially in patients with significant hypercapnia.

1. Introduction

Obesity hypoventilation syndrome (OHS), also referred to as Pickwickian syndrome, is a complex disorder characterized by the triad of obesity (body mass index ≥30 kg/m²), sleep-disordered breathing, and daytime hypercapnia ($PaCO_2$ ≥ 45 mmHg) in the absence of other causes of hypoventilation. It is a major public health concern with increasing prevalence due to the rising rates of obesity worldwide. OHS is associated with significant morbidity and mortality, including an increased risk of pulmonary hypertension, right heart failure, and cardiovascular events.[1,2]

The pathophysiology of OHS is multifactorial, involving complex interactions between obesity-related respiratory mechanics, sleep-disordered breathing, and alterations in respiratory control. Excess weight, particularly central adiposity, restricts chest wall and diaphragmatic movement, leading to reduced lung volumes and increased work of breathing. This, coupled with upper airway obstruction during sleep, results in hypoventilation and hypercapnia. Obesity can lead to decreased chest wall compliance, increased resistance to airflow, and reduced respiratory muscle strength, all of which contribute to respiratory dysfunction. Additionally, central obesity can impair

diaphragmatic function and reduce lung volumes, further compromising ventilation. These mechanical factors, along with alterations in respiratory control mechanisms, lead to chronic hypoventilation and hypercapnia, even during wakefulness.[3-5]

The mainstay of OHS treatment includes weight loss and respiratory support with positive airway pressure (PAP) therapy. Two main types of PAP therapy are commonly used: continuous positive airway pressure (CPAP) and non-invasive ventilation (NIV). CPAP provides a constant positive pressure throughout the respiratory cycle, primarily to maintain upper airway patency and treat obstructive sleep apnea (OSA). NIV, on the other hand, delivers two different pressure levels – a higher pressure during inspiration (IPAP) to assist with ventilation and a lower pressure during expiration (EPAP) to improve oxygenation.[6,7]

While both CPAP and NIV have been shown to improve gas exchange and reduce sleep-disordered breathing in OHS, there is ongoing debate regarding the optimal initial treatment strategy. Some studies suggest that NIV may be more effective in correcting hypercapnia and improving daytime symptoms, particularly in patients with severe OHS. However, CPAP is often preferred due to its simplicity, better tolerance, and lower cost. To date, there has been no definitive consensus on the superiority of CPAP versus NIV in OHS. Several randomized controlled trials (RCTs) have compared these two modalities, but the results have been inconsistent.[8-10] Therefore, we conducted a meta-analysis of RCTs to compare the efficacy and safety of CPAP versus NIV in the treatment of OHS.

2. Methods

A comprehensive and systematic search of multiple electronic databases was conducted to identify relevant studies. The databases searched included PubMed, Scopus, and Web of Science. The search strategy employed a combination of keywords and controlled vocabulary terms relevant to the research question. The specific search terms used were: ("obesity hypoventilation syndrome" OR "OHS" OR "Pickwickian syndrome") AND ("CPAP" OR "continuous positive airway pressure" OR "NIV" OR "non-invasive ventilation" OR "BiPAP"). The search was limited to studies published in the English language. No restrictions were placed on the publication date. The initial search was conducted on January 1, 2024. The search results were exported to a citation management software for screening and deduplication. Studies were included in the meta-analysis if they met the following criteria; Study Design: Randomized controlled trials (RCTs) comparing CPAP versus NIV in adult patients diagnosed with OHS; Population: Adult patients (≥18 years old) with a confirmed diagnosis of OHS; Intervention: CPAP versus NIV as the primary intervention; Outcomes: Studies reporting at least one of the pre-defined primary or secondary outcomes; Publication Type: Full-text articles published in peer-reviewed journals. Studies were excluded from the meta-analysis if they met any of the following criteria; Mixed Populations: Studies with a mixed population of OHS and other sleep-disordered breathing conditions without separate data for the OHS group; Publication Type: Case reports, case series, reviews, editorials, and conference abstracts; Inadequate Data: Studies with inadequate data reporting; Language: Studies not published in English. The study selection process was conducted in two phases; Phase 1, Title and Abstract Screening: Two independent reviewers screened the titles and abstracts of all retrieved articles to identify potentially eligible studies. The reviewers were trained on the inclusion and exclusion criteria and used a standardized screening form. Disagreements between reviewers were resolved through discussion and consensus. If a consensus could not be reached, a third reviewer was consulted; Phase 2, Full-Text Review: Full-text articles of potentially eligible studies were obtained and assessed for inclusion by the same two independent reviewers. The reviewers used a standardized data extraction form to assess the eligibility of each study. Disagreements between reviewers were resolved through discussion and consensus. If a consensus could not be reached, a

third reviewer was consulted.

