Sleep Advances, 2024, **5**, zpae016
https://doi.org/10.1093/sleepadvances/zpae016
Advance access publication 13 March 2024
Original Article

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A comparison of two obesity-related hypoventilation disorders: Impact on sleep, quality of life and neurocognitive outcomes and the effects of positive airway pressure therapy

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Abstract

Study Objectives: Symptom impact and neurocognitive function have not been previously compared between patients with obesity-associated hypoventilation disorders (obesity hypoventilation syndrome [OHS]) and hypoventilation in the setting of obesity and obstructive airways disease (OHAD). The aim of this study is to compare baseline sleep-related symptoms, health-related quality of life, and neurocognitive function between OHS and OHAD and the impact of PAP therapy on these outcomes.

Methods: Epworth Sleepiness Scale (ESS), Pittsburgh Sleepiness Quality Index (PSQI), SF36, and various neurocognitive tests, in addition to anthropometric, polysomnography, lung function, and blood gas data from participants with OHS and participants with OHAD, were included in the analysis. These data were originally collected in their respective randomized clinical trials, comparing the efficacy of different PAP modes (bilevel PAP vs. CPAP) in resolving hypercapnia. Between groups (OHS vs OHAD), pre- and post-treatment (with 3 months of positive airway pressure) comparisons were made using linear mixed modeling.

Results: 45 OHS participants (mean age 51 years old, 33% female, BMI 52 kg/m^2, FER 0.81, $PaCO_2$ 54 mmHg, AHI 87/h) and 32 OHAD participants (mean age 61years old, 31% female, BMI 43kg/m^2, FER 0.60, $PaCO_2$ 54 mmHg, AHI 59/h) were included in the analysis. Both OHS and OHAD had similar baseline ESS (14(5.6) vs. 12(5.4)), Global PSQI (10(3.2) vs. 11(4.8)), SF36 and neurocognitive test performances (other than OHAD had lower digit symbol substitution test performance). Treatment with PAP therapy resulted in similar ESS, Global PSQI, and SF36 improvements in both groups. Neurocognitive performance did not significantly improve after PAP therapy in either group.

Conclusions: The symptom impact between two separate hypoventilation disorders (OHS and OHAD), in terms of sleepiness, sleep quality, quality of life, and cognitive function, were similar. OHS and OHAD had similar treatment responses in these parameters after 3 months of PAP therapy.

Nocturnal ventilatory support in OHS.

Key words: chronic obstructive pulmonary disease; obstructive sleep apnea; overlap syndrome; obesity; hypercapnic respiratory failure; positive airway pressure therapy; sleepiness; quality of life; neurocognitive function

Statement of Significance

Hypoventilation syndromes in the setting of obesity, with and without airway disease, are associated with poor sleep quality, increased sleepiness, neurocognitive dysfunction, and lower quality of life. This study compares these patient-centered outcomes between these groups (obesity hypoventilation syndrome and hypoventilation in the setting of obesity and obstructive airway disease) before and after positive airway pressure therapy, which has not been previously performed.

Submitted for publication: October 25, 2023; **Revised:** December 29, 2023

Introduction

Hypoventilation during sleep occurs in several disorders associated with obesity, lung disease, or both. Obesity hypoventilation syndrome (OHS) is diagnosed based on obesity and sleep-disordered breathing in the presence of awake alveolar hypoventilation not attributable to other causes [1]. Patients with lung disease are excluded from this diagnosis. Consequently, patients with a combination of obesity/obstructive sleep apnea (OSA) and chronic obstructive pulmonary disease (COPD), resulting in chronic hypoventilation, are generally excluded in clinical studies examining either COPD or OHS. Those with OSA and COPD will be classified as overlap syndrome, although neither obesity nor hypercapnia are necessary for the diagnosis.

Previous studies have documented poor sleep quality, increased sleepiness, and lower quality of life among patients with OHS [2–4]. These parameters have been compared to eucapnic controls, obese participants, and OSAS [2]. The characteristics of patients with hypoventilation in the setting of obesity and obstructive airways disease (OHAD) are less well known but have been described as also having low quality of life scores, reduced sleep quality, and more daytime sleepiness [5]. These two hypoventilation cohorts (OHS and OHAD) have not been directly compared in previous research.

