

Development of CPAP Dose Response for Patients with Obstructive Sleep Apnea: Secondary Analysis

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A thesis submitted in partial fulfillment of the requirements for the degree of:  
Master of Science – Epidemiology, Clinical and Translational Research Track

University of Washington

2022

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Abstract

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### Background

First-line treatment for obstructive sleep apnea (OSA) is continuous positive airway pressure therapy (CPAP). Although CPAP is efficacious, the definition of adequate use (effectiveness) is known to be arbitrary. We aimed to characterize a CPAP dose response for short term outcomes, including sleepiness severity and quality of life.

### Methods

We performed secondary analysis on a prospective, observational cohort study of adult patients ( $\geq 18$  years old) with newly diagnosed OSA (no CPAP, baseline) and six-months after receiving a CPAP device (follow-up). Objective CPAP use was defined as average minutes of CPAP use per night over all nights during the four-week interval before the end of follow-up. Change in Epworth Sleepiness Scale (ESS) and Symptoms of Nocturnal Obstructions and Related Events (SNORE-25) were primary and secondary outcomes, respectively. Multivariate linear regression was performed, adjusting for demographic factors and severity of OSA at baseline.

### Results

Two hundred forty-two patients (mean age 47 +/- 12, 65% male, AHI 33 +/- 25) were enrolled. Patients used their CPAP devices for an average of 258 +/- 153 minutes per night over all nights (range 0-545 minutes). Mean baseline ESS was 10.0 +/- 4.8 and mean score change was -2.9 +/- 4.0. Mean baseline

SNORE-25 was 1.5 +/- 0.8 and mean score change was -0.6 +/- 0.7. There was no association between average CPAP use per night over all nights and change in ESS scores ( $p=0.18$ , 95% CI -0.005 – 0.001), after adjusting for confounders. However, for each additional 30 minutes per night of CPAP use, there was a 0.024 improvement in SNORE-25 score, and this was a statistically significant association ( $p=0.002$ , 95% CI -0.001- -0.0002).

## Conclusion

This suggests for a *minimal* clinically important change of 0.2 for SNORE-25, patients would need to use their CPAP an additional 250 minutes (i.e., 4 hours and 10 minutes) per night, on average. This work fits within a larger context aimed to develop a validated definition(s) for adequate CPAP use associated with measures of sleep apnea burden, alter CPAP counseling/troubleshooting, and build evidence-based criteria for considering secondary OSA treatments.

## INTRODUCTION

Obstructive sleep apnea (OSA) carries major burdens for long-term health, quality of life, daytime function, and healthcare costs.<sup>1</sup> First-line treatment for OSA is continuous positive airway pressure therapy (CPAP). Although CPAP is efficacious, the definition of adequate use is known to be arbitrary. The commonly employed definition of adequate use is greater than four hours per night on five or more nights per week, which amounts to a minimum of 20 hours per week. This definition is utilized by the Centers for Medicare and Medicaid Services (CMS), which has broad implications for patient care. Unfortunately, 46 to 83% of patients with OSA are “nonadherent,”<sup>2</sup> and many others are undertreated despite “adherence.” Moreover, the clinical effectiveness of CPAP is not binary (“adherence” vs “nonadherence”), but rather continuous, with greater clinical effectiveness expected with greater use. This creates a significant untapped opportunity to optimize CPAP’s role in management of OSA, and the potential for significant residual OSA burden among patients who are “adherent” with CPAP treatment and may not be offered other medical or surgical therapies.

There is a dose-response relationship between nightly CPAP use duration and the percentage of patients whose outcomes (Epworth Sleepiness Scale (ESS), objective sleepiness, and function) normalize.<sup>3</sup> Greater nightly CPAP use is associated with a greater proportion of patients achieving normal levels of daytime sleepiness and daily functioning.<sup>3,4</sup> However, focusing on the proportion of ‘normal’ values ignores information on the degree of improvement: some individuals may achieve an important difference in daytime sleepiness and functioning but remain short of ‘normal’ values, whereas others may have a trivial improvement from barely ‘abnormal’ to ‘normal’ and be classified as having experienced clinical benefit. Thus, these findings are difficult to apply within a clinical context, and the pattern of the dose-response relationship between CPAP use and clinical effectiveness is still poorly understood.