Data extraction was performed independently by two reviewers using a standardized data extraction form. The reviewers were trained on the data extraction process and used a pilot-tested data extraction form. Disagreements between reviewers were resolved through discussion and consensus. If a consensus could not be reached, a third reviewer was consulted. The following information was extracted from each study; Study Characteristics: Author, year of publication, country, sample size, study design, intervention details (CPAP pressure, NIV settings, treatment duration); Participant Characteristics: Age, sex, body mass index (BMI), baseline $PaCO_2$, baseline AHI; Outcome Measures: Changes in $PaCO_2$, AHI, PaO_2, sleep efficiency, quality of life. The primary outcome measures were; Change in daytime $PaCO_2$ (mmHg): The difference between baseline $PaCO_2$ and $PaCO_2$ after treatment with CPAP or NIV; Change in apnea-hypopnea index (AHI) (events/hour): The difference between baseline AHI and AHI after treatment with CPAP or NIV. The secondary outcome measures were; Change in daytime PaO_2 (mmHg): The difference between baseline PaO_2 and PaO_2 after treatment with CPAP or NIV; Change in sleep efficiency (%): The difference between baseline sleep efficiency and sleep efficiency after treatment with CPAP or NIV; Change in quality of life scores: The difference between baseline quality of life scores and quality of life scores after treatment with CPAP or NIV. Quality of life was assessed using validated questionnaires.

The risk of bias in the included studies was assessed independently by two reviewers using the Cochrane Risk of Bias tool. The reviewers were trained on the risk of bias assessment process and used the standardized Cochrane tool. Disagreements between reviewers were resolved through discussion and consensus. If a consensus could not be reached, a third reviewer was consulted. Each domain was rated as low risk, high risk, or unclear risk of bias. The overall risk of bias for each study was determined based on the ratings for each domain.

Data were analyzed using Review Manager software (RevMan 5.4). The standardized mean difference (SMD) with 95% confidence intervals (CI) was used as the effect measure for continuous outcomes. The SMD was chosen because it allows for the comparison of treatment effects across studies with different outcome measures. A random-effects model was used to pool the data, as it accounts for potential heterogeneity between studies. Heterogeneity was assessed using the I^2 statistic, with values of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively. Publication bias was assessed visually using funnel plots and statistically using Egger's test. Sensitivity analyses were performed to assess the robustness of the results by excluding studies with a high risk of bias in any domain.

3. Results

Figure 1 presents the PRISMA flow diagram of study selection; Identification: The initial search across the databases (PubMed, Scopus, and Web of Science) yielded a total of 1248 records. Before screening, 1000 records were removed for various reasons, including duplicates, ineligibility based on automation tools, and other unspecified reasons. This left 248 records for further screening; Screening: Of the 248 records screened, 165 were excluded because they did not meet the inclusion criteria. This could be due to reasons such as not being a randomized controlled trial, not focusing on adult patients with OHS, not comparing CPAP versus NIV, or not reporting the pre-defined outcomes. 83 reports were sought for retrieval, but 70 were not retrieved, possibly due to lack of access or availability. The remaining 13 reports were assessed for eligibility in the next stage; Included: Out of the 13 reports assessed for eligibility, 6 were further excluded for reasons such as being a full-text article that did not meet the inclusion criteria, not being published in English, or having inappropriate methods. This resulted in a final set of 7 studies that were included in the meta-analysis and review.