Adequate sleep quality is important for aspects of both memory and non-memory cognitive function [6], and poor sleep is a risk factor for cognitive decline [7]. Obesity-related hypoventilation disorders represent extreme sleep-disordered breathing and are expected to have a high impact of sleep fragmentation and hypoxemia—two factors proposed to be predictors of cognitive dysfunction in OSA [8]. Likewise, cognitive deficits are also seen in COPD [9], a comorbid condition in OHAD. The degree of cognitive impairment appears to correlate with the severity of COPD, reflected by an increase in dynamic lung volumes, degree of hypoxia, and the presence of hypercapnia [10].

Treatment of sleep-disordered breathing, often OSA, is associated with improved neurocognitive performance in several domains [8, 11]. PAP therapy is expected to improve gas exchange and reduce sleep fragmentation [12] in hypoventilation disorders. However, the resolution of hypercapnia appears more mode-dependent (CPAP vs. Bilevel PAP) in OHAD than in OHS [4, 5, 13, 14]. Sleepiness and sleep quality also improve with PAP therapy [5, 12], but it is not clear if one cohort is more responsive to PAP treatment or a particular mode of PAP with respect to symptoms or neurocognitive function.

The aim of this study was to compare baseline symptom impact and neurocognitive function between participants with OHS and participants with OHAD, and the impact of PAP therapy on these outcomes.

Materials and Methods

Data source and study design

This retrospective cross-sectional study aimed at exploring and comparing symptom impact and neurocognitive function between two different groups of patients with obesity-related hypoventilation disorders. We obtained data from two separate clinical trials, one involved participants who met the diagnostic criteria for (OHS, recruited from 2003 to 2006) [4] and the second involved participants with awake hypoventilation in the setting of obesity and obstructive airways disease (OHAD, recruited from 2003 to 2012) [5].

Both studies enrolled patients with obesity (BMI > 30 kg/m^2) and stable daytime hypercapnia ($PaCO_2$ > 45 mmHg) at presentation to the Sleep Disorders Center, Royal Prince Alfred Hospital. Patients without significant respiratory or neuromuscular disorders were diagnosed as OHS. Patients in whom an obstructive ventilatory defect on spirometry was found (ratio of forced expiratory volume in 1 second/forced vital capacity or FER < 0.7) or clinician-diagnosed COPD were included in the OHAD group. Other inclusion criteria included (1) no neuromuscular or chest wall skeletal disorders, (2) not currently being treated with positive airway pressure therapy, and (3) no major psychiatric illness or unstable medical conditions that would affect the participant's ability to participate in the trial. Participants did not need to have symptoms of sleep-disordered breathing to be included in this trial [4, 5].

The original randomized clinical trials compared the efficacy of different PAP modes (1:1 randomized to either bilevel positive airway pressure therapy, BPAP, or continuous positive airway pressure therapy, CPAP) in reducing hypercapnia as the primary endpoints. The clinical trials also included sleep and neurocognitive data pre- and post-PAP intervention. Additional analysis was performed looking at the effects of PAP therapy. Three out of 32 OHAD participants and 2 out of 45 OHS participants dropped out at 3 months post-PAP therapy follow-up. See the attached Supplementary Information regarding PAP-related protocol.

The Human Research Ethics Committees at The Royal Prince Alfred Hospital approved this cross-sectional study. The original clinical studies were registered at anzctr.org as part of ACTRN12605000096651.

Study assessments

Participants were evaluated on two occasions, at baseline (prior to PAP treatment) and at three months (post-initiating PAP treatment). Polysomnography data, arterial blood gases, anthropometric data, spirometry indices, Epworth Sleepiness Scale (ESS) [15], sleep quality using the Pittsburgh Sleepiness Quality Index (PSQI) [16], and health-related quality of life using the Medical Outcomes Survey Short Form 36 (SF 36) [17] were collected at both occasions. Adherence to therapy was recorded at follow-up. Neurocognitive evaluations included: psychomotor vigilance test (sustained attention, reaction time), digit span task (working memory), trail-making test (executive functioning), and digit symbol substitution test (DSST) (cognitive dysfunction). Procedural details are included in Supplementary Material.

