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Changes in sleepiness and 24-h blood pressure following 4 months of CPAP treatment are not mediated by ICAM-1

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Abstract

Objective Continuous positive airway pressure (CPAP) therapy reduces circulating intercellular adhesion molecule 1 (ICAM-1) in adults with obstructive sleep apnea (OSA). ICAM-1 levels may affect the daytime sleepiness and elevated blood pressure associated with OSA. We evaluated the association of changes from baseline in ICAM-1 with changes of objective and subjective measures of sleepiness, as well as 24-h ambulatory blood pressure monitoring (ABPM) measures, following 4 months of CPAP treatment.

Methods The study sample included adults with newly diagnosed OSA. Plasma ICAM-1, 24-h ABPM, Epworth Sleepiness Scale (ESS), and psychomotor vigilance task (PVT) were obtained at baseline and following adequate CPAP treatment. The associations between changes in natural log ICAM-1 and changes in the number of lapses on PVT, ESS score, and 24-h mean arterial blood pressure (MAP) were assessed using multivariate regression models, controlling for a priori baseline covariates of age, sex, BMI, race, site, smoking status, physical activity, anti-hypertensive medications, AHI, and daily hours of CPAP use.

Results Among 140 adults (83% men), mean (± SD) body mass index (BMI) was 31.5 ± 4.2 kg/m^2, and apnea-hyopnea index (AHI) was 36.8 ± 15.3 events/h. Sleepiness measures, although not ICAM-1 or ABPM measures, improved significantly following CPAP treatment. We observed no statistically significant associations between the change in ICAM-1 and changes in sleepiness, MAP, or other ABPM measures.

Conclusion Changes in ICAM-1 levels were not related to changes in sleepiness or ABPM following CPAP treatment of adults with OSA. Future work should explore whether or not other biomarkers may have a role in mediating these treatment outcomes in adults with OSA.

Keywords Intercellular adhesion molecule-1 · Obstructive sleep apnea · Continuous positive airway pressure · Sleepiness · Ambulatory blood pressure monitoring

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Introduction

Obstructive sleep apnea (OSA), a leading public health problem, is characterized by cyclical intermittent hypoxia and sleep fragmentation, which increase inflammation [1] and are felt to cause daytime sleepiness and increased risk of cardiovascular disorders in adults with OSA. Inflammation plays an important role in the development of daytime sleepiness and cardiovascular disease and may therefore be mediating these responses [1]. Circulating adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) are upregulated as part of an inflammatory response [1]. Higher ICAM-1 levels are present in adults with self-reported sleep duration less than 6 h per night or those reporting poor sleep [2, 3].

ICAM-1 increases endothelial cell activation and may contribute to the development of atherosclerotic lesions [4].

ICAM-1 levels are reported to be elevated in adults with untreated OSA [1, 5] and to decrease following CPAP treatment [5–8]. Other studies, however, did not find that CPAP treatment improves inflammatory biomarkers, including ICAM-1 [9, 10]. de la Peña Bravo et al. found no differences in inflammatory biomarkers (ICAM-1, IL-6, TNF-α) between untreated OSA patients with and without excessive sleepiness [11]. Jin et al. reported that inflammatory factors (ICAM-1, VCAM-1, IL-8, TNF-α, CRP, E-selectin, and P-selectin) and systolic and diastolic blood pressure (SBP and DBP) significantly improved in response to 3 months of CPAP treatment, but they did not directly evaluate whether a change in inflammation was associated with a change in blood pressure [12].

To our knowledge, no studies have examined the possible mechanisms underlying changes in sleepiness and blood pressure with CPAP treatment in the context of ICAM-1. Our goal was to evaluate the association between changes in ICAM-1 and both objective and subjective measures of sleepiness, as well as 24-h ambulatory blood pressure monitor (ABPM) measurements, in adults with OSA following 4 months of adherence to CPAP treatment. We analyzed data from the Penn Iceland Sleep Apnea (PISA; NCT03176732) cohort and hypothesized that change in ICAM-1 would be significantly associated with a change in sleepiness measures and 24-h ABPM after 4 months of CPAP treatment in adults with OSA.

