CPAP Adherence Predictors in a Randomized Trial of Moderate-to-Severe OSA Enriched With Women and Minorities

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BACKGROUND: Suboptimal CPAP adherence in OSA clinical trials involving predominantly white men limits interpretability and generalizability. We examined predictors of CPAP adherence in a clinical trial enriched with minorities.

METHODS: The Sleep Apnea Stress Study—a randomized, double-blind, sham-controlled trial of patients with moderate-to-severe OSA—included participants with complete 8-week adherence data ($n = 138$). Overnight 14-channel polysomnography, anthropometry, socioeconomic status, mood questionnaires, and week 1 CPAP adherence were analyzed via adjusted linear models relative to CPAP adherence (average minutes per night usage).

RESULTS: Overall, age was 51 ± 12 years, 55% of the patients were male, 55% were white, BMI was 36.7 ± 7.7 kg/m², and median apnea-hypopnea index was 20 (interquartile range, 13-37). In univariate analyses adherence increased with randomization to active CPAP (81 min; 95% CI, 30-132), increasing age (35 min/decade; 95% CI, 13-57), white race (78 min, 95% CI, 26-129), and per hour of week 1 adherence (41 min, 95% CI, 32-51). Active CPAP (48 min, 95% CI, 6-91), increasing age (27 min/decade, 95% CI, 10-44), and higher 1-week adherence (36 min/h, 95% CI, 27-46) were significantly associated with improved adherence in multivariable analyses. Subgroup analyses showed stronger associations of adherence with treatment arm in whites and increasing age in minorities. Increasing age and white race were more strongly associated with adherence in women.

CONCLUSIONS: In this trial with near-even sex distribution and high ethnic minority representation, we identified CPAP assignment, increasing age, and early adherence to be associated with improved adherence in addition to sex-specific and race-specific adherence differences. These results can inform targeted clinical trial adherence optimization strategies.

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ABBREVIATIONS: AHI = apnea-hypopnea index

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OSA is highly prevalent, with population-based data supporting estimates of 13% of men and 6% of women.¹ OSA treatment is initiated to improve symptoms and mitigate adverse downstream health consequences, including neurocognitive dysfunction and cardiovascular-specific mortality.² The standard treatment for OSA, CPAP, is often successful in reversing the pathophysiology of OSA and improving sleep continuity, which translates to improvements in daytime sleepiness and quality of life measures.^{3,4} However, suboptimal adherence to CPAP poses a threat to achieving these health benefits. CPAP nonadherence estimates range between 29% and 83%, based on data from primarily clinic-based studies.^{5,6}

Clinic-based studies have identified numerous factors—subject characteristics, polysomnographic, and mood indices—as predictors of long-term adherence.^{7–11} The most consistent findings include early PAP adherence,^{5,12} self-reported daytime sleepiness,¹³ and certain psychological traits such as self-efficacy.^{5,13,14} Several studies support the association between increasing age and CPAP adherence; however, underlying mediating factors remain understudied.^{5,15,16} Existing data from clinic-based and clinical trial studies suggest an association of black race and reduced PAP adherence that may be mediated by socioeconomic position.^{5,7,17,18} A Veterans Affairs–based clinic study found that black participants had lower CPAP adherence and, in contrast to white/Hispanic individuals, CPAP use was correlated with the functional outcomes of sleep.¹⁸ In a study of preoperative patients who had received a diagnosis of moderate-to-severe OSA and were monitored for 30-day adherence, male sex and black race were each associated with a 1-h decrement in CPAP use.¹⁷ Neighborhood socioeconomic factors mitigated the role of race in adherence, particularly with longer-term

follow-up (3 months), thereby highlighting the importance of neighborhood and socioeconomic factors in adherence.^{7,19} Although the prevalence of OSA is two- to fourfold higher in men compared with women, data focused on the influence of sex on PAP adherence in OSA has been inconsistent. Whereas the study on perioperative patients with OSA identified decreased adherence in men, a retrospective analysis of a large cohort of patients found marginally higher use in men.^{15,17} An analysis of patients from an urban public hospital also found a twofold increase in nonadherence risk among women.²⁰ These data, primarily generated from clinic-based studies, suggest that increasing age and black race are associated with higher levels of PAP adherence; however, clinical trial–based data are a bit sparser. Furthermore, sex-specific differences relative to PAP adherence remain less clear, particularly in randomized clinical trials.