Statistical analysis

Baseline characteristics were expressed as mean and *SD* or percentages with 95% CIs and compared using Student's *t*-test and chi-squared analysis, respectively. Analysis of sleepiness, sleep quality, quality of life measures, and neurocognitive outcomes were done using a linear mixed model for repeated measures. The model included fixed effects for the disease group (OHS or OHAD), treatment arm (BPAP or CPAP), time (baseline and 3 months), and their interaction, age, and a participant-level random intercept. There was no imputation for missing data. The differences were reported as a mean with 95% confidence interval and *p*-value, with the significance test based on a two-sided α of 0.05. Multiple linear regression was used to assess if arousal index and $PaCO_2$ were associated with sleepiness and sleep quality. Data management was performed using SPSS software (IBM SPSS Statistics).

Results

Participant baseline characteristics

A total of 32 participants with obesity-related hypoventilation with airways disease (OHAD) and 45 participants with OHS were included in the analysis.

Table 1 summarizes the baseline demographic data, lung function, blood gas measurements, and sleep study parameters. The OHS group was younger than the OHAD group, had a greater degree of obesity and was less likely to be a current or ex-smoker. The OHAD group had lower FEV_1 and FER but similar FVC on spirometry. Arterial blood gas measurements were similar between groups. The OHS group had a higher AHI, but the hypoxic costs (total sleep time oxygen saturation spent less than 80% and 90%) was similar (both groups had seven patients each, requiring supplemental oxygen during their initial diagnostic study). No other statistically significant differences were noted in the other sleep study parameters.

Comparison of sleepiness and sleep quality

No difference in baseline (pre-PAP therapy) sleepiness (ESS) or sleep quality (Global PSQI) was seen between the two disorders (Table 2). Both OHS and OHAD groups had improved sleep quality and reduced sleepiness after 3 months of PAP therapy compared to their respective baselines (Table 3). There were no intergroup differences to suggest either group responded better to PAP therapy (Table 3). The mode of PAP therapy allocated (CPAP or Bilevel PAP) did not appear to influence an outcome difference in either disorder (Supplementary Data).

Comparison of quality of life

There were no statistically significant differences in the combined mental component or physical component of quality-of-life measures (based on SF36 questionnaire) at baseline, as shown in Table 2. There were statistically significant improvements in both physical and mental components in the OHS group while only the mental component significantly improved in the OHAD group post 3 months of allocated PAP therapy (Table 3). However, the intergroup differences were not statistically significant, indicating that the underlying hypoventilation disease did not influence responsiveness to PAP therapy (Table 3).

Comparison of neurocognitive testing outcomes

The OHAD group had lower baseline digit symbol substitution performance compared to the OHS group. There were no other significant between-group differences in neurocognitive tests at baseline (Table 4). Post-PAP therapy, only one of three measures of

Table 1. Baseline Characteristics Displayed as Mean (Standard Deviation), Except for %TST < 90% and %TST < 80%, Which are Displayed as Median (Interquartile Range)

	OHS (N = 45)	OHAD (N = 32)	P-value
Age (years)	51 (14)	61 (11)	0.002
Gender (% female)	33	31	0.85
BMI (kg/m^2)	52 (8.5)	43 (7.2)	<0.001
Neck circumference (cm)	50 (4.7)	48 (4.5)	0.17
Waist circumference (cm)	145 (14)	133 (10)	<0.001
Hip circumference (cm)	149 (18)	134 (15)	0.001
Smoking status (% smoker)^	51	97	<0.001
Spirometry			
FEV1 (L)	1.9 (0.77)	1.4 (0.58)	N/A
FEV1 (% predicted)	60 (19)	48 (19)	0.007
FVC (L)	2.4 (0.97)	2.3 (0.84)	0.19
FVC (% predicted)	62 (18)	64 (22)	0.57
FER (%)	81 (5.9)	60 (9.7)	N/A
ABG			
$PaCO_2$ (mmHg)	54 (8.2)	54 (7.4)	0.86
PaO_2 (mmHg)	64 (15)	59 (10)	0.09
Bicarbonate (mmol)	32 (6.4)	32 (4.6)	0.75
Base excess (mmol)	6 (3.9)	6 (4.0)	0.88
pH	7.39 (0.03)	7.39 (0.03)	0.46
PSG~			
AHI (events/hour)	87 (34)	59 (35)	<0.001
Arousal (events/hour)	63 (38)	51 (32)	0.22
%TST < 90%	76 (29)	78 (25)	0.77
%TST < 80%	39 (30)	26 (22)	0.08
%NREM sleep	89 (7.7)	89 (8.8)	0.68
%SWS	14 (18)	14 (15)	0.99
%REM sleep	11 (7.7)	11 (8.8)	0.66

^Smokers included ex-smokers (OHAD = 17, OHS = 13) and current smokers (OHAD = 14, OHS = 10).
N/A—not applicable.
~Seven participants were on supplemental oxygen in both OHS and OHAD groups.