Methods

PISA study design

PISA was an observational study evaluating clinical and molecular characteristics responsible for blood pressure changes in adults with OSA adherent to CPAP. The study screened adults aged 40 to 65 years with no prior history of treatment for OSA; individuals were included in the study if they were found to have moderate to severe OSA (apnea-hypopnea index [AHI] ≥ 15 to < 75 events/h based on full-night diagnostic polysomnography). Individuals were excluded if they had an unstable or new medical condition in the month prior to screening, severe arterial hypertension (SBP > 180 mmHg; DBP > 110 mmHg), BMI > 40 kg/m^2, routine consumption of more than two alcoholic beverages per day, or excessive caffeine use (> 10 cups/day). Women who were pregnant and individuals regularly taking sedative/hypnotics were also excluded. Individuals were recruited from the University of Pennsylvania and Landspitali – The National University Hospital of Iceland. The protocol was approved by the Institutional Review Boards at the respective sites and written consent was obtained from all participants.

Shulman et al. detail the PISA study specifications [13] and Kuna et al. report the primary BP results [14]. Following the baseline assessment, participants were started on auto-adjusting or fixed PAP treatment (ResMed S9, ResMed, Inc., San Diego, CA). The PAP device's SD card was downloaded to obtain daily hours of the mask on time, an objective measure of treatment use. The outcome assessments were repeated following 4 months of treatment in participants who had an average daily PAP use ≥ 4 h/day over at least 90 days. For this secondary endpoint analysis, the inclusion and exclusion criteria were expanded and required that participants had an ICAM-1 level measured at baseline and the 4-month follow-up, and either ABPM or psychomotor vigilance task (PVT) results were available at baseline and follow-up.

Sleepiness outcomes

Epworth Sleepiness Scale

Participants completed the Epworth Sleepiness Scale (ESS) at baseline and the 4-month follow-up. The ESS is an eight-item questionnaire to assess perceived daytime sleepiness [15].

Psychomotor vigilance task

Participants were also administered the PVT at baseline and the 4-month follow-up. The PVT is a gold standard measure of reaction time (RT) and used as an objective measure of daytime sleepiness [16, 17]. The test had a duration of 10 min.

Our primary outcome was based on the number of lapses, defined as RT > 500 ms, a common outcome measure in PVT studies [16]. As this variable is distributed according to a Poisson process, a variance-stabilizing transformation equal to the sum of the square root of the number of lapses plus the square root of the number of lapses plus 1 is applied, as described previously [17]. This transformed primary outcome is referred to as the "square root-transformed lapses." In addition, similar to prior work [17], we present data on the median of correct RTs (ms), the average fastest 10% RTs (ms), the average of the slowest 10% of reciprocal reaction times (RRT; 1/s), and the total incorrect responses.

Blood pressure measurement

Twenty-four-hour ABPM was performed at baseline and 4 months using Spacelabs model 90207 and 90217 monitors [18] (Spacelabs Healthcare, Snoqualmie, WA). Arm circumference was measured to determine the appropriate cuff size. Blood pressure was measured every 30 min over the 24-h period; the minimum acceptable number of readings was 16 from 6 AM to midnight and six from midnight to 6 AM. If the minimum number of readings for a valid ABPM interpretation

was not achieved, the participant was asked to repeat the study.

Based on these ABPM recordings, we quantified mean arterial pressure (MAP) (the primary measure), systolic blood pressure (SBP), and diastolic blood pressure (DBP) over 24 h and separately during wake and sleep, based on information collected from the participant on sleep diary. Additional information regarding ABPM endpoints can be found in our prior publications [13, 14].

Statistical analysis

Patient demographics, clinical characteristics, and ICAM-1 values are summarized using mean (SD) or median (interquartile range) for continuous variables and frequency (percentage) for categorical variables. Continuous demographics were compared using Student's *t* test and categorical variables were compared using the chi-squared test.

Primary analyses included assessments of change in ICAM-1, ABPM measures, and sleepiness-related endpoints before and following 4 months of CPAP adherence, as well as evaluating the associations between change in ICAM-1 and change in both APBM measures and sleepiness. Analysis of whether outcomes significantly changed from baseline was performed using linear mixed models with subject as a random effect, evaluating the significance of an indicator for time (baseline vs. follow-up). Analyses were restricted to participants with non-missing values at both baseline and follow-up. For associations between changes in ICAM-1 and changes in sleepiness and ABPM, we utilized linear regression models. In addition to estimates on the observed scale, we calculated standardized mean changes from baseline and standardized beta coefficients equal to the expected standard deviation change in outcome for a 1 standard deviation increase in ICAM-1 change. Analyses are performed both unadjusted and controlling for a priori covariates of hours per day of CPAP use and baseline age, BMI, sex, AHI, smoking status, physical activity (steps/day), race, site, and number of antihypertensive medications.