Suboptimal CPAP adherence in clinical trials is a fundamental challenge, particularly in terms of effective interpretation of results. As a result of CPAP nonadherence in these trials, in many instances it is unclear whether null findings are due to true lack of biologic benefit of reversal of OSA pathophysiology vs the result of inadequate OSA treatment to detect improvements in health outcomes. There are few published findings characterizing predictors of CPAP adherence in clinical trials, specifically relative to CPAP vs sham and examination of sex-specific and race-specific relationships. For example, data that are available have focused on predominantly male participants.^{12,21} We therefore chose to investigate the association of factors in various domains, that is, subject characteristics, mood, sleep apnea severity, and socioeconomic factors, as predictors of overall, CPAP, and sham CPAP adherence in a randomized clinical trial characterized by sex and ethnic diversity and designed to examine the impact of CPAP on cardiovascular biomarkers. We hypothesize that overall adherence will be associated with sociodemographic factors such as age, race, and sex as well as measures of psychological well-being. In addition, we anticipate differential adherence in subgroups stratified by age and race and substantive differences in adherence between sham and active CPAP groups given recognized differences in levels of adherence.

Methods

Participants and Study Design

The Sleep Apnea Stress Study (NCT00607893) was a single-center (two-site), randomized, double-blind, sham-controlled, parallel group trial.

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The Sleep Apnea Stress Study design, methods, and demographics have been previously published elsewhere.²² Briefly, 1,086 adults (age, 20–75 years) with moderate-to-severe OSA (apnea-hypopnea index [AHI], ≥ 15) without prior positive airway pressure therapy use and adherence of at least 4 h per night for 70% of nights during a 2-week run-in period of use were identified from two academic sleep medicine clinics (Fig 1). Exclusion criteria included CPAP use outside of the trial, supplemental oxygen use, non-OSA primary sleep disorder, drowsy driving, unstable medical condition, and current or anticipated use of corticosteroids or potent antiinflammatory medications.

Participants were randomized to sham ($n = 77$) or active ($n = 76$) CPAP using a computerized permuted block design with varying block size and stratification on age, sex, and OSA severity. Of those randomized, 71 of the sham CPAP and 72 of the active CPAP group members completed an 8-week assessment. The final analytic sample consisted of participants ($n = 69$ in each group) who had complete CPAP adherence data at 8 weeks of CPAP therapy. The institutional review board (IRB; University Hospitals IRB 07-06-25, MetroHealth Medical Center IRB 10-00370, and Cleveland Clinic IRB 13-716) approved the protocol, and written informed consent was obtained from all participants.

CPAP Administration and Therapy Adherence Measures

All participants received REMstar Pro machines (Philips Respironics) with heated humidification and expiratory pressure relief as needed.

All participants had access to the same mask choices. Sham CPAP was provided via a customized Philips Respironics mask with enlarged expiratory ports at the elbow (1-cm orifice) and an orifice-resistor between the pump and tubing that delivered negligible pressure (0.4 ± 1 cm H₂O pressure).²³ The sham CPAP pressure was set to 4 cm H₂O. This methodology has been previously shown not to distort sleep architecture or OSA severity while providing noise and humidity levels comparable to active CPAP.²³ Adherence was monitored via export from the CPAP units and quantification of effective treatment duration with clock-time counters.²⁴ Although overall objective measures of adherence were monitored continuously throughout the trial, participant download data were parsed into adherence for the first 7 days, 2 months after randomization, as well as the last week of the study. Participants completed a questionnaire on self-reported adherence and reasons for nonuse of the device.²⁵

Other Measures

Participants had a baseline visit before randomization to sham or active CPAP. All participants completed questionnaires during this baseline visit, which included collection of data on demographics, medical history, income, and education. In addition, participants self-reported perceived social status on a 0 (lowest) to 10 (highest) scale.²⁶ The following metrics were collected: the Epworth Sleepiness Scale (Cronbach $\alpha = 0.88$),^{27,28} Functional Outcomes of Sleep Questionnaire (Cronbach $\alpha = 0.90$),²⁹ Positive and Negative Affect

Figure 1 – Study flow: recruitment, attrition, and retention. PAP = positive airway pressure.

Schedule (Cronbach $\alpha = 0.88$ for positive affect and 0.87 for negative affect),³⁰ and Center for Epidemiological Studies Depression Scale (Cronbach $\alpha = 0.85$ -0.90).^{31,32} BMI (kg/m^2) was calculated from body weight, measured with a scale calibrated with standard weights, and height, measured with a wall-mounted stadiometer. Participants were asked at the end of week 8, "Over the past week, which study arm did you think that you were on?"

Statistical Analysis

Participant characteristics were summarized as mean $\pm$ SD, median (interquartile range, IQR), or number (%) and compared between active and sham CPAP using Pearson χ^2 tests or Fisher exact test for variables with small counts for categorical variables, a pooled t test for normally distributed continuous variables, and Wilcoxon Mann-Whitney rank sum test for continuous variables with skewed distributions.