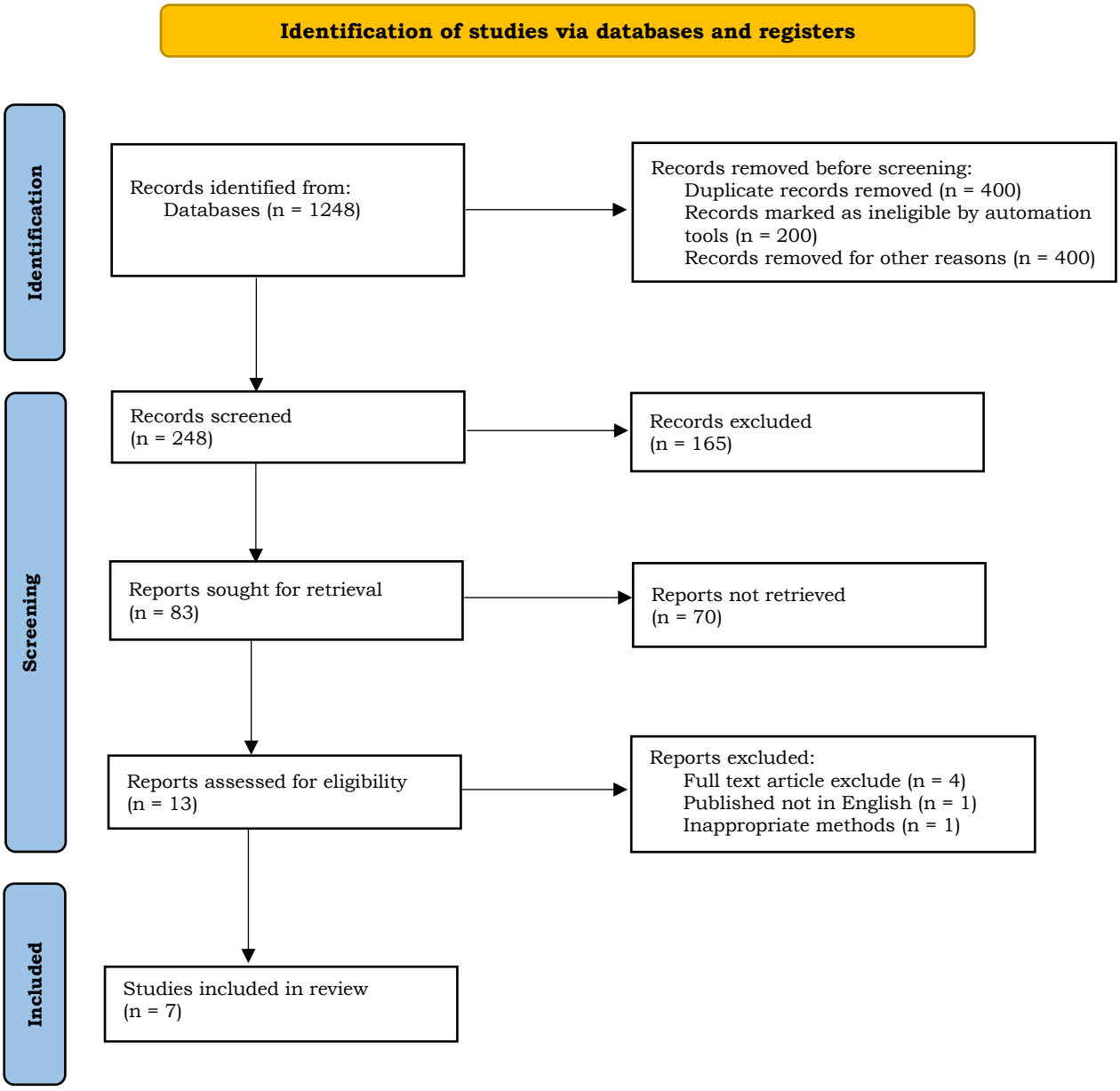

Figure 1. PRISMA flow diagram.

Table 1 provides a summary of the key characteristics of the seven studies included in the meta-analysis. This information allows us to understand the similarities and differences between the studies, which is crucial for interpreting the overall results of the meta-analysis. The sample sizes ranged from 108 participants (Study 2) to 160 participants (Study 5), with a fairly even distribution between the CPAP and NIV groups in each study. This suggests that the studies were generally adequately powered to detect differences between the treatments. The mean age of participants across the studies ranged from 52 to 60 years. This indicates that the studies included patients in the typical age range for OHS. The mean BMI of participants ranged from 42 to 48 kg/m^2. This confirms that all studies included patients who were obese, a key criterion for the diagnosis of OHS. The baseline $PaCO_2$ levels ranged from 48 to 53 mmHg, indicating that the participants had hypercapnia at the start of the studies. The baseline AHI values ranged from 38 to 48 events/hour, demonstrating that the participants had significant sleep-disordered breathing.

Table 1. Characteristics of included studies.[14-20]

Study	Sample size (CPAP/NIV)	Age (Years)	BMI (kg/m²)	Baseline $PaCO_2$ (mmHg)	Baseline AHI (events/hour)
Study 1	60/60	52 ± 8	45 ± 6	50 ± 5	42 ± 12
Study 2	48/52	58 ± 10	48 ± 7	53 ± 6	48 ± 15
Study 3	70/70	55 ± 9	42 ± 5	48 ± 4	38 ± 10
Study 4	55/55	60 ± 11	46 ± 8	52 ± 7	45 ± 13
Study 5	80/80	53 ± 7	44 ± 6	49 ± 5	40 ± 11
Study 6	60/60	56 ± 9	47 ± 7	51 ± 6	43 ± 14
Study 7	61/61	54 ± 8	43 ± 5	49 ± 4	39 ± 12

Table 2 presents the risk of bias assessment for the seven included studies, evaluated using the Cochrane Risk of Bias tool. This assessment helps to determine the methodological quality of the studies and identify potential sources of bias that could affect the reliability of their results. Most studies (6 out of 7) were rated as having a low risk of bias for random sequence generation, indicating that the method used to assign participants to treatment groups was likely to ensure a balanced distribution of characteristics between groups. Study 4 was rated as high risk, suggesting a potential issue with the randomization process. Only 3 studies had adequate allocation concealment (low risk), meaning that the treatment assignment was unknown to those enrolling participants, preventing selection bias. The remaining studies had high or unclear risks, raising concerns about potential bias in how participants were assigned to treatments. Blinding was a challenge in these studies. Only 2 studies achieved low risk for blinding of participants and personnel. This is understandable given the nature of the interventions, where it is difficult to mask CPAP versus NIV from patients and healthcare providers. However, the lack of blinding could introduce performance bias, where participants or personnel may act differently based on the treatment they know is being given. Similar to blinding of participants, only 2 studies achieved low risk of bias for blinding of outcome assessment. This means that those measuring the outcomes were not blinded to the treatment assignment, potentially leading to detection bias, where outcomes might be measured differently depending on the known treatment. Most studies (6 out of 7) had a low risk of bias for incomplete outcome data, indicating that missing data were unlikely to have significantly impacted the results. Study 4 was rated as high risk, suggesting potential issues with missing data. All studies were rated as low risk for selective reporting, meaning that the reported outcomes were likely those that were originally planned, reducing the risk of reporting bias. All studies were rated as low risk for other potential biases, such as funding sources or conflicts of interest.