Table 2. Baseline Quality of Life, Quality of Sleep and Sleepiness Scores in OHS and OHAD

	OHS (Mean [*SD*])	OHAD (Mean [*SD*])	Baseline intergroup differences[-]	
	Baseline	**Baseline**	**Mean (CI)**	***P*-value**
ESS	14 (5.6)	12 (5.4)	−1.1 (−4.0, 1.1)	0.27
Global PSQI	10 (3.2)	11 (4.8)	0.66 (−1.3, 2.6)	0.50
SF36				
Physical component	29 (9)	32 (11)	2.6 (−2.3, 7.5)	0.30
Mental component	33 (18)	27 (17)	−5.7 (−14, 2.9)	0.19

ESS, Epworth Sleepiness Scale; PSQI, Pittsburg Sleep Quality Index; SF36, Medical Outcome Survey Short Form 36.
[-]Adjusted for baseline values of the variables analyzed and age.

Table 3. Comparison of Impact of PAP Therapy on Quality of Life, Quality of Sleep and Sleepiness Scores in OHS and OHAD

	OHS (Mean [*SD*])		OHAD (Mean [*SD*])		Intergroup differences[-]	
	Baseline	**Post-PAP (3 m)**	**Baseline**	**Post-PAP (3 m)**	**Mean (CI)**	***P*-value**
ESS	14 (5.6)	6.3 (5.2)**	12 (5.4)	6.4 (5.4)**	1.5 (−2.1, 5.1)	0.42
Global PSQI	10 (3.2)	6.3 (4.2)**	11 (4.8)	7.2 (3.4)**	0.19 (−2.6, 3.0)	0.90
SF36						
Physical Component	29 (9)	35 (13)*	32 (11)	34 (11)	−4.2 (−12, 3.6)	0.28
Mental Component	33 (18)	41 (19)*	27 (17)	41 (16)**	4.4 (−7.9, 16)	0.48

Abbreviations: ESS, Epworth Sleepiness Scale; PSQI, Pittsburg Sleep Quality Index; SF36, Medical Outcome Survey Short Form 36.
[-]Adjusted for baseline values of the variables analyzed and age.
*$p < 0.05$ intragroup difference (Post-PAP (3 m)–baseline).
**$p < 0.01$ intragroup difference (Post-PAP (3 m)–baseline).
BPAP adherence in OHS: 6.1 (±2.1) hours.
CPAP adherence in OHS: 5.8 (±2.4) hours.
BPAP adherence in OHAD: 4.1 (±2.5) hours.
CPAP adherence in OHAD: 5.6 (±2.3) hours.

Table 4. Baseline Neurocognitive Outcomes in OHS and OHAD

	OHS (Mean [*SD*])	OHAD (Mean [*SD*])	Baseline intergroup differences~	
	Baseline	**Baseline**	**Mean (CI)**	***P*-value**
PVT				
Lapses	9.2 (12)	8.9 (11)	−0.3 (−6.0, 5.4)	0.92
Median: RT (ms)	338 (96)	338 (82)	0.2 (−44, 44)	0.99
Mean slowest 10% 1/RT (1/s)	1.9 (0.89)	1.9 (0.63)	0.002 (−0.38, 0.39)	0.99
Digit span forward	7.3 (2.8)	7.2 (2.0)	−0.03 (−1.3, 1.2)	0.96
Digit span backward	5.2 (2.5)	5.2 (2.0)	−0.03 (−1.2, 1.1)	0.96
Trail-making test (s)	116 (54)	132 (51)	15 (−14, 44)	0.30
Digit symbol substitution	43 (13)	36 (11)	−7.7 (−14, −1.4)	0.02

Abbreviations: PVT, psychomotor vigilance test; RT, reaction time.
[~]Adjusted for baseline values of the variables analyzed and age.
*$p < 0.05$ intragroup difference (3 m–baseline).

the Psychomotor Vigilance Test improved within group, as seen in the OHAD arm. As shown in Table 5, there were no intergroup differences in neurocognitive testing outcomes between disorders post-PAP therapy.