In this analysis, we aimed to quantify the dose-response between nightly CPAP use and short-term clinical outcomes, particularly changes in ESS from baseline to six-month follow-up and, secondarily, changes in Symptoms of Nocturnal Obstruction and Related Events-25 (SNORE-25).

## **METHODS**

We performed a secondary analysis on a prospective, observational cohort study of adult patients ( $\geq 18$  years old) with newly diagnosed OSA (defined as apnea-hypopnea index (AHI) $\geq 5$  on diagnostic polysomnography). This dataset includes 235 of 242 (97.1%) enrolled subjects from a parent randomized trial of a treatment to facilitate CPAP use, with recruitment between September 1, 2007 to June 30, 2010. Objective CPAP use was defined as average minutes per night of CPAP use over all nights during four-week interval before the end of follow-up and was recorded and downloaded from an embedded data card on patient's CPAP device. Outcome measures included ESS and SNORE-25, measured at diagnosis (no CPAP, baseline) and six-months after CPAP use (follow-up). De-identified data was used in analysis. The parent study had IRB approval from the University of Washington for the original data collection.

### Epworth Sleepiness Scale

The Epworth Sleepiness Scale (ESS), a validated subjective measure of sleepiness (symptom severity),<sup>5</sup> was evaluated as the primary outcome of interest. It is an eight-item survey assessing sleepiness severity on a Likert scale (0-3).<sup>5</sup> The sum of the individual item scores is the final score (range 0-24, with higher scores indicating greater sleepiness).<sup>5</sup> Scores above 10 represent excessive daytime sleepiness, and scores above 16 represent severe sleepiness.<sup>5</sup>

### SNORE-25

The validated SNORE-25, a 25-item survey assessing OSA-specific quality of life,<sup>6</sup> was evaluated as a secondary outcome. Each item on the SNORE-25 is scored on a Likert scale (0-5) (i.e., over the past two weeks, rate how "bad" OSA limits productivity at certain times of day).<sup>6</sup> The total instrument score is the mean of the scored items (range 0-5), with higher scores indicating poorer OSA-specific quality of life.<sup>6</sup>

## DATA ANALYSIS

In our primary analysis, we tested the association between objective CPAP use (defined as average minutes per night CPAP used over all nights in four-week interval before the end of follow-up) and change in ESS at follow-up compared to baseline. We performed multivariate regression to account for confounders measured at baseline. Included confounders were selected *a priori*, and included age, sex, race, body mass index (BMI), education history, comorbidities (Functional Comorbidity Index),<sup>7</sup> AHI, 3% oxyhemoglobin desaturation index (ODI), and baseline outcome measure. Variable data were collected through chart review of sleep surgery records and diagnostic polysomnography. In the model, all variables were treated as continuous variables, except sex, race, education history, and comorbidities which were treated as indicator variables as categorized in Table 1. We used linear regression to discern the relationship between objective CPAP use and change in ESS for the CPAP dose response, based off prior published findings.<sup>3,4</sup> Similar analyses were performed for the secondary outcome, SNORE-25. We examined the F statistic and p value for the overall model and the p values for the individual predictor variable for objective CPAP use. Patient characteristics that were continuous variables are reported as means and standard deviations; categorical variables are reported as proportions.

We also performed exploratory analyses to examine the relationship between percentage of nights CPAP used over four-week interval prior to the end of follow-up and change in ESS and SNORE-25.

## RESULTS

Two hundred and forty-two patients with newly diagnosed OSA were included. On average, members of the study population were middle aged (mean age 47 +/- standard deviation (SD) 12 years old), overweight (mean BMI 32 +/- 7), predominantly male (65% male), and experienced moderate-severe sleep apnea (mean AHI 33 +/- 25). All were prescribed CPAP for initial management. Sixty-nine percent of patients used CPAP over the six-month period (range 0-545 minutes per night over all nights on

average over the four-week interval prior to the end of follow-up), and among CPAP users, the average minutes per night over all nights over the four-week interval prior to the end of follow-up was 259 +/- 153 minutes (Table 1).

### Epworth Sleepiness Scale

At baseline, patients on average had borderline excessive sleepiness (baseline mean ESS scores 10.0 +/- 4.8). Dividing into subsets of CPAP non-users, all CPAP users, CPAP users with <240 minutes per night on average over all nights, and CPAP users with  $\geq$ 240 minutes per night on average over all nights, the mean baseline ESS scores were 9.7 +/- 4.7, 10.0 +/- 4.9, 10.6 +/- 4.8, and 9.9 +/- 4.8, respectively.