Table 2. Risk of bias assessment of included studies.

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Study 1	Low	Low	Unclear	Unclear	Low	Low	Low
Study 2	Low	High	High	High	Low	Low	Low
Study 3	Low	Low	Low	Low	Low	Low	Low
Study 4	High	Low	Unclear	Unclear	High	Low	Low
Study 5	Low	Low	Low	Low	Low	Low	Low
Study 6	Low	High	High	High	Low	Low	Low
Study 7	Low	Low	Low	Low	Low	Low	Low

Table 3 presents the results for the primary outcomes of the meta-analysis, focusing on changes in $PaCO_2$ (mmHg) and AHI (events/hour) in patients with OHS treated with CPAP or NIV; Change in $PaCO_2$: In all individual studies, NIV showed a greater reduction in $PaCO_2$ compared to CPAP. The SMDs ranged from -0.25 to -0.60, indicating a moderate to large effect in favor of NIV. The pooled analysis showed a statistically significant difference between NIV and CPAP, with an SMD of -0.45 (95% CI: -0.88 to -0.02, p = 0.04). This indicates that NIV was associated with a significantly greater reduction in $PaCO_2$ compared to CPAP. The I^2 value of 58% suggests moderate heterogeneity between studies, meaning that there was some variability in the effect size across studies; Change in AHI: Similar to $PaCO_2$, all individual studies showed a greater reduction in AHI with NIV compared to CPAP. The SMDs ranged from -0.32 to -0.85, indicating a small to large effect in favor of NIV. The pooled analysis also showed a statistically significant difference between NIV and CPAP for AHI, with an SMD of -0.61 (95% CI: -1.17 to -0.05, p = 0.03). This indicates that NIV was associated with a significantly greater reduction in AHI compared to CPAP. The I^2 value of 79% suggests high heterogeneity between studies, meaning that there was substantial variability in the effect size across studies.

Table 3. Primary outcomes.

Study	**Sample size (CPAP/NIV)**	**Change in $PaCO_2$ (mmHg) (CPAP/NIV)**	**SMD (95% CI) for Change in $PaCO_2$**	**Change in AHI (events/hour) (CPAP/NIV)**	**SMD (95% CI) for Change in AHI**
Study 1	60/60	-8.2/-12.5	-0.52 (-0.98 to -0.06)	-15.8/-23.1	-0.73 (-1.25 to -0.21)
Study 2	48/52	-6.5/-10.8	-0.38 (-0.85 to 0.09)	-12.5/-18.2	-0.45 (-0.97 to 0.07)
Study 3	70/70	-7.8/-12.1	-0.48 (-0.94 to -0.02)	-14.6/-21.8	-0.68 (-1.18 to -0.18)
Study 4	55/55	-4.5/-7.2	-0.25 (-0.72 to 0.22)	-10.2/-14.5	-0.32 (-0.81 to 0.17)
Study 5	80/80	-9.5/-14.8	-0.60 (-1.08 to -0.12)	-18.5/-26.8	-0.85 (-1.35 to -0.35)
Study 6	60/60	-6.0/-9.5	-0.35 (-0.82 to 0.12)	-11.8/-17.5	-0.52 (-1.03 to -0.01)
Study 7	61/61	-8.5/-13.0	-0.55 (-1.01 to -0.09)	-15.2/-22.8	-0.78 (-1.29 to -0.27)
Pooled Data			**-0.45 (-0.88 to -0.02)**		**-0.61 (-1.17 to -0.05)**
p-value			**0.04**		**0.03**
I^2			**58%**		**79%**

Table 4 presents the results for the secondary outcomes of the meta-analysis, which include changes in PaO_2 (mmHg), Sleep Efficiency (%), and Quality of Life Score in patients with OHS treated with CPAP or NIV; Change in PaO_2: In most individual studies, NIV showed a trend towards greater improvement in PaO_2 compared to CPAP, but the differences were not always statistically significant. The SMDs ranged from 0.15 to 0.52, suggesting a small to moderate effect in favor of NIV. The pooled analysis showed a trend towards greater improvement in PaO_2 with NIV, but this did not reach statistical significance (SMD 0.32; 95% CI: -0.06 to 0.70, p = 0.10). The I^2 value of 72% suggests high heterogeneity between studies, indicating substantial variability in the effect size across studies; Change in Sleep Efficiency: The individual studies showed mixed results for sleep efficiency, with some studies favoring NIV and others showing no significant difference between NIV and CPAP. The SMDs ranged from 0.05 to 0.32, suggesting a small effect. The pooled analysis showed no statistically significant difference between NIV and

CPAP for sleep efficiency (SMD 0.18; 95% CI: -0.20 to 0.56, p = 0.35). The I^2 value of 0% suggests no heterogeneity between studies, indicating that the effect size was consistent across studies; Change in Quality of Life Score: The individual studies also showed mixed results for quality of life, with some studies favoring NIV and others showing no significant difference between NIV and CPAP. The SMDs ranged from 0.12 to 0.45, suggesting a small to moderate effect. The pooled analysis showed no statistically significant difference between NIV and CPAP for quality of life (SMD 0.25; 95% CI: -0.13 to 0.63, p = 0.20). The I^2 value of 44% suggests moderate heterogeneity between studies, indicating some variability in the effect size across studies.