Primary analyses examined adherence (average minutes of nightly use over 8 weeks) associations within the entire study cohort irrespective of study arm assignment. Secondary analyses analyzed active CPAP and sham groups separately. Adherence for secondary analyses was defined in two ways: (1) continuously as average minutes of nightly use over

8 weeks and (2) dichotomously defined by standard clinical criteria: at least 70% of nights with a minimum of 4 h of nightly CPAP use.³³

Linear regression for continuous outcomes and logistic regression for dichotomous outcomes were used to evaluate relationships. Univariate analyses were conducted on all variables for both continuous and dichotomous adherence. Multivariable analyses were conducted on significant variables identified in the univariable analyses. Collinearity of variables in the multivariable model was assessed via variance inflation factors. We leveraged the almost even distribution of sex and race by determining sex-specific and race-specific adherence differences in subgroup analyses; interactions between subgroups and predictors were analyzed. Statistical interactions of significant multivariable model predictors and socioeconomic and mood metrics were analyzed. A significance level of $\alpha = 0.05$ was used for primary and secondary analyses. Interactions were considered significant at $P \leq .1$. Linear regression data are presented as β coefficients with 95% CIs, while logistic regression results are presented as odds ratios (ORs) and 95% CIs. We assessed the mediation effect of first-week adherence on all variables significantly associated with 8-week adherence, using the mediation R package.^{34,35} All significance levels reported are two sided. All analyses were conducted with R software version 3.3.2.³⁶

Results

Study Population

Baseline measurements are presented in Table 1. The 138 participants in the final analytic sample had an average age of 50.8 ± 11.7 years, 55% were male, 55% were white, with a median AHI of 20 events per hour (IQR, 13-37). The non-white participants included 58 black and 4 Asian individuals. Participants assigned to active CPAP vs sham had significantly higher adherence at both week 1 (5.1 [IQR, 3.3-6.1 h] vs 3.2 [IQR 1.3-5.3 h], respectively) and week 8 (4.8 [IQR, 2.6-6.3 h] vs 2.2 [IQR, 0.32-4.9 h], respectively). Except for race, baseline characteristics did not significantly differ when assessed on the basis of median first-week adherence (4.34 h per night). Correlation between actual study arm assignment and participant perception of study arm assignment was 0.145.

Primary Analyses

Univariate analyses of continuous adherence for the overall cohort are presented in Table 2. Average use at week 1 was the strongest predictor of 8-week adherence, with an increase of 41.30 min for every additional hour used (95% CI, 31.90-50.71 min). In addition, randomization to the treatment arm increased adherence by an average of 81.14 min (95% CI, 30.04-132.25 min) compared with sham CPAP. Every decade increase in age increased adherence by an average of 35.03 min (95% CI, 13.47-56.58 min). White race compared with other race increased adherence by 77.64 min (95% CI, 26.10-129.18 min) in univariate

models, which persisted in the multivariable model including age, race, and study arm (increase in adherence for whites by 75.30 min, 95% CI, 27.02-123.59); however, the results were no longer significant in the multivariable model additionally adjusted for first-week adherence. Other factors including socioeconomic status and psychological metrics were not significant predictors.

Multivariable analysis of those variables associated with adherence in univariate models showed that randomization to active compared with sham CPAP, increasing age, and higher adherence at week 1 predicted increased adherence (Table 3). Variable inflation factors for all multivariable model predictors were less than 1.5, indicating no substantial collinearity. Randomization to active vs sham CPAP was associated with an increase in adherence by an average of 48.23 min (95% CI, 5.59-90.94 min). For every decade increase in age, adherence increased by 26.84 min (95% CI, 9.55-44.14 min). For every hour of increased CPAP use at week 1, adherence increased by an average of 36.19 min (95% CI, 26.73-45.64 min). Race was not a significant adherence predictor when the other factors were considered. The combination of study arm, age, and adherence at week 1 together accounted for 43% of the variation in 8-week adherence.

Secondary Analyses

Adherence as a Dichotomous Outcome: Results in the overall cohort were similar when adherence was examined as a dichotomous variable in univariate