At follow-up, the CPAP non-users had the smallest average change in sleepiness severity (mean ESS score 8.0 +/- 4.8, change from baseline of -1.7 +/- 3.5). In comparison, CPAP users overall reported, on average, clinically meaningful improvement (defined as change of at least -3, which has sensitivity of 80% and specificity of 88%)<sup>8</sup> (mean change from baseline of -3.1 +/- 3.9). Among CPAP users, there was no difference between those with <240 minutes of use per night on average (mean change from baseline of -3.1 +/- 3.1) and those with  $\geq$ 240 minutes of use per night on average (mean change from baseline of -3.2 +/- 4.4). Compared to non-users, patients who used their CPAP had statistically significant improvements in sleepiness severity ( $p < 0.0001$ ) (Table 2).

Using multivariate linear regression, CPAP use duration was not associated with statistically significant improvements in ESS scores between baseline and the end of follow-up, after adjustment for covariates and baseline ESS ( $p = 0.18$ , 95% CI -0.005 - 0.001) (Figure 1).

### SNORE-25

At baseline, patients reported on average mild to slight quality of life burden (baseline mean SNORE-25 scores 1.5 +/- 0.8). Dividing cohort into subsets of CPAP non-users, all CPAP users, CPAP users with <240 minutes per night on average over all nights, and CPAP users with  $\geq$ 240 minutes per night on

average over all nights, mean baseline SNORE-25 scores were 1.5 +/- 0.8, 1.5 +/- 0.7, 1.4 +/- 0.6, and 1.4 +/- 0.7, respectively.

At six-months, the CPAP non-users had the smallest average change in quality of life (mean SNORE-25 score at end of follow-up of 1.2 +/- 0.8, change from baseline of -0.3 +/- 0.6). In comparison, CPAP users reported on average clinically meaningful improvement (defined as change in -0.6 (anchor method))<sup>9</sup> of -0.6 +/- 0.7, -0.5 +/- 0.7, and -0.7 +/- 0.7 for all CPAP users, CPAP users with <240 minutes per night on average over all nights, and CPAP users with ≥240 minutes per night on average over all nights, respectively (Table 3).

Then, we tested the association of objective CPAP use (average minutes per night CPAP used over all nights during four-week interval prior to follow-up) and change in SNORE-25 scores. Using multivariate linear regression, for every 30 minutes per night on average increase in CPAP use over all nights, there was a -0.024 change in SNORE-25, after covariate adjustment (p=0.002, 95% CI -0.001- -0.0002) (Figure 2). In other words, to reach a *minimal* clinically important change of 0.2 for SNORE-25 (distribution method),<sup>9</sup> patients would need to use their CPAP an additional 250 minutes per night (i.e., four hours and 10 minutes) on average over all nights.

## EXPLORATORY ANALYSIS

There was no statistically significant association between percentage of nights with CPAP use and change in ESS score, after covariate adjustments (p=0.36, 95% CI -0.018 – 0.007) (Figure 3). However, for every additional night of CPAP used over a four-week interval, there was a statistically significant improvement of 0.01 change in SNORE-25 (p=0.017, 95% CI -0.005 - -0.005). Thus, to reach a *minimal* clinically important change of 0.2 for SNORE-25 (distribution method),<sup>9</sup> patients would need to use their CPAP an additional 20 nights over a four-week period.

## DISCUSSION

The development of CPAP dose responses has broad implications for patient care, in terms of counseling and providing evidence for adequate use. These dose responses would also be helpful when discussing anticipated CPAP-associated improvements with patients. In some cases, desired improvements in burden measures may be infeasible given severity of burden and corresponding duration of CPAP use to achieve desired improvement. However, in other cases, having the dose response may be motivating for patients to understand the additional benefit of an additional hour or night of CPAP use.