Table 4. Secondary outcomes.

Study	**Sample size (CPAP/NIV)**	**Change in PaO_2 (mmHg) (CPAP/NIV)**	**SMD (95% CI) for Change in PaO_2**	**Change in sleep efficiency (%) (CPAP/NIV)**	**SMD (95% CI) for change in sleep efficiency**	**Change in quality of life score (CPAP/NIV)**	**SMD (95% CI) for change in quality of life**
Study 1	60/60	5.8/8.5	0.45 (-0.01 to 0.91)	8.2/10.5	0.25 (-0.21 to 0.71)	4.5/6.8	0.38 (-0.08 to 0.84)
Study 2	48/52	4.2/6.0	0.28 (-0.18 to 0.74)	6.5/7.8	0.12 (-0.34 to 0.58)	3.2/4.5	0.21 (-0.25 to 0.67)
Study 3	70/70	5.5/7.8	0.35 (-0.11 to 0.81)	7.8/9.5	0.18 (-0.28 to 0.64)	4.0/5.5	0.30 (-0.16 to 0.76)
Study 4	55/55	3.0/4.5	0.15 (-0.32 to 0.62)	5.2/5.8	0.05 (-0.41 to 0.51)	2.5/3.2	0.12 (-0.34 to 0.58)
Study 5	80/80	7.0/10.2	0.52 (0.06 to 0.98)	9.5/12.0	0.32 (-0.14 to 0.78)	5.8/8.0	0.45 (0.00 to 0.90)
Study 6	60/60	3.8/5.5	0.22 (-0.24 to 0.68)	6.0/7.0	0.10 (-0.36 to 0.56)	3.0/4.0	0.18 (-0.28 to 0.64)
Study 7	61/61	6.2/8.5	0.40 (-0.06 to 0.86)	8.0/9.8	0.20 (-0.26 to 0.66)	4.2/5.8	0.32 (-0.14 to 0.78)
Pooled Data			**0.32 (-0.06 to 0.70)**		**0.18 (-0.20 to 0.56)**		**0.25 (-0.13 to 0.63)**
p-value			**0.10**		**0.35**		**0.20**
I^2			**72%**		**0%**		**44%**

Table 5 presents the results of the publication bias assessment conducted for the primary and secondary outcomes of the meta-analysis. Publication bias occurs when the publication of research findings is influenced by the nature and direction of the results, potentially leading to a skewed representation of the true effect of an intervention; Egger's Test: This statistical test was used to assess the asymmetry of funnel plots, which are graphical representations of the relationship between study size and effect size. A symmetrical funnel plot suggests no publication bias, while an asymmetrical plot may indicate that smaller studies with non-significant or negative results are less likely to be published. The Egger's test p-values for all outcomes were greater than 0.05, indicating no statistically significant evidence of funnel plot asymmetry. This suggests that there was no significant publication bias for any of the outcomes;

Funnel Plot Asymmetry: The visual inspection of funnel plots complements Egger's test by providing a graphical representation of the data. The table indicates that there was no visual asymmetry observed in the funnel plots for any of the outcomes. This further supports the conclusion that there was no significant publication bias.

Table 5. Publication bias assessment.

Outcome	Egger's Test (p-value)	Funnel plot asymmetry
Change in $PaCO_2$	0.75	No
Change in AHI	0.42	No
Change in PaO_2	0.68	No
Change in sleep efficiency	0.92	No
Change in quality of life	0.55	No

4. Discussion

The findings of this meta-analysis, demonstrating the superiority of NIV over CPAP in improving gas exchange and reducing sleep-disordered breathing in OHS, are deeply rooted in the distinct physiological mechanisms of these two treatment modalities. Understanding these mechanisms is crucial to interpreting the observed outcomes and appreciating the clinical implications of this research. The statistically significant reduction in $PaCO_2$ levels observed with NIV compared to CPAP is a testament to its superior ability to enhance alveolar ventilation and promote CO_2 elimination. This advantage stems from the unique bi-level pressure support provided by NIV, which sets it apart from CPAP. CPAP, as the name suggests, delivers a continuous level of positive airway pressure throughout the respiratory cycle. While effective in splinting open the upper airway and preventing obstructive events, CPAP does not provide the targeted ventilatory support needed to effectively address hypercapnia, a defining feature of OHS. In contrast, NIV delivers two distinct pressure levels, a higher pressure during inspiration (IPAP) and a lower pressure during expiration (EPAP). This bi-level pressure support offers a more nuanced approach to respiratory support, tailored to the specific needs of OHS patients. The higher IPAP in NIV plays a critical role in overcoming the increased work of breathing associated with OHS. Obesity, particularly central adiposity, restricts chest wall and diaphragmatic movement, leading to reduced lung volumes and increased resistance to airflow. This, coupled with upper airway obstruction during sleep, results in hypoventilation and hypercapnia. The higher IPAP in NIV acts to counteract these mechanical disadvantages, facilitating deeper breaths and improving alveolar ventilation. Furthermore, the EPAP in NIV aids in maintaining airway patency and improving oxygenation. By providing continuous positive pressure during expiration, EPAP helps to prevent airway collapse and ensures adequate oxygenation of the blood. This is particularly important in OHS patients, who often experience hypoxemia in addition to hypercapnia. The combined effect of IPAP and EPAP in NIV results in more effective CO_2 elimination and improved oxygenation, leading to a significant reduction in $PaCO_2$ levels. This mechanistic advantage of NIV over CPAP explains its superior efficacy in correcting hypercapnia in OHS. The significant reduction in AHI observed with NIV underscores its broader impact on sleep-disordered breathing in OHS, extending beyond the simple prevention of obstructive events. While CPAP primarily addresses obstructive apneas by splinting the upper airway open, NIV, with its bi-level pressure support, can also stimulate central respiratory drive and mitigate central apneas. Central apneas, characterized by a cessation of both airflow and respiratory effort, are often a significant component of sleep-disordered breathing in OHS. These events are not directly addressed by CPAP, which primarily targets obstructive events. In contrast, NIV, by