Correlation of sleepiness and sleep quality to arousal index and $PaCO_2$

Multiple linear regression was used to test if arousal index and $PaCO_2$ significantly predicted change in ESS and Global PSQI. The overall regression was statistically significant for independent parameters: ESS in OHAD (R^2 0.317) and OHS (R^2 0.346); and for Global PSQI in OHAD (R^2 0.391) and OHS (R^2 0.271). Table 6 displays the change in arousal index and $PaCO_2$ post-PAP therapy.

Discussion

This is the first study to compare two different obesity-related hypoventilation disorders in their impact on sleep quality, sleepiness, quality of life, and neurocognitive function. Although there were expected differences in participant characteristics such as their degree of obesity, lung function abnormality, and

Table 5. Impact of PAP Therapy on Outcomes of Neurocognitive Tests in OHS and OHAD

	OHS (Mean [*SD*])		OHAD (Mean [*SD*])		Intergroup differences~	
	Baseline	Post-PAP (3 m)	Mean (CI)	Post-PAP (3 m)	Mean (CI)	*P*-value
PVT						
Lapses	9.2 (12)	5.5 (12)	8.9 (11)	6.0 (11)	0.8 (−7.5, 9.1)	0.85
Median: RT (ms)	338 (96)	310 (89)	338 (82)	306 (67)	−4.6 (−64, 56)	0.88
Mean slowest 10% 1/RT (1/s)	1.9 (0.89)	2.2 (0.74)	1.9 (0.63)	2.2 (0.59)*	−0.02 (−0.54, 0.50)	0.95
Digit span forward	7.3 (2.8)	7.6 (2.9)	7.2 (2.0)	8.2 (2.0)	0.65 (−1.25, 2.5)	0.49
Digit span backward	5.2 (2.5)	5.7 (2.5)	5.2 (2.0)	5.4 (1.9)	−0.24 (−1.9, 1.4)	0.77
Trail-making test (s)	116 (54)	96 (36)	132 (51)	116 (43)	4.2 (−32, 40)	0.82
Digit symbol substitution	43 (13)	47 (11)	36 (11)	40 (13)	0.6 (−8.3, 9.5)	0.89

Abbreviations: PVT, psychomotor vigilance test; RT, reaction time.
~Adjusted for baseline values of the variables analyzed and age.
*$p < 0.05$ intragroup difference (Post-PAP [3 m]–baseline).
BPAP adherence in OHS: 6.1 (±2.1) hours.
CPAP adherence in OHS: 5.8 (±2.4) hours.
BPAP adherence in OHAD: 4.1 (±2.5) hours.
CPAP adherence in OHAD: 5.6 (±2.3) hours.

Table 6. Post-PAP Treatment Characteristics Displayed as Mean (Standard Deviation), Separated by Disease Group and Allocated PAP Mode

	OHS (*N* = 45)		OHAD (*N* = 32)	
	CPAP	BPAP	CPAP	BPAP
Number of participants	23	22	16	16
Adherence (mean PAP use in hours)^				
Intention to treat	5.4 (±2.5)	5.7 (±2.4)	5.3 (±2.6)	3.6 (±2.5)
As per protocol	5.8 (±2.4)	6.1 (±2.1)	5.6 (±2.3)	4.1 (±2.5)
ABG^				
$PaCO_2$ (mmHg)	46 (±6)	42 (±6)	47 (±6)	44 (±8)
Change in $PaCO_2$ (mmHg)	−5.8 (±8)	−6.9 (±7)	−3.4 (±7)	−11 (±10)
PSG~				
Arousal index (/hour)	18 (±11)	17 (±13)	14 (±10)	20 (±13)
Change in arousal index (/hour)				
%NREM Sleep	90 (±7)	89 (±9)	89 (±9)	88 (±9)
%SWS	19 (±15)	22 (±12)	17 (±11)	22 (±17)
%REM sleep	10 (±7)	11 (±9)	11 (±9)	12 (±9)

^ABG and adherence data based on 3 months post-PAP treatment.
~PSG data based on initial PAP titration study.

severity of comorbid OSA, the symptom impact and neurocognitive performance appear similar between OHS and OHAD participants.

Both studies recruited participants with similar severity of hypercapnic respiratory failure at baseline. The contribution of lower lung function in the development of daytime respiratory failure in the OHAD group appears to be balanced by the greater degree of obesity and impact of sleep apnea seen in the OHS group. Although the exact mechanism of the development of hypercapnia is poorly understood in both disorders, some of the proposed factors include changes in respiratory mechanics, diaphragmatic dysfunction, sleep apnea syndrome, and altered respiratory drive [18]—all likely to feature to varying degrees between the two groups, but also between individuals within the same disorder.