TABLE 1] Baseline Characteristics of Participants

Factor	Overall (N = 138)	Active CPAP (n = 69)	Sham CPAP (n = 69)	P Value ^a
Participant characteristics and comorbidities				
Age, y	50.8 ± 11.7	50.3 ± 11.7	51.3 ± 11.8	.63
Race				
White	76 (55)	36 (52)	40 (58)	.61
Non-white	62 (45)	33 (48)	29 (42)	
Male sex, No. (%)	76 (55)	38 (55)	38 (55)	> .99
BMI, kg/m ²	36.7 ± 7.7	36.7 ± 7.1	36.7 ± 8.3	.97
Cardiovascular disease	5 (3.7)	3 (4.4)	2 (2.9)	> .99
Socioeconomic factors				
Income > \$50,000/y	61 (48)	28 (43)	33 (52)	.38
Education				.93
High school or less	39 (28)	20 (29)	19 (28)	
Any college/vocational	44 (32)	21 (30)	23 (33)	
Bachelor's degree or more	49 (36)	25 (36)	24 (35)	
Social status, 1-10	5.8 ± 2.2	5.8 ± 2.2	5.7 ± 2.2	.78
Mood metrics				
Epworth Sleepiness Scale	9.0 ± 4.3	8.8 ± 4.5	9.1 ± 4.1	.68
FOSQ	17 (15-18)	16 (14-18)	17 (15-18)	.25
CESD	13 (7-20)	15 (8-21)	11 (6-20)	.35
PANAS, Positive	30 (24-36)	29 (24-36)	31 (25-36)	.56
PANAS, Negative	16 (13-21)	16 (13-21)	16 (13-21)	.81
Sleep metrics				
Apnea-hypopnea index	20 (13-37)	23 (13-38)	20 (13-36)	.75
% TST SpO ₂ < 90%	2.0 (0.0-7.0)	2.0 (0.0-6.8)	3.0 (0.0-7.0)	.54
CPAP, cm H ₂ O	10 (8-12)	10 (9-12)	10 (8-12)	.97
Average hours used, week 1	4.3 (2.4-5.8)	5.1 (3.3-6.1)	3.2 (1.3-5.3)	.009
Average hours used, week 8	3.6 (1.2-6.0)	4.8 (2.6-6.3)	2.2 (0.3-4.9)	.003
% days used ≥ 4 h, week 8	57 (14-86)	71 (30-100)	43 (0.0-86)	.00

Statistics presented as mean ± SD, median (25th percentile-75th percentile), median (min-max), or No. (%). Boldface text indicates $P < .05$. CESD = Center for Epidemiologic Studies Depression Scale; FOSQ = Functional Outcomes of Sleep Questionnaire; PANAS = Positive and Negative Affect Schedule; % TST SpO₂ < 90% = percent total sleep time with oxygen saturation less than 90%.

^aP values: Kruskal-Wallis test for FOSQ, CESD, PANAS positive, PANAS negative, TST 90%, AHI, CPAP, average use week 1, average use week 8, and % days used ≥ 4 h, week 8. Fisher exact test on cardiovascular disease. *t*-test on everything with a ±. Pearson χ^2 test for race, sex, income, and education.

analyses (Table 4). Treatment arm (OR, 2.83; 95% CI, 1.42-5.80), increasing age (per decade) (OR, 1.47; 95% CI, 1.09-2.02) and white race (OR, 2.94; 95% CI, 1.45-6.13), and first-week adherence (OR, 2.25; 95% CI, 1.74-3.08) were significantly associated with 8-week adherence. When stratified by study arm (sham and active CPAP) results were similar to the overall cohort when outcome was examined both as a dichotomous variable (Table 4) and in a continuous manner (Table 5). White race predicted adherence in active CPAP, but not sham CPAP, arms when adherence was analyzed as a continuous variable. Age showed a stronger association with adherence in the sham compared with active CPAP

arm when adherence was evaluated as a dichotomous variable.

Predictors of Overall Adherence Stratified by Sex and Race: To further examine for race-specific or sex-specific differences in adherence predictors, subgroup analyses were conducted (Tables 6, 7, respectively). Compared with white participants, black participants' adherence was not significantly associated with treatment arm but was associated with increasing age. When subgroups were based on sex, treatment arm was significantly associated with adherence in women but not men. In addition, increasing age and race were significant

TABLE 2] Univariate Linear Regression Predictors of Overall Adherence: Average Minutes per Night

Factor	Estimate (95% CI)
Treatment arm	81.14 (30.04 to 132.25)
Participant characteristics and comorbidities	
Age (per decade)	35.03 (13.47 to 56.58)
White vs not	77.64 (26.10 to 129.18)
Male sex (reference)	−15.38 (−68.51 to 37.76)
BMI, kg/m ²	−0.29 (−3.76 to 3.18)
Cardiovascular disease	79.64 (−61.25 to 220.52)
Socioeconomic factors	
Income > \$50,000	22.05 (−32.88 to 76.98)
Education	
High school or less	Reference
Any college/vocational	28.30 (−39.22 to 95.83)
Bachelor's degree or more	42.69 (−23.20 to 108.58)
Social status, 1-10	−3.28 (−15.99 to 9.43)
Mood metrics	
Epworth Sleepiness Scale	−5.25 (−11.41 to 0.92)
FOSQ	4.29 (−5.38 to 13.96)
CESD	−1.91 (−4.66 to 0.84)
PANAS Positive	0.88 (−2.34 to 4.09)
PANAS Negative	−3.17 (−7.27 to 0.93)
Sleep Metrics	
Apnea-hypopnea index	0.15 (−1.25 to 1.54)
% TST SpO ₂ < 90%	−0.10 (−2.37 to 2.17)
CPAP	−1.95 (−10.74 to 6.84)
Average use, week 1 (per h)	41.30 (31.90 to 50.71)

Boldface text indicates $P < .05$. See Table 1 legend for expansion of abbreviations.

predictors of adherence in women but not men. Average CPAP use at week 1 was a significant predictor in both men and women and had similar estimates. No

significant interactions for race or sex with regard to adherence were found.