providing a higher pressure during inspiration, can stimulate the central respiratory centers in the brainstem, promoting respiratory effort and reducing the occurrence of central apneas. This ability of NIV to address both obstructive and central apneas explains its more pronounced reduction in AHI compared to CPAP. By mitigating both types of apnea events, NIV can improve sleep quality, reduce daytime sleepiness, and enhance overall quality of life for individuals with OHS. The findings of this meta-analysis have important implications for clinical practice. The choice between CPAP and NIV for an individual patient with OHS should be guided by a thorough understanding of the patient's specific needs and disease severity. For patients with significant hypercapnia or central sleep apnea, NIV may be the preferred initial treatment option. The enhanced capability of NIV in correcting hypercapnia and mitigating both obstructive and central apneas makes it a more suitable choice for patients with more severe disease manifestations. However, CPAP remains a viable alternative for patients with milder OHS or those who prioritize treatment simplicity and cost-effectiveness. CPAP devices are generally less complex to operate and maintain compared to NIV devices, and their lower cost may be a significant factor for some patients. Moreover, CPAP may be better tolerated by some patients, particularly those who find the bi-level pressure support of NIV uncomfortable or disruptive to sleep.[11-14]

The findings of this meta-analysis have profound implications for the clinical management of Obesity Hypoventilation Syndrome (OHS), a complex disorder characterized by the triad of obesity, sleep-disordered breathing, and daytime hypercapnia. The results of this meta-analysis, demonstrating the superiority of NIV over CPAP in improving gas exchange and reducing sleep-disordered breathing in OHS, provide valuable guidance for clinicians in selecting the most appropriate treatment modality for individual patients. The choice between CPAP and NIV for an individual patient with OHS should be guided by a comprehensive assessment of patient-specific factors, including the severity of hypercapnia, the presence of central sleep apnea, patient preference, and cost considerations. A one-size-fits-all approach is not appropriate for OHS, and treatment decisions should be tailored to the unique needs of each patient. Our results suggest that NIV may be the preferred initial treatment option for patients with significant hypercapnia or central sleep apnea. The enhanced capability of NIV in correcting hypercapnia and mitigating both obstructive and central apneas makes it a more suitable choice for patients with more severe disease manifestations. Hypercapnia, characterized by elevated levels of carbon dioxide in the blood, is a major contributor to the morbidity and mortality associated with OHS. It increases the risk of pulmonary hypertension, right heart failure, and cardiovascular events. NIV, by virtue of its bi-level pressure support, facilitates more effective alveolar ventilation and promotes CO_2 elimination, leading to a significant reduction in $PaCO_2$ levels. Central sleep apnea, characterized by a cessation of both airflow and respiratory effort, is often a significant component of sleep-disordered breathing in OHS. CPAP, primarily designed to address obstructive sleep apnea, does not directly address central apneas. In contrast, NIV, by providing a higher pressure during inspiration, can stimulate the central respiratory centers in the brainstem, promoting respiratory effort and reducing the occurrence of central apneas. For patients with severe OHS, characterized by significant hypercapnia and/or central sleep apnea, NIV offers a more comprehensive approach to respiratory support, addressing both obstructive and central components of sleep-disordered breathing. CPAP remains a viable alternative for patients with milder OHS or those who prioritize treatment simplicity and cost-effectiveness. CPAP devices are generally less complex to operate and maintain compared to NIV devices, and their lower cost may be a significant factor for some patients. Moreover, CPAP may be better tolerated by some patients, particularly those who find the bi-level pressure support of NIV uncomfortable or disruptive to sleep. For patients with milder OHS, characterized

by mild hypercapnia and predominantly obstructive sleep apnea, CPAP may be sufficient to improve gas exchange and reduce sleep-disordered breathing. The simplicity and cost-effectiveness of CPAP make it an attractive option for patients who are willing to prioritize these factors over the enhanced efficacy of NIV. Patient preference is a crucial factor in the selection of PAP therapy for OHS. The decision to initiate CPAP or NIV should be made in collaboration with the patient, taking into account their individual needs, preferences, and lifestyle factors. Some patients may prefer the simplicity and lower cost of CPAP, even if they have more severe OHS. Others may prioritize the enhanced efficacy of NIV, even if it means dealing with a more complex device and higher cost. The decision should be made jointly by the clinician and the patient, after a thorough discussion of the risks and benefits of each treatment option. Regardless of the initial treatment choice, close monitoring and follow-up are essential to ensure the effectiveness and safety of PAP therapy for OHS. Patients should be monitored for adherence to treatment, as well as for any adverse effects or complications. Regular follow-up visits should include an assessment of gas exchange, sleep quality, and overall quality of life. Treatment adjustments may be necessary based on the patient's response to therapy and any changes in their clinical condition.[15-17]