Our primary outcome measures included square root-transformed lapses for objective sleepiness, Epworth Sleepiness Scale score for subjective sleepiness, and 24-h MAP for ABPM measurements. For each of these outcomes, statistical significance was based on a $p < 0.05$. For secondary measures of objective sleepiness from PVT or blood pressure results from ABPM, statistical significance was determined using the Hochberg step-up procedure [19]. All analysis was performed using SAS version 9.4 (SAS Institute, Cary, NC) and R version 3.6 (www.r-project.org).

Results

Participant characteristics

Characteristics of study participants are shown in Table 1, including all participants with OSA (n = 188) and stratified into those with data on ICAM-1 change from baseline (primary analysis sample; n = 140) and those without (lost to follow-up; n = 48). Descriptively, at baseline, participants with available data on the change in ICAM-1 tended to be older, included a higher proportion of Caucasians, were less sleepy and had lower blood pressure compared to participants excluded from further analyses due to a missing ICAM-1 result.

Comparisons of participants adherent (n = 106) and non-adherent (n = 34) to CPAP therapy among the 140 participants with ICAM-1 at follow-up are shown in Table 2. There are no statistically significant differences in baseline characteristics between patients that were compliant to CPAP and patients non-compliant.

Change from baseline in clinical measurements

We first evaluated the changes from baseline in ICAM-1, sleepiness, and ABPM measurements among participants adherent to PAP treatment. Unadjusted results are presented in Table S.1 (see online supplement), and changes from baseline adjusted for clinical covariates are presented in Table 3. We observed no significant reduction in ICAM-1 following 4 months of CPAP treatment. However, there were statistically significant or nominally significant changes in nearly all measures of sleepiness based on PVT, except for the average of the fastest 10% of RT (p = 0.184) and a more than 4 point reduction in the ESS (mean [95% CI] change = − 4.38 [− 5.18, − 3.57]; $p < 0.0001$). In addition, we found nominal reductions in mean diastolic BP over 24 h (− 1.18 [− 2.33, − 0.03] mmHg; p = 0.044) and during wakefulness (− 1.36 [− 2.61, − 0.11]; p = 0.033).

Associations between change in ICAM-1 and change in sleepiness or ABPM measures

We next evaluated whether there were associations between the magnitude of change in ICAM-1 and changes in either sleepiness or ABPM measures following PAP treatment. Results are presented unadjusted (Table S.2) and adjusted for a priori clinical covariates (Table 4). Overall, there was no association between the change in ICAM-1 and change in sleepiness or blood pressure. We also explored the adjusted change from baseline for ICAM-1 and ABPM measures based on four groupings defined by the combination of PVT and ESS-defined sleepiness at baseline (Table S.3). There were no significant differences in adjusted change from baseline for ICAM-1 and ABPM measures among groups. Overall,

Table 1 Characteristics of participants

	Baseline (n = 188)		With ICAM FU (n = 140)		Without ICAM FU (n = 48)		$p^{\dagger}$
	N	Estimate	N	Estimate	N	Estimate	
Demographics							
Age, years	188	53.6 (6.9)	140	54.3 (6.8)	48	51.4 (6.6)	0.01
Female, n (%)	188	31 (17%)	140	23 (16%)	48	8 (17%)	> 0.99
Caucasian, n (%)	188	139 (74%)	140	112 (80%)	48	27 (56%)	< 0.01
Weight, kg	188	97.7 (15.5)	140	97.6 (15.2)	48	97.8 (16.6)	0.92
BMI, kg/m^2	188	31.7 (4.2)	140	31.5 (4.19)	48	32.3 (4.4)	0.27
AHI, events/h	188	36.1 (15.8)	140	36.8 (15.3)	48	34.2 (17.4)	0.32
Primary endpoint at baseline							
ICAM-1, ng/mL	174	288.79 (80.2)	140	284.59 (78.6)	34	306.10 (85.5)	0.16
LN ICAM-1	174	5.63 (0.25)	140	5.62 (0.25)	34	5.69 (0.25)	0.12
Sleepiness							
PVT: square root-transformed lapses	186	2.7 (2.4)	139	2.4 (1.7)	47	3.8 (3.6)	< 0.01
PVT: median of correct RT, ms	186	248.8 (51.8)	139	241.4 (37.5)	47	270.7 (77.0)	< 0.01
PVT: average of fastest 10% RT, ms	186	197.5 (29.4)	139	193.7 (20.3)	47	208.7 (45.5)	< 0.01
PVT: average of slowest 10% RRT, 1/s	186	2.6 (0.6)	139	2.7 (0.6)	47	2.4 (0.7)	0.01
PVT: total incorrect responses, n	186	3.1 (4.5)	139	3.2 (4.4)	47	2.9 (4.9)	0.74
ESS score	183	9.9 (4.8)	138	10.0 (4.9)	45	9.5 (4.5)	0.57
Blood pressure							
MAP 24 h, mmHg	188	97.2 (9.3)	140	96.2 (7.9)	48	100.3 (12.1)	0.01
MAP wake, mmHg	188	100.2 (9.7)	140	99.2 (8.3)	48	103.2 (12.5)	0.01
MAP sleep, mmHg	188	88.8 (10.4)	140	87.5 (9.1)	48	92.6 (12.8)	< 0.01
DBP 24 h, mmHg	188	80.3 (8.9)	140	79.4 (7.7)	48	83.0 (11.5)	0.02
DBP wake, mmHg	188	83.3 (9.3)	140	82.4 (8.0)	48	85.8 (12.0)	0.03
DBP sleep, mmHg	188	72.1 (9.7)	140	70.9 (8.5)	48	75.5 (12.0))	< 0.01
SBP 24 h, mmHg	188	131.6 (11.8)	140	130.1 (10.5)	48	135.4 (14.5)	0.01
SBP wake, mmHg	188	134.7 (12.1)	140	133.4 (10.9)	48	138.3 (14.7)	0.02
SBP sleep, mmHg	188	122.4 (13.3)	140	120.6 (11.8)	48	127.8 (16.0)	< 0.01