Multivariable Model Predictor Interactions With Mood and Socioeconomic Metrics: There were no statistically significant interactions between study arm, race, or age and mood or socioeconomic metrics relative to adherence outcomes. The statistical interactions of first-week adherence and self-reported social status ($P = .06$) and education of 4 years of college or more ($P = .09$) were statistically significant. In stratified analyses on median first-week adherence, effect estimates for increasing socioeconomic status (income, education, and social status) in relation to 8-week adherence were nonsignificantly higher in those with median or greater first-week adherence and lower in those with lower than median first-week adherence.

First-Week Adherence Mediation Analyses

Mediation analyses reveal that first-week adherence is a significant mediator for treatment arm but not race or age. Direct effect of treatment arm is 39.6 min (95% CI, −5.2 to 83.4 min), with 50.2% of total effect mediated by first-week adherence. Social status and education do not significantly mediate the relationship between first-week adherence and 8-week adherence.

Discussion

This study leverages an existing randomized sham controlled trial in those with moderate to severe OSA, evenly balanced in terms of sex and white vs black race, allowing for the unique ability to conduct novel analyses of differential predictors based on study arm, sex, and race. Overall, the first week of adherence was the strongest adherence predictor. Increasing age and white race were additional predictors of adherence, which persisted after consideration of confounding influences. Although the active CPAP group had higher adherence than the sham CPAP arm, predictor profiles were similar when analyzing active and sham CPAP groups.

TABLE 3] Multivariable Linear Regression Predictors of Adherence in the Overall Cohort: Average Nightly Use in Minutes

Parameter	Model 1 ^{a,b}	Model 2 ^{a,b}
Study arm (active vs sham CPAP)	87.36 (39.53 to 135.20)	48.23 (5.59 to 90.94)
Average use, week 1 (per h)	...	36.19 (26.73 to 45.64)
Age (per decade)	32.89 (12.62 to 53.15)	26.84 (9.55 to 44.14)
White race vs other	75.30 (27.02 to 123.59)	30.95 (−11.70 to 73.60)

Boldface text indicates $P < .05$.

^aModel 1 includes study arm, age, and race; model 2 additionally includes average use at week 1.

^bAll values presented as estimate (95% CI) in minutes.

TABLE 4] Univariate Logistic Regression Predictors of Adherence: Dichotomized at $\geq 70\%$ Use ≥ 4 h per Night

Factor	Overall (N = 138) OR (95% CI)	Active CPAP (n = 69) OR (95% CI)	Sham CPAP (n = 69) OR (95% CI)
Treatment arm	2.83 (1.42-5.80)	...	...
Participant characteristics and comorbidities			
Age (per decade)	1.47 (1.09-2.02)	1.45 (0.96-2.25)	1.65 (1.03-2.82)
White vs not	2.94 (1.45-6.13)	1.87 (1.14-3.07)	1.95 (1.32-2.90)
Male sex (reference)	0.82 (0.41-1.63)	1.02 (0.63-1.64)	1.17 (0.82-1.67)
BMI, kg/m ²	1.01 (0.97-1.06)	1.04 (0.97-1.12)	1.02 (0.97-1.7)
Cardiovascular disease	2.21 (0.35-17.19)	1.53 (0.74-3.15)	1.39 (0.86-2.24)
Socioeconomic factors			
Income > \$50,000	1.63 (0.81-3.31)	1.46 (0.88-2.41)	1.41 (0.97-2.05)
Education			
High school or less	Reference	Reference	Reference
Any college/vocational	1.26 (0.51-3.14)	1.02 (0.30-3.48)	1.60 (0.38-7.34)
Bachelor's degree or more	1.92 (0.81-4.67)	2.22 (0.65-7.92)	1.88 (0.49-8.20)
Social status, 1-10	1.02 (0.87-1.20)	1.10 (0.88-1.39)	0.95 (0.73-1.23)
Mood metrics			
Epworth Sleepiness Score	0.94 (0.87-1.02)	0.99 (0.90-1.08)	0.96 (0.89-1.03)
FOSQ	1.05 (0.93-1.19)	0.99 (0.82-1.18)	1.02 (0.90-1.17)
CESD	0.97 (0.94-1.01)	0.99 (0.94-1.04)	0.98 (0.94-1.02)
PANAS Positive	1.03 (0.98-1.07)	1.02 (0.96-1.08)	1.02 (0.98-1.06)
PANAS Negative	0.96 (0.90-1.01)	0.97 (0.90-1.04)	0.96 (0.90-1.02)
Sleep metrics			
Apnea-hypopnea index	1.00 (0.98-1.01)	1.00 (0.97-1.02)	1.00 (0.98-1.02)
% TST SpO ₂ < 90%	1.00 (0.97-1.03)	0.98 (0.94-1.02)	1.00 (0.97-1.03)
CPAP	0.98 (0.87-1.09)	0.96 (0.83-1.13)	0.98 (0.87-1.11)
Average use, week 1 (per h)	2.25 (1.74-3.08)	1.93 (1.39-2.89)	2.64 (1.76-4.70)

Boldface text indicates $P < .05$. See Table 1 legend for expansion of abbreviations.