In our study, we did not observe a significant association between objective CPAP use (measured as average minutes per night used over all nights of CPAP over four-week interval prior to follow-up) and change in ESS from six-month follow-up to baseline. This is contrary to our hypothesis and published literature, which suggested longer CPAP use leads to greater improvement.<sup>3,4</sup> Weaver et al published a multisite study of patients with severe OSA and compared percentage of patients with abnormal scores who improved to normal scores in ESS and other measures (ESS abnormal scores were set at 11 and normal scores defined as <10).<sup>3</sup> After three months of CPAP use, the study concluded longer duration of CPAP use leads to a greater proportion of the sample achieving normal levels of sleepiness, but the pattern of optimal CPAP use varied by outcome.<sup>3</sup>

Weaver et al findings were consistent with other studies. Antic et al reported a multisite study of patients with moderate to severe OSA, and the effect of CPAP use on ESS and FOSQ, using similar cutoffs of abnormal vs normal scores and reporting proportion of normal scores at three-month follow-up. There was reported variation in response to CPAP use, specifically 60% of patients had a normal ESS value after three months of CPAP use, whereas only 35% had a normal FOSQ total score after three months of CPAP use.<sup>4</sup> The presence of abnormal scores after three months of CPAP use is concerning, though may be caused by variable use of CPAP relative to the expected normal sleep time, incomplete treatment of OSA (meaning incomplete control of the upper airway), other compromise of sleep quality (CPAP-induced

or other sleep disorders), or that the selected normal thresholds for the outcome measures were inappropriate (though validated in cohorts of people with and without sleep disorders, and consistent with the previous study).<sup>4</sup> More importantly, the shape of the ESS and FOSQ trend lines were substantially different from Weaver et al,<sup>3</sup> as the trend lines in this study do not appear to plateau at seven hours and possibly suggest an even greater proportion of the sample would achieve normal ESS or FOSQ values with extended use, which suggests the current standard for adequate use may be inadequate.<sup>4</sup>

Contrary to these two studies, our study found no association between change in ESS and objective CPAP use. Major differences in analysis include 1) using change in ESS adjusted for baseline vs proportion of abnormal vs normal scores with arbitrary cutoffs and 2) more granular interpretation of objective CPAP use (minutes per night vs hours per night). We believe our analysis to be more interpretable for application to individual patient use, in terms of predicting changes in ESS score with CPAP use that are not biased by arbitrary cutoffs that may not be meaningful to the individual patient.

We recognize that these negative findings are surprising, and we are confident in our results. This dataset is robust, stemming from a prior NIH funded study with a 97.1% response rate and consistent recording by trained research coordinators. The cohort was enrolled from both private and academic practices and collectively share representative demographics of patients with OSA. Additionally, the objective CPAP use data was downloaded from the device, with an even spread across average minutes per night CPAP used over all nights (range 0 – 545 minutes per night) and percentage of nights used (0-100% of nights used). Future analysis that could aid in further interpretation includes proportion of night with CPAP used and expected normal sleep time, presence of incomplete treatment with CPAP alone, or other underlying sleep disorders. All of these could impact the interpretation of objective CPAP use variable and provide explanation for the worsening score changes in outcome measures.

Secondarily, we did observe a statistically significant association between objective CPAP use (measured as average minutes per night used over all nights of CPAP over four-week interval prior to follow-up and percentage of nights used over same period) and change in SNORE-25 scores. However, for these

relationships to be clinically meaningful, using the *minimal* clinically important difference of -0.2 (distribution method)),<sup>9</sup> patients would have to increase their CPAP use by an additional 250 minutes (i.e., four hours and 10 minutes) on average over all nights or increase their nights used over four-week period by 20 nights.<sup>9</sup> Depending on the patient's current CPAP usage, these increases in use may not always be feasible. Thus, we found the associations between objective CPAP use and changes in SNORE-25 not to be clinically useful. These findings may stem from SNORE-25 capturing multiple aspects of quality of life, and while important, potentially a portion of the items are not directly improved with CPAP use alone (i.e., marital strain, stress, tension)

Despite the negative findings, future work remains. Immediate next steps include further investigation into the patients with worsened ESS and SNORE-25 scores at follow-up, especially in terms of 1) CPAP use per night vs normal sleep time and 2) complete vs incomplete treatment of OSA. This would illuminate potential causes of the symmetric and steadily increasing variation in the change in scores with higher percentage of nights with CPAP use, given its contradiction to the evidence that more CPAP use would lead to more improvements. One possibility is that some motivated patients may attempt to use CPAP most nights, despite side effects (i.e., waking up gasping, etc.) that worsen their overall sleep quality or shorten their CPAP use, in comparison to their normal sleep time. This may explain the worsen in outcome scores with CPAP use and may highlight a certain subset of patients who may need additional coaching and troubleshooting.