† p value from t test or chi-squared test comparing groups with and without ICAM-1 follow-up data; *BMI*, body mass index; *AHI*, apnea-hypopnea index; *ICAM-1*, intercellular adhesion molecule 1 level; *LN ICAM-1*, natural log ICAM-1 level; *PVT*, psychomotor vigilance task; *RT*, response time; *RRT*, reciprocal response time; *ESS*, Epworth Sleepiness Scale score; *MAP*, mean arterial blood pressure; *DBP*, diastolic blood pressure; *SBP*, systolic blood pressure

results suggest that the changes observed in these outcomes following PAP treatment, in particular improvements in sleepiness, were not associated with changes in ICAM-1.

Discussion

Objective measures of daytime function on psychomotor vigilance task (PVT) and subjective sleepiness, but not ICAM-1 or ABPM measures, significantly improved after 4 months of CPAP adherence. Specifically, we observed statistically or nominally significant changes in nearly all measures of sleepiness based on PVT, except for the average of the fastest 10% of RT, and there was a more than 4 point reduction in the ESS score. In addition, we found nominal reductions from baseline in mean 24-h diastolic BP and diastolic BP during wakefulness. Our results do not support changes in ICAM-1 as the main component of the biological pathway linking changes in sleepiness or ABPM with CPAP treatment.

Studies have previously examined the impact of CPAP on PVT outcomes directly or indirectly [20–23]. Bhat et al. examined both objective (PVT) and subjective (ESS) sleepiness in 92 individuals with mild to moderate OSA (average AHI = 17.5 events/h) and 90 individuals with severe OSA (average AHI = 63.8 events/h) after at least 1 month of adequate CPAP use (minimum of 4 h/night for 60% of nights). They found objective improvement in sleepiness only in those with severe OSA, and significant improvements observed in subjective daytime sleepiness (ESS) and fatigue were not predictive of improvement in PVT scores [23]. Another study of 114 adults

Table 2 Characteristics of participants with a change in ICAM-1 comparing CPAP adherent and non-adherent participants