Our study demonstrated that although the OHAD participants had a lower average awake arterial partial pressure of oxygen, the nocturnal hypoxic impacts tended to be greater in the OHS group, reflected in the proportion of total sleep time with an oxygen saturation lower than 80%. This is surprising as the combination of parenchymal disease and V/Q mismatch in COPD is expected to compound the effects of sleep-disordered breathing seen in overlap syndrome [19]. However, awake oxygen saturation is not the only factor affecting nocturnal hypoxemia, and previous studies have shown BMI [20], expiratory reserve volume [21, 22], and ventilatory sensitivity to hypercapnia [23] are also important determinants of nocturnal oxygen desaturation. VQ mismatch is also apparent in OHS populations due to higher closing volume to functional residual capacity ratio [24], which is further exacerbated in the supine position [25]. In addition, morbid obesity is

associated with reduced functional residual capacity and thereby lung oxygen reserve. Greater obesity also increases whole-body oxygen demand [26].

In our study, despite the differences in AHI between and OHAD groups, the proportion of slow wave sleep and REM sleep were similar. Participants in both our obesity-related hypoventilation groups also reported similar levels of daytime sleepiness, sleep quality, and quality of life. Both groups were more sleepy and experienced lower health-related quality of life than previous reports of these measures in non-hypercapnic OSA participants and healthy controls [27, 28].

CPAP therapy reduces daytime sleepiness and improves quality of life in patients with OSA [29, 30], but this is influenced by disease severity [31]. In the current study, both hypoventilation groups showed an equally impressive reduction in ESS and PSQI. Only the mental component of SF36 improved in the OHAD group with therapy, whereas both mental and physical components improved in the OHS group. It is possible that the improvement in hypercapnia and sleep-related symptoms is sufficient to improve the physical function of participants with OHS, but among participants with OHAD, they are still limited by their airway disease.

In our OHS and OHAD participants, daytime sleepiness and self-reported sleep quality correlated with improvements in hypercapnia and sleep fragmentation (arousal index). Carbon dioxide narcosis is a known complication of hypercapnic respiratory failure [32] and has an anesthetic effect in animal models [33]. Slowing of electroencephalographic activity on spectral analysis is a proposed link between hypercapnia and daytime sleepiness [34]. Arousal index appears to be a predictor of excessive daytime sleepiness in patients with OSA in several studies [35–37], but this has not been a consistent finding [38]. The underlying mechanism and sleep study characteristics that influence sleepiness and sleep quality are yet to be fully defined. Similarly, hypercapnia and arousal index only appeared to be of small overall contribution in our study. Although not explored, some of the other potential factors among our studied population include comorbid medical disease, physical inactivity, psychological factors, and mental health illness. Obesity and the associated proinflammatory state have also been proposed as causes of excessive daytime sleepiness [36].

Interest in the neurocognitive impact of sleep-disordered breathing has been increasing; however, only a few studies have investigated the neurocognitive function of OHS and OHAD. Both conditions share similar features of hypoxia, hypercapnia, and sleep fragmentation in these disorders [10]. In addition, both conditions are also associated with higher rates of vascular disease. Despite this, baseline results from our cohorts did not differ significantly from previous reports of neuropsychological function in OSAS and COPD samples [39, 40].

At baseline, both groups did not differ significantly in neurocognitive performance, except for DSST where the OHS group averaged a better performance. This test assesses the integration of multiple cognitive domains, including motor speed, attention, and visuo-perceptual functions [41]. Age has a major influence on DSST performance, accounting for 86% of the variance [42]. Even after adjustment for age as a covariate, OHAD participants performed worse than OHS participants in DSST at baseline.