Additionally, the dataset is robust and includes other time points, specifically ESS and SNORE-25 scores at three-months and 12-months of CPAP use. We selected the six-month time point because we assumed that most patients would have completed the CPAP troubleshooting phase, in terms of mask fittings and acclimatization; however, some patients may still be working on consistent use and have not fully appreciated the improvements in symptom severity and quality of life. It is possible that CPAP-associated improvements would be maximized at 12-months, compared to six-months, given more time to acclimatize and troubleshoot, as well as a more real-world measure of CPAP use. Alternatively, at three-months CPAP use may represent the best-performance in terms of duration and highest percentage of

nights used, as patients are often motivated by insurance and internal desire for improvements. This time point could be helpful in terms of understanding CPAP-associated improvement under ideal usage; however, these early patterns of CPAP use are often not sustained in the real-world, demonstrated by poor adherence, thus less helpful in terms of predicting short-term outcomes and counseling patients.<sup>2</sup>

In conclusion, this work was intended to answer the critical remaining questions of the dose-response effect of CPAP on common clinical outcomes for individuals (not just populations). Instead of relying on set thresholds that may be meaningless to patient's sleep apnea burden, these CPAP dose responses were designed to allow for interpretation for the individual's benefit based on the outcome most relevant to them. Overall, the impact of this work takes steps toward developing validated definition(s) for adequate CPAP use associated with measures of sleep apnea burden, altering CPAP counseling / troubleshooting, and building evidence-based criteria for considering secondary OSA treatments.

## **CONCLUSION**

The definition of adequate CPAP use (effectiveness) is known to be arbitrary. We aimed to develop a CPAP dose response for short term outcomes, including sleepiness severity (Epworth Sleepiness Scale) and quality of life (SNORE-25). Using secondary analysis on a robust dataset of adult patients with newly diagnosed OSA, we found there was no association between objective CPAP use (average minutes per night over all nights) and change in ESS at follow-up. However, there was a statistically significant association between objective CPAP use and change in SNORE-25 at follow-up. This suggests for patients to achieve a *minimal* clinically important change in SNORE-25, they would need to use their CPAP an additional 250 minutes per night (i.e., four hours and 10 minutes) or 20 additional nights on average over a four-week period. Further investigation into the data is needed to understand these relationships and future work includes integration of other time points.

**Table 1: Patient Characteristics**

For continuous variables, mean and standard deviation are listed. For categorical variables, proportions are listed.

	Cohort (n=242)
Age (years)	47 +/- 12
Sex (male)	65%
BMI	32 +/- 7
Education	
Grade 9 -11	1.2%
Grade 12 or GED	11.2%
Some college	32.6%
College degree	29.8%
Advanced degree	24.0%
Missing	1.2%
Race	
White	76.9%
Black	11.6%
Asian	7.9%
Other	3.6%
Functional Comorbidity Index (0-18)	2 +/- 2
Baseline Sleep Study	
Apnea-Hypopnea Index	33 +/- 25
3% Oxyhemoglobin Desaturation Index	18 +/- 20
CPAP use (among CPAP users, 69% of cohort)	
Minutes per night used on all nights	258 +/- 153