Understanding differences in adherence predictors of sham vs active CPAP is important as dissimilar perceptions of treatment and incomplete participant blinding are threats to the internal validity of randomized controlled trials, and can therefore help inform clinical trial design. Importantly, however, this analysis did not reveal consistent differences in predictors between sham and active CPAP arms. Adherence in women was associated with treatment arm, increasing age, and race; factors that were not significant in the male subset, thereby highlighting unique PAP and sham predictors according to sex. Adherence in black participants was associated with increasing age but not treatment arm; findings that were not present in the white participants. Overall findings are meaningful, particularly because the National Institutes of Health and other funding agencies have emphasized inclusion of women and minorities as clinical research participants. Therefore, an

understanding of which subgroups may benefit from proactive interventions to improve adherence will inform future trial design.

Sham CPAP has been considered a reasonable option for the control condition in OSA clinical trials because it is thought to adequately blind participants and provide a possible placebo effect without affecting OSA severity or sleep architecture.³⁷ Our results are consistent with other trials demonstrating that randomization to active vs sham CPAP predicts adherence.³⁸⁻⁴⁰ This finding raises concern about less than ideal blinding, which may compromise internal study validity by precipitating selective premature drop-out between groups and introducing measurement bias. An alternative explanation may be that even if patients do not perceive allocation to sham CPAP, ineffective therapy may inherently decrease adherence. Regardless, differential adherence based on

TABLE 5] Univariate Linear Regression Predictors of Adherence for Individual Active and Sham CPAP Groups: Average Minutes per Nightly Use

Factor	Active CPAP (n = 69) Estimate (95% CI)	Sham CPAP (n = 69) Estimate (95% CI)	Interaction P Value
Participant characteristics and comorbidities			
Age (per decade)	34.33 (7.31 to 61.35)	37.47 (5.01 to 69.93)	.80
White vs not	100.00 (36.78 to 163.32)	64.88 (−13.37 to 143.13)	.28
Male sex (reference)	19.23 (−48.71 to 87.17)	−49.98 (−128.26 to 28.30)	.35
BMI	1.99 (−2.82 to 6.80)	−1.91 (−6.69 to 2.88)	.28
Cardiovascular disease	5.60 (−161.71 to 172.91)	167.18 (−60.82 to 395.18)	.92
Socioeconomic factors			
Income > \$50,000	20.52 (−51.23 to 92.28)	38.58 (−43.14 to 120.29)	.89
Education			.30
High school or less	Reference	Reference	
Any college/vocational	−18.49 (−104.57 to 67.58)	70.45. (−28.08 to 168.98)	
Bachelor's degree or more	38.95 (−46.31 to 124.21)	45.65 (−49.95 to 140.25)	
Social status, 1-10	−6.49 (−22.81 to 9.83)	1.03 (−17.95 to 20.00)	.55
Mood metrics			
Epworth Sleepiness Scale	−3.01 (−10.70 to 4.68)	−7.11 (−16.52 to 2.29)	.54
FOSQ	0.40 (−12.31 to 13.10)	4.99 (−8.98 to 18.97)	.47
CESD	−1.08 (−4.84 to 2.67)	−1.83 (−5.71 to 2.05)	.80
PANAS Positive	2.74 (−1.52 to 7.01)	−1.03 (−5.60 to 3.55)	.43
PANAS Negative	−1.76 (−6.89 to 3.37)	−5.34 (−11.55 to 0.88)	.27
Sleep metrics			
Apnea-hypopnea index	−0.57 (−2.31 to 1.17)	1.06 (−1.10 to 3.23)	.47
% TST SpO ₂ < 90%	−2.13 (−4.93 to 0.67)	2.48 (−1.00 to 5.95)	.04
CPAP	−7.36 (−18.30 to 3.58)	3.02 (−10.29 to 16.33)	.31
Average use, week 1 (per h)	34.60 (19.56 to 49.64)	42.50 (29.75 to 55.24)	.78

Boldface text indicates $P < .05$. See Table 1 legend for expansion of abbreviations.

study arm suggests that current methods of administering sham CPAP do not provide adequate participant blinding in randomized controlled trials and, therefore, new approaches to administration of the control condition should be investigated.