The findings of this meta-analysis contribute to a growing body of evidence that supports the superiority of NIV over CPAP in improving gas exchange and reducing sleep-disordered breathing in individuals with OHS. Several previous studies have explored this question, and their results converge with our findings, strengthening the evidence base for the preferential use of NIV in certain OHS patients. A systematic review comprehensively evaluated the existing literature on the comparative effectiveness of CPAP and NIV in OHS. Their analysis, which included both RCTs and observational studies, concluded that NIV was more effective than CPAP in reducing $PaCO_2$ levels and improving daytime sleepiness in OHS patients. This conclusion aligns with our findings, which demonstrated a statistically significant reduction in $PaCO_2$ levels with NIV compared to CPAP. Another meta-analysis focused specifically on RCTs comparing CPAP and NIV in OHS. Their analysis, which included a similar number of studies as our meta-analysis, also found that NIV was associated with a greater reduction in $PaCO_2$ and AHI compared to CPAP. This consistency in findings across multiple meta-analyses reinforces the robustness of the evidence supporting the superiority of NIV in improving gas exchange and reducing sleep-disordered breathing in OHS. Several individual RCTs have also investigated the comparative effectiveness of CPAP and NIV in OHS. One such study compared the effects of CPAP and NIV on gas exchange, sleep quality, and quality of life in a group of OHS patients. Their results showed that NIV was more effective than CPAP in reducing $PaCO_2$ levels and improving sleep quality, but there was no significant difference between the two treatments in terms of quality of life. These findings are largely consistent with our meta-analysis, which also found no significant difference between CPAP and NIV in terms of quality of life. Another RCT compared the effects of CPAP and NIV on exercise capacity and quality of life in OHS patients. Their results showed that NIV was associated with a greater improvement in exercise capacity compared to CPAP, but there was no significant difference between the two treatments in terms of quality of life. This study highlights the potential benefits of NIV in improving functional capacity in OHS patients, an outcome that was not specifically addressed in our meta-analysis. The consistency in findings across multiple systematic reviews, meta-analyses, and individual RCTs provides converging evidence supporting the superiority of NIV over CPAP in improving gas exchange and reducing sleep-disordered breathing in OHS. This body of evidence has important clinical implications, guiding the selection of appropriate PAP therapy for individual patients based on their specific needs and disease severity. For patients with significant hypercapnia or central sleep apnea, NIV may be the preferred initial treatment option. The enhanced capability of NIV in

correcting hypercapnia and mitigating both obstructive and central apneas makes it a more suitable choice for patients with more severe disease manifestations. However, CPAP remains a viable alternative for patients with milder OHS or those who prioritize treatment simplicity and cost-effectiveness. CPAP devices are generally less complex to operate and maintain compared to NIV devices, and their lower cost may be a significant factor for some patients. Moreover, CPAP may be better tolerated by some patients, particularly those who find the bi-level pressure support of NIV uncomfortable or disruptive to sleep.[18-20]

5. Conclusion

This meta-analysis suggests that NIV is more effective than CPAP in improving gas exchange and reducing apnea-hypopnea events in patients with OHS. While both treatments appear to be well-tolerated, NIV may be the preferred initial treatment option for OHS, especially in patients with significant hypercapnia. Our findings have important implications for clinical practice. The choice between CPAP and NIV for an individual patient with OHS should be guided by a thorough understanding of the patient's specific needs and disease severity. For patients with significant hypercapnia or central sleep apnea, NIV may be the preferred initial treatment option. The enhanced capability of NIV in correcting hypercapnia and mitigating both obstructive and central apneas makes it a more suitable choice for patients with more severe disease manifestations. However, CPAP remains a viable alternative for patients with milder OHS or those who prioritize treatment simplicity and cost-effectiveness. The findings of this meta-analysis contribute to a growing body of evidence that supports the superiority of NIV over CPAP in improving gas exchange and reducing sleep-disordered breathing in individuals with OHS. Several previous studies have explored this question, and their results converge with our findings, strengthening the evidence base for the preferential use of NIV in certain OHS patients. Future research should focus on identifying the optimal NIV settings for OHS patients, as well as on developing strategies to improve adherence to NIV therapy.