**Table 2: Baseline and Follow-up ESS Scores for CPAP Non-users and CPAP Users**

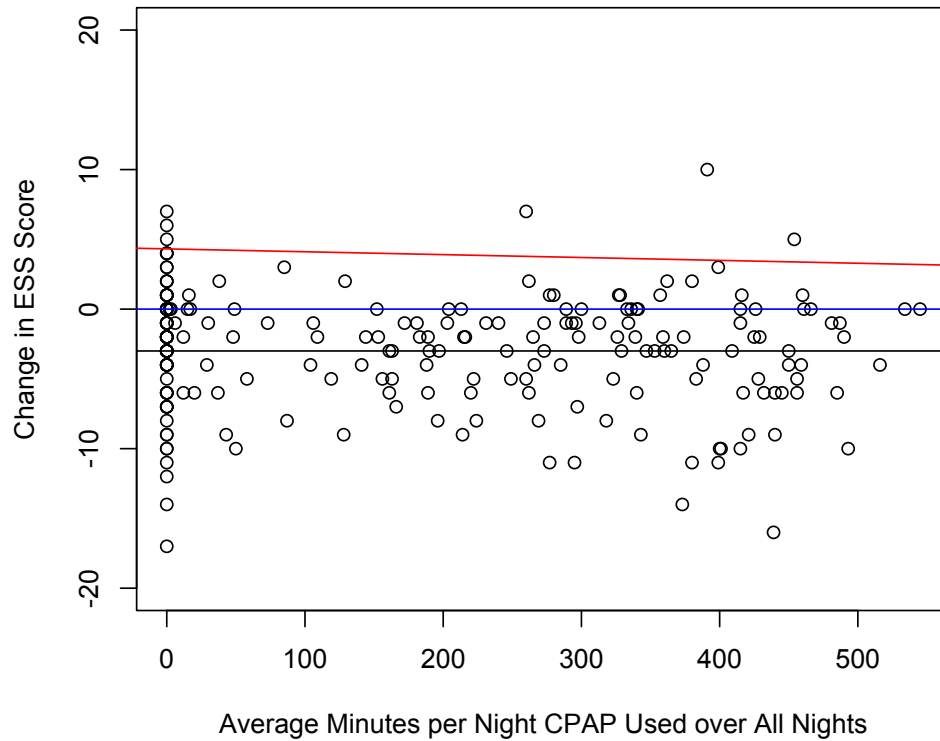
CPAP non-users were defined as patients with no CPAP use recorded over four-week interval prior to follow-up. CPAP users were defined as patients with any CPAP use recorded over four-week interval prior to follow-up. The CPAP user cohort was then divided into two groups, those with average use less than 240 minutes per night over all nights and average use of 240 or more minutes per night over all nights. A two-sided t-test was performed to compare change in ESS between CPAP non-users and CPAP users.

	<b>Baseline</b>	<b>Follow-up</b>	<b>Mean Change</b>	<b>P value</b>	<b>95% CI</b>
All patients	10.0 +/- 4.8	7.1 +/- 4.6	-2.9 +/- 4.0		
CPAP non-users	9.7 +/- 4.7	8.0 +/- 4.8	-1.7 +/- 3.5		
CPAP users	10.0 +/- 4.9	7.0 +/- 4.3	-3.1 +/- 3.9	<0.0001	(3.10 – 4.13)
<240 minutes per night over all nights	10.6 +/- 4.8	7.4 +/- 4.6	-3.1 +/- 3.1	<0.0001	(3.39 – 4.42)
≥240 minutes per night over all nights	9.9 +/- 4.8	6.7 +/- 4.0	-3.2 +/- 4.4	<0.0001	(3.39 – 4.42)

**Table 3: Baseline and Follow-up SNORE-25 Scores for CPAP Non-users and CPAP Users**

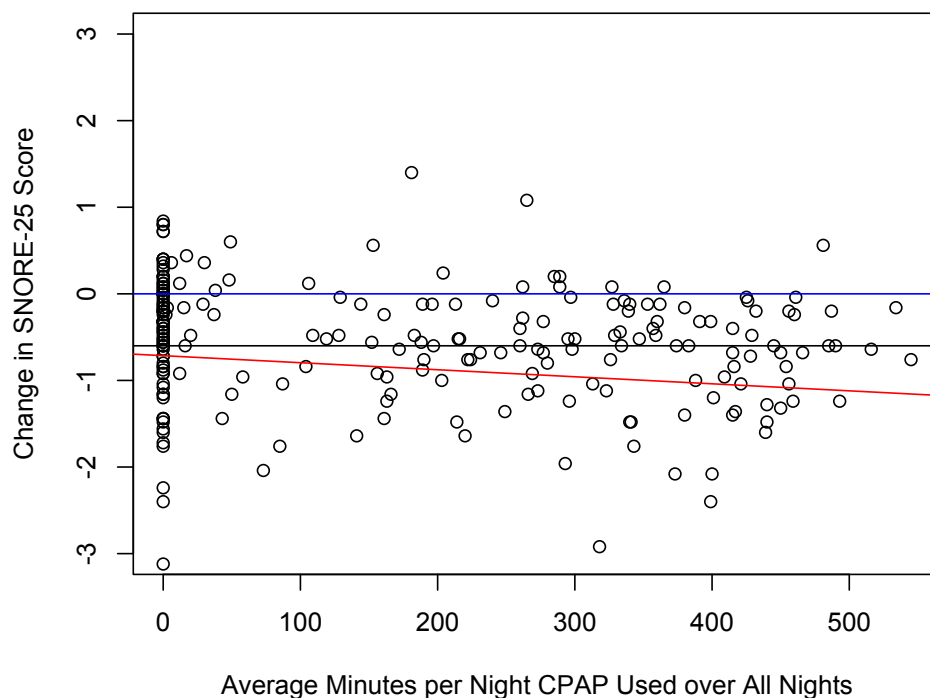
CPAP non-users were defined as patients with no CPAP use recorded over four-week interval prior to follow-up. CPAP users were defined as patients with any CPAP use recorded over four-week interval prior to follow-up. The CPAP user cohort was then divided into two groups, those with average use less than 240 minutes per night over all nights and average use of 240 or more minutes per night over all nights. A two-sided t-test was performed to compare change in SNORE-25 between CPAP non-users and CPAP users.