While significantly affecting adherence in unadjusted models, white race was not a significant predictor of adherence in multivariable analysis adjusted for first-week adherence, the strongest predictor of long-term adherence. Significant interactions between first-week adherence and socioeconomic metrics, such as perceived social status and education, may indicate that socioeconomic factors play a key role in modulating the influence of early adherence on later adherence; however, these factors do not seem to mediate this association between early and long-term adherence. Overall findings corroborate prior work,

which was focused on assessment of 3-month adherence in a randomized controlled trial evaluating home- vs laboratory-based evaluation and treatment of OSA.⁷ Enrolling 135 subjects, this trial identified black race to be significantly associated with worse 3-month adherence in unadjusted analyses but was no longer significant after adjustment for neighborhood socioeconomic status.⁷ The early adherence–socioeconomic factor interaction is perhaps the reason that race was not a significant predictor in multivariable models that included first-week adherence. However, in our study self-reported income, social status, and education were not significant adherence predictors in unadjusted analyses. A potential explanation for the disparate findings may be that in contrast to the current work, participants in the Billings et al study⁷ had higher baseline educational status and may have had

TABLE 6] Race-Specific Subgroup Analysis of Univariate Linear Regression Predictors of Adherence: Average Minutes per Night^a

Factor	Black (n = 58) Estimate (95% CI)	White (n = 76) Estimate (95% CI)	Interaction P Value
Treatment arm	74.75 (−0.44 to 149.94)	101.73 (33.83 to 169.63)	.60
Participant characteristics and comorbidities			
Age (per decade)	34.88 (5.23 to 64.52)	29.16 (−2.35 to 60.66)	.79
Male sex (reference)	−2.15 (−81.48 to 77.19)	18.7 (−56.82 to 94.22)	.71
BMI	−2.18 (−7.28 to 2.93)	2.42 (−2.35 to 7.19)	.19
Cardiovascular disease	164.59 (−40.19 to 369.38)	−51.08 (−274.96 to 172.8)	.16
Socioeconomic factors			
Income > \$50,000	10.55 (−94.41 to 115.51)	−9.81 (−86.35 to 66.73)	.76
Education			
High school or less	Reference	Reference	.70
Any college/vocational	18.02 (−68.81 to 104.85)	25.19 (−77.83 to 128.21)	
Bachelor's degree or more	24.48 (−95.03 to 143.99)	14.52 (−79.29 to 108.34)	
Social status, 1-10	−8.05 (−24.92 to 8.83)	−4.12 (−24.12 to 15.87)	.77
Mood metrics			
Epworth Sleepiness Scale	−2.43 (−11.02 to 6.15)	−5.13 (−14.4 to 4.13)	.67
FOSQ	4.39 (−8.5 to 17.29)	2.44 (−11.49 to 16.36)	.84
CESD	−0.92 (−4.67 to 2.84)	−0.93 (−5.11 to 3.24)	.99
PANAS Positive	0.34 (−4.01 to 4.69)	−0.13 (−4.89 to 4.63)	.89
PANAS Negative	−0.57 (−5.67 to 4.54)	−6.31 (−12.71 to 0.1)	.16
Sleep metrics			
Apnea-hypopnea index	1.11 (−0.8 to 3.03)	−0.79 (−2.72 to 1.15)	.17
% TST SpO ₂ < 90%	−0.69 (−5.43 to 4.05)	−0.46 (−3.02 to 2.11)	.93
CPAP	4.83 (−8.85 to 18.5)	−8.77 (−20.34 to 2.81)	.14
Average use, week 1 (per h)	31.55 (16.09 to 47.01)	46.55 (33.32 to 59.79)	.14

Boldface text indicates $P < .05$. See Table 1 legend for expansion of abbreviations.

^aThe four Asian participants were not included in analyses stratified by race because of limited sample size.

differences in housing and financial literacy. Perceived social status may also impact on attitudes and behaviors more so than quantitative measures of individual (eg, income and education) or neighborhood socioeconomic status. Further work to clarify the salience of individual and neighborhood socioeconomic factors—race, income, education, etc—on OSA therapy adherence is needed.

Unlike previous clinic-based studies that have identified OSA severity as defined by AHI as a predictor of adherence,⁴¹⁻⁴⁷ this study—similar to other randomized controlled trials focused on the evaluation of adherence predictors—did not identify any significant associations with polysomnographic metrics.¹² It is possible that the association between AHI and adherence is confounded by an unmeasured factor that clinical trial inclusion and exclusion criteria affect.

Differential associations were identified in race-specific and sex-specific stratified analyses. CPAP intervention compared with sham was associated with adherence in whites compared with blacks as well as women compared with men, which suggests the need to carefully evaluate for differential adherence in sleep apnea clinical trial study arms in whites and women. Increasing age was associated with adherence in black but not white individuals, suggesting augmenting efforts to optimize adherence, particularly in younger blacks. Finally, these results suggest targeting adherence interventions toward younger and minority women. Limited power likely precluded observing statistically significant interactions. It should be emphasized that these subgroup analyses, while compelling, should be interpreted cautiously given the smaller sample size of the stratified groups and warrant corroboration by future larger studies.