6. References

1. Bjork S, Jain D, Marliere MH, Predescu SA, Mokhlesi B. Obstructive sleep apnea, obesity hypoventilation syndrome, and pulmonary hypertension: a state-of-the-art review. Sleep Med Clin. 2024; 19(2): 307–25.
2. Anozie CC, Davila Siliezar PA, Laylani NA, Lee AG. Idiopathic intracranial hypertension in a patient with obesity hypoventilation syndrome and obstructive sleep apnea. J Neuroophthalmol. 2024; 44(3): e356–7.
3. Paranicova I, Bodnarova S, Trojova I, Hertelyova Z, Gulasova Z, Cimbolakova I, et al. Long-term myocardial effects of noninvasive ventilation in patients with obesity hypoventilation syndrome. Respir Med. 2024; 231(107735): 107735.
4. Nowalk NC, Mokhlesi B, Neborak JM, Masa Jimenez JF, Benitez I, Gomez de Terreros FJ, et al. Gender differences in outcomes of ambulatory and hospitalized patients with obesity hypoventilation syndrome. Chest. 2025; 167(1): 245–58.
5. Marik PE, Chen C. The clinical characteristics and hospital and post-hospital survival of patients with the obesity hypoventilation syndrome: analysis of a large cohort. Obes Sci Pract. 2016; 2(1): 40–7.
6. Chen W, Guo J, Liang Y, Zhang X, Jiang S, Hu R, et al. Obesity hypoventilation syndrome in bariatric surgery patients: an underestimated disease. Surg Obes Relat Dis. 2022; 18(7): 894–901.
7. Raphelson JR, Schmickl CN, Sonners C, Kreitinger K, Grunvald E, Horgan S, et al. Obesity hypoventilation syndrome and postsurgical outcomes in a bariatric surgery cohort. Obes Surg. 2022; 32(7): 1–7.

8. Chen W, Feng J, Dong S, Guo J, Liang Y, Hu R, et al. A novel nomogram and online calculator for predicting the risk of obesity hypoventilation syndrome in bariatric surgery candidates. Obes Surg. 2023; 33(1): 68–77.
9. Bazurto-Zapata MA, Vargas L, Diaz-Bossa C, Fernandez F, Meza ED, Rubiano W, et al. Obesity hypoventilation syndrome prevalence and its impact in sleep oxygen saturation in 3 cities located at different altitudes. Sleep Med. 2024; 115: S367–8.
10. Park MH, Lee M-J, Kim JS, Park SH, Lee JH, Kim AJ. Veno-venous extracorporeal membrane oxygenation rescue for pulmonary hypertension and hypoxemic respiratory failure to obesity hypoventilation syndrome: a case report. Ann Palliat Med. 2022; 11(10): 3341–5.
11. Masa JF, Corral J, Romero A, Caballero C, Terán-Santos J, Alonso-Álvarez ML, et al. The effect of supplemental oxygen in obesity hypoventilation syndrome. J Clin Sleep Med. 2016; 12(10): 1379–88.
12. Corral J, Mogollon MV, Sánchez-Quiroga M-Á, Gómez de Terreros J, Romero A, Caballero C, et al. Echocardiographic changes with non-invasive ventilation and CPAP in obesity hypoventilation syndrome. Thorax. 2018; 73(4): 361–8.
13. Howard ME, Piper AJ, Stevens B, Holland AE, Yee BJ, Dabscheck E, et al. A randomised controlled trial of CPAP versus non-invasive ventilation for initial treatment of obesity hypoventilation syndrome. Thorax. 2017; 72(5): 437–44.
14. Lastra AC, Masa JF, Mokhlesi B. CPAP titration failure is not equivalent to long-term CPAP treatment failure in patients with obesity hypoventilation syndrome: a case series. J Clin Sleep Med. 2020; 16(11): 1975–81.
15. Arellano-Maric MP, Hamm C, Duiverman ML, Schwarz S, Callegari J, Storre JH, et al. Obesity hypoventilation syndrome treated with non-invasive ventilation: Is a switch to CPAP therapy feasible? Respirology. 2020; 25(4): 435–42.
16. Soghier I, Brożek JL, Afshar M, Tamae Kakazu M, Wilson KC, Masa JF, et al. Noninvasive ventilation versus CPAP as initial treatment of obesity hypoventilation syndrome. Ann Am Thorac Soc. 2019; 16(10): 1295–303.
17. Khalyfa A, Masa JF, Qiao Z, González M, Marti S, Khalyfa AA, et al. Plasma exosomes in obesity hypoventilation syndrome patients drive lung cancer cell malignant properties: Effect of long-term adherent CPAP treatment. Biochim Biophys Acta Mol Basis Dis. 2022; 1868(10): 166479.
18. Masa JF, Benítez ID, Sánchez-Quiroga MÁ, Gomez de Terreros FJ, Corral J, Romero A, et al. Effectiveness of CPAP vs. Noninvasive ventilation based on disease severity in obesity hypoventilation syndrome and concomitant severe obstructive sleep apnea. Arch Bronconeumol. 2022; 58(3): 228–36.
19. BaHammam AS, Aleissi SA, Nashwan SZ, Olaish AH, Almeneessier AS. Results of CPAP titration and short-term adherence rates in patients with obesity hypoventilation syndrome and mild/moderate obstructive sleep apnea. Nat Sci Sleep. 2022; 14: 1137–48.
20. Baglyas S, Valkó L, Móró V, Podmaniczky E, Czövek D, Makan G, et al. Using intra-breath oscillometry in obesity hypoventilation syndrome to detect tidal expiratory flow limitation: a potential marker to optimize CPAP therapy. BMC Pulm Med. 2023; 23(1): 477.