	<b>Baseline</b>	<b>Six Months</b>	<b>Mean Change</b>	<b>P value</b>	<b>95% CI</b>
All patients	1.5 +/- 0.8	0.9 +/- 0.8	-0.5 +/- 0.7		
CPAP non-users	1.5 +/- 0.8	1.2 +/- 0.8	-0.3 +/- 0.6		
CPAP users (all)	1.5 +/- 0.7	0.8 +/- 0.7	-0.6 +/- 0.7	<0.0001	(1.17 – 1.38)
<240 minutes per night over all nights	1.4 +/- 0.6	0.9 +/- 0.7	-0.5 +/- 0.7	<0.0001	(1.48 – 1.65)
≥240 minutes per night over all nights	1.4 +/- 0.7	0.7 +/- 0.6	-0.7 +/- 0.7	<0.0001	(1.48 – 1.65)



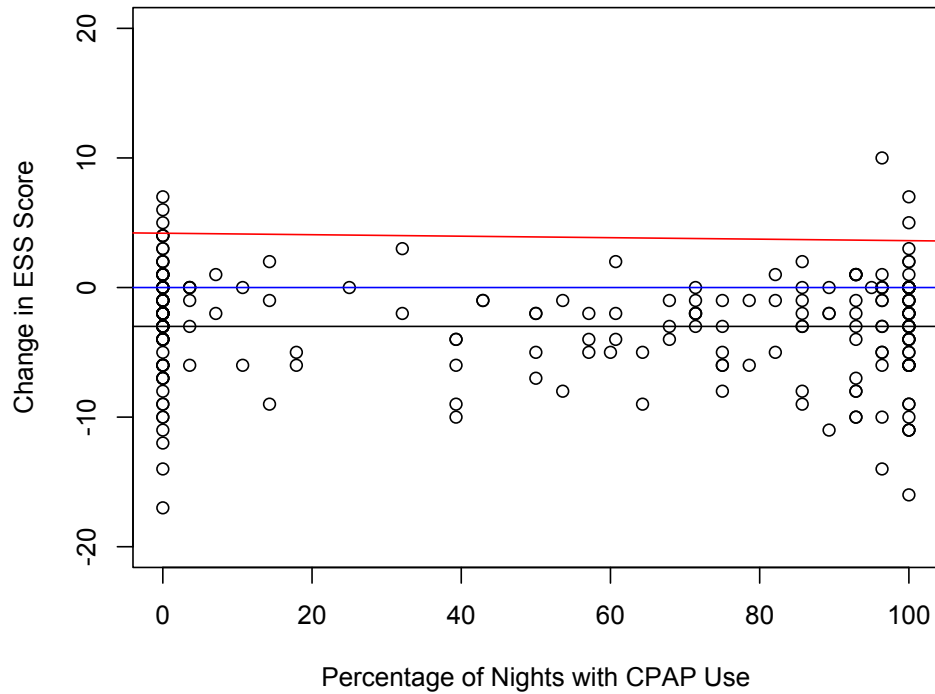
**Figure 1: Change in ESS Score vs Average Minutes per Night CPAP Used over All Nights between Baseline and Follow-up**

Negative change in ESS indicates improvement from baseline. Blue line indicates no improvement. Black line indicates minimal clinically important threshold for improvement in sleepiness, change in ESS of -3.<sup>8</sup> Red line indicates adjusted linear model. There was no statistically significant association between average minutes per night CPAP used over all nights and change in ESS score, after a priori covariate adjustments (p=0.18, 95% CI -0.005 – 0.001).