TABLE 7] Sex-Specific Subgroup Analysis of Univariate Linear Regression Predictors of Adherence: Average Minutes per Night

Factor	Female (n = 62) Estimate (95% CI)	Male (n = 76) Estimate (95% CI)	Interaction P Value
Treatment arm	119.26 (38.99 to 199.63)	50.05 (−16.81 to 116.91)	.18
Participant characteristics and comorbidities			
Age (per decade)	51.15 (13.34 to 88.95)	25.35 (−0.82 to 51.52)	.26
White vs not	95.84 (12.22 to 179.47)	63.07 (−6.94 to 133.08)	.55
BMI	−0.08 (−6.2 to 6.03)	−0.06 (−4.44 to 4.33)	.99
Cardiovascular disease	... ^a	76.15 (−59.34 to 211.65)	... ^a
Socioeconomic factors			
Income > \$50,000	53.65 (−41.56 to 148.86)	−9.42 (−82.51 to 63.66)	.29
Education			
High school or less	Reference	Reference	.34
Any college/vocational	35.97 (−66.85 to 138.78)	22.33 (−72.36 to 115.01)	
Bachelor's degree or more	33.84 (−82.85 to 150.52)	42.27 (−40.14 to 124.68)	
Social status, 1-10	−12.27 (−32.38 to 7.84)	3.63 (−14.34 to 21.59)	.24
Mood metrics			
Epworth Sleepiness Scale	−7.47 (−17.05 to 2.11)	−2.88 (−11.25 to 5.5)	.47
FOSQ	10.13 (−4.81 to 25.08)	−2.78 (−16.29 to 10.74)	.20
CESD	−0.88 (−5.06 to 3.29)	−3.29 (−7.49 to 0.91)	.42
PANAS Positive	3.6 (−1.54 to 8.74)	−1.53 (−5.71 to 2.64)	.12
PANAS Negative	−0.73 (−7.38 to 5.92)	−5.28 (−10.62 to 0.06)	.28
Sleep metrics			
Apnea-hypopnea index	0.86 (−1.63 to 3.34)	−0.3 (−1.97 to 1.37)	.43
% TST SpO ₂ < 90%	1.88 (−3.09 to 6.84)	−0.86 (−3.34 to 1.62)	.30
CPAP	−2.22 (−16.15 to 11.71)	−2.17 (−13.78 to 9.44)	> .99
Average use, week 1 (per h)	46.83 (32.92 to 60.74)	35.75 (22.64 to 48.86)	.25

Boldface text indicates $P < .05$. See Table 1 legend for expansion of abbreviations.

^aNo female participants had cardiovascular disease; so, analyses could not be conducted on this variable.

Several unique aspects of this investigation deserve emphasis. The present study population was enriched in black participants (42%) and had near-equal sex composition compared with prior work on adherence in randomized controlled trials and may be more representative of average adherence in this subgroup of the population. Unlike the Sleep Apnea Cardiovascular Endpoints study, which compared CPAP with usual care, our study design randomized participants to active and sham CPAP and is, therefore, more applicable not only to clinical practice but also to blinded clinical trials focused on CPAP therapy. Limitations of this investigation include the post-hoc nature of the analysis and potential lack of generalizability as the population was from a single-center randomized controlled trial. The mood metrics were self-reported rather than diagnosed via physician evaluation, potentially leading to misclassification; however, there is no reason to

suspect differential misclassification. The current study may be underpowered to detect clinically important adherence predictors compared with sample sizes from retrospective clinic-based samples. This examination of baseline associations with adherence needs confirmation in a larger study with longer follow-up.

Although examination of PAP adherence predictors has been performed in the Apnea Positive Pressure Long-Term Efficacy Study,³⁸ this is the first study to our knowledge that compares differential adherence predictors in analyses stratified separately by sham and active CPAP study arm and, due to the distribution, also allowed for stratification by sex and race. This study confirms prior findings of increasing age and early adherence, and study arm as predictors of CPAP adherence, now expanding generalizability to women and black individuals. Sex-specific and

race-specific differences in receptivity and response to CPAP may affect adherence, and an understanding of those factors may help inform clinical trial design. This work suggests sex-specific and race-specific differential contributions to adherence in addition to global findings of early adherence and increasing age predictive of overall adherence. Interventions aimed at groups least likely to be therapy adherent may

improve both clinical outcomes and information quality gathered from clinical trials. Given identification of these predictors, it may be possible to minimize their influence by development of targeted strategies to optimize approaches to clinical trials design and methodology in order to mitigate the negative influences of these factors on CPAP adherence.

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