PAP therapy over 3 months did not appear to significantly improve neurocognitive test performances, a finding similar to a previous study of OHS participants undergoing PAP therapy over the same treatment period [43]. Several factors likely explain this lack of improvement. Firstly, and rather surprisingly, the baseline digit span tests (forward assessing verbal working memory and attention, while backward also tests cognitive control and executive function [44]) were not different from previously reported results from population studies [44, 45], so significant improvements may not have been possible. It is also unclear whether further improvements could occur beyond that of the 3-month therapy period. Overall, there was a trend towards improvement in all the neurocognitive tests in both study groups compared to their baseline values, suggesting that correction of the respiratory failure and sleep-disordered breathing improves neurocognitive function, irrespective of the underlying disorder. In OSA, CPAP therapy is associated with improvements in sustained attention, recall, and some of the components of executive function [46]. Although statistically significant improvements were not demonstrated across a 3-month treatment period, we postulate long-term PAP therapy is likely to be neuroprotective and will improve neurocognitive performance in several domains among the obese hypercapnic cohort. However, it is also possible that neurocognitive function may not revert to normal despite resolution or improvement of hypercapnia/sleep-disordered breathing due to permanence of injury or other contributing factors.

There are several limitations to this study. The study data comes from a single center in stable participants with chronic respiratory failure presenting to a sleep laboratory. The data analysis was performed retrospectively and the data of interest were not the original outcomes of the trial. There may have been a selection bias towards patients with more symptoms or alternatively less severe respiratory failure. Both disorders had small number of recruited participants and likely lacked significant power to detect meaningful differences, as seen in the neurocognitive data. The OHAD group also took longer to recruit and two of its participants were lost to follow-up due to death unrelated to respiratory failure.

Questionnaires were used to assess sleepiness and sleep quality rather than objective measures of sleepiness such as Maintenance of Wakefulness Test, driving simulation, or daytime EEG quantification. Other potential factors, outside of participant age, were not adjusted for with respect to neurocognitive performance—such as education status, socioeconomic status, underlying neurodegenerative/neurovascular disease, obesity, and psychiatric illness.

Both bilevel PAP and CPAP were used in the post-PAP comparisons. At least in the OHAD population, there may be differences in treatment efficacy in the two PAP modalities [5]. Nonetheless, we did further compare the data of interest between bilevel PAP and CPAP without finding any significant influence related to the mode of PAP therapy in either disorder. During the time the original trials were conducted, the PAP models used were also older than what is currently available.

Larger population data with longer periods of data collection are required to confirm and address some of the issues raised in this study. Future research should involve the collection of data from multicenter sleep registries and aim to further phenotype these patient groups based on sleep study measurements, patient characteristics, comorbidities, and other biomarkers. The impact of PAP therapy needs to be assessed in relation to participants' baseline symptomatology as well as followed for a longer period. The various features of newer PAP devices in addition to different modes and pressure settings should also be explored.

Conclusion

In this single-center cross-sectional study, the symptom severity between two separate hypoventilation disorders (OHS and OHAD), in terms of sleepiness, sleep quality, quality of life, and cognitive function were similar, despite differences in baseline lung function, anthropometric and PSG characteristics. Both OHS and OHAD were similarly responsive to 3 months of PAP therapy, resulting in reduced symptoms. Greater attention and research into neurocognitive function and quality of life in patients with obesity-related hypoventilation is needed.

Supplementary Material

http://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12605000096651

Funding

No funding was received for conducting this study.

Conflicts of Interest

Yizhong Zheng, Brendon J Yee, and Keith Wong certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, and knowledge or beliefs) in the subject matter or materials discussed in this manuscript. Ronald R. Grunstein is an NHMRC Investigator Awardee Level 3 and serves on an advisory committee for Lilly. Amanda J. Piper has received personal fees for educational presentations from ResMed and Philips, manufacturers of positive airway pressure devices.

Author Contributions

Yizhong Zheng (Conceptualization [Supporting], Formal analysis [Equal], Writing—original draft [Lead]), Brendon Yee (Conceptualization [Equal], Methodology [Equal], Supervision [Equal], Writing—review & editing [Equal]), Keith Wong (Methodology [Equal], Supervision [Equal], Writing—review & editing [Equal]), Ron Grunstein (Conceptualization [Equal], Supervision [Supporting], Writing—review & editing [Equal]), and Amanda Piper (Conceptualization [Equal], Data curation [Lead], Investigation [Lead], Methodology [Equal], Supervision [Equal], Writing—review & editing [Equal]).

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Statement

The Human Research Ethics Committees at The Royal Prince Alfred Hospital approved this cross-sectional study. All procedures performed in the study involving human participants were in accordance with the ethical standard of the Human Research Ethics Committees at The Royal Prince Alfred Hospital and with the 1964 Declaration of Helsinki and its later amendments.

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