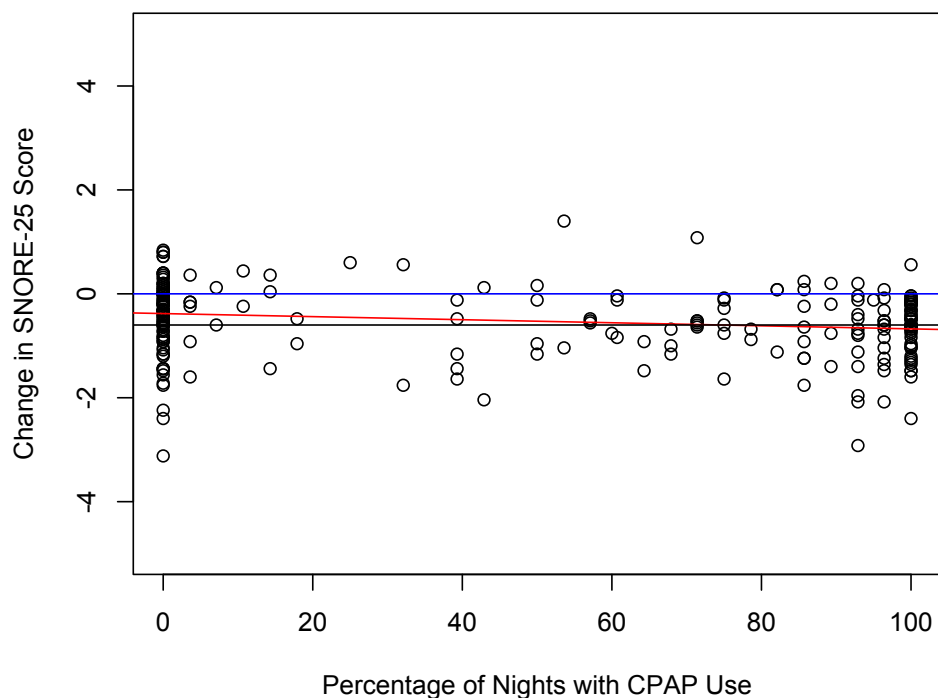
**Figure 2: Change in SNORE-25 Score vs Average CPAP Use over All Nights between Baseline and Follow-up**

Negative change in SNORE-25 indicates improvement from baseline. Blue line indicates no improvement. Black line indicates minimal clinically important threshold for improvement in quality of life, change in SNORE-25 of -0.6 (anchor method).<sup>9</sup> Red line indicates adjusted linear model. For every 30-minute increase on average CPAP use over all nights in four-week interval, there is a -0.024 change in SNORE-25 that is statistically significant, after a priori covariate adjustments (p=0.002, 95% CI -0.001- -0.0002).



**Figure 3: Change in ESS Score vs Percentage of Nights with CPAP Use between Baseline and Follow-up**

Negative change in ESS indicates improvement from baseline. Blue line indicates no improvement. Black line indicates minimal clinically important threshold for improvement (-3).<sup>8</sup> Red line indicates adjusted linear model. There was no significant association between percentage of nights with CPAP use and change in ESS score, after a priori covariate adjustments ( $p=0.36$ , 95% CI -0.018 – 0.007).



**Figure 4: Change in SNORE-25 Score vs Percentage of Nights with CPAP Use between Baseline and Follow-up**

Negative change in SNORE-25 indicates improvement from baseline. Blue line indicates no improvement. Black line indicates minimal clinically important threshold for improvement in quality of life, change in SNORE-25 of -0.6 (anchor method).<sup>9</sup> Red line indicates adjusted linear model. For every additional night of CPAP used over a four-week interval, there was a -0.01 change in SNORE-25, after a priori covariate adjustments, which was statistically significant ( $p=0.017$ , 95% CI -0.005 - -0.005).

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