	CPAP adherent ($N = 106$)		CPAP non-adherent ($N = 34$)		$p^{\dagger}$
	N	Estimate	*N*	Estimate	
Demographics					
Age, years	106	54 (7.1)	34	54 (6.1)	> 0.99
Female, *n* (%)	106	17 (16%)	34	6 (18%)	> 0.99
Caucasian, *n* (%)	106	87 (82%)	34	25 (74%)	0.40
Weight, kg	106	97.7 (15.4)	34	97.4 (14.7)	0.93
BMI, kg/m^2	106	31.4 (4.2)	34	31.5 (4.2)	0.91
AHI, events/h	106	37.3 (15.9)	34	35.3 (13.2)	0.52
Primary endpoint at baseline					
ICAM-1, ng/mL	106	286.31 (74.0)	34	279.23 (92.7)	0.65
LN ICAM-1	106	5.63 (0.23)	34	5.59 (0.29)	0.39
Sleepiness					
PVT: square root-transformed lapses	105	2.36 (1.6)	34	2.49 (2.1)	0.70
PVT: median of correct RT, ms	105	240.4 (33.0)	34	244.6 (50.0)	0.57
PVT: average of fastest 10% RT, ms	105	193.6 (19.0)	34	194.0 (24.4)	0.93
PVT: average of slowest 10% RRT, 1/s	105	2.70 (0.53)	34	2.63 (0.63)	0.49
PVT: total incorrect responses, *n*	105	3.19 (4.3)	34	3.21 (4.6)	0.98
ESS score	105	9.65 (4.7)	34	11.1 (5.3)	0.14
Blood pressure					
MAP 24 h, mmHg	106	95.8 (7.8)	34	97.4 (8.3)	0.32
MAP wake, mmHg	106	98.8 (8.1)	34	100.7 (8.7)	0.24
MAP sleep, mmHg	106	87.4 (9.1)	34	87.9 (9.0)	0.79
DBP 24 h, mmHg	106	79.0 (7.5)	34	80.8 (8.0)	0.23
DBP wake, mmHg	106	81.9 (7.8)	34	84.2 (8.4)	0.14
DBP sleep, mmHg	106	70.8 (8.5)	34	71.2 (8.8)	0.81
SBP 24 h, mmHg	106	129.7 (10.4)	34	131.6 (10.7)	0.36
SBP wake, mmHg	106	132.9 (10.8)	34	135.1 (11.1)	0.30
SBP sleep, mmHg	106	120.4 (11.7)	34	121.3 (12.1)	0.69

† *p* value from *t* test or chi-squared test comparing adherent and non-adherent groups; *BMI*, body mass index; *AHI*, apnea-hypopnea index; *ICAM-1*, intercellular adhesion molecule 1 level; *LN ICAM-1*, natural log ICAM-1 level; *PVT*, psychomotor vigilance task; *RT*, response time; *RRT*, reciprocal response time; *ESS*, Epworth Sleepiness Scale; *MAP*, mean arterial blood pressure; *DBP*, diastolic blood pressure; *SBP*, systolic blood pressure

with OSA (average AHI = 37.8, 96.5% males) reported that CPAP adherence was significantly associated with a reduction in the number of minor PVT lapses and mean reaction time after 6 months of treatment [22]. These results are congruent with our findings of significant changes with CPAP in nearly all PVT measures of sleepiness. There are also studies showing no improvement in PVT scores after CPAP [20]. Sparrow et al. reported no significant improvement in PVT scores in a randomized clinical trial of 250 patients assigned to either an interactive voice response system designed to improve CPAP adherence or to an attention placebo control for 12 months [20]. However, CPAP adherence was low in both the treatment and control groups, which may have impacted results [20]. Overall, studies with larger sample sizes, greater baseline OSA severity, and higher CPAP adherence for a longer duration tend to show improvements in PVT performance after CPAP therapy.

Our question of whether a change in ICAM-1 is associated with a change in sleepiness and blood pressure after 4 months of CPAP treatment is driven by the idea that sleepiness in OSA is associated with inflammation caused by cyclical intermittent hypoxia and sleep fragmentation during sleep and that CPAP keeps the airway patent, thus preventing associated sequelae. There are inconsistencies in the results of studies examining inflammatory biomarkers and their associations with subjective and objective measures of sleepiness [24–26]. Our prior work in adults with untreated OSA showed that subjective sleepiness measured by ESS is associated with inflammation, as measured by C1qTNF, and higher 24-h MAP [27]. A study by Prasad et al. suggests increased pro-

Table 3 Adjusted change from baseline for ICAM-1, sleepiness, and ABPM measures

Outcome	*N*	Estimate (95% CI)		$p^{\dagger}$
		Observed scale	Standardized*	
ICAM-1 (ng/mL)	100	2.976 (− 5.945, 11.897)	0.065 (− 0.130, 0.260)	0.510
LN (ICAM-1)	100	0.004 (− 0.024, 0.032)	0.028 (− 0.168, 0.224)	0.761
PVT: square root-transformed lapses	81	− 0.331 (− 0.637, − 0.025)	− 0.225 (− 0.433, − 0.017)	0.034
PVT: median of correct RT, ms	81	− 5.747 (− 10.506, − 0.988)	− 0.264 (− 0.483, − 0.045)	0.019
PVT: average of fastest 10% RT, ms	81	− 2.015 (− 5.004, 0.975)	− 0.149 (− 0.371, 0.072)	0.184
PVT: average of slowest 10% RRT, 1/s	78	0.230 (0.131, 0.329)	0.509 (0.290, 0.728)	< 0.0001
PVT: total incorrect responses, *n*	81	− 1.056 (− 1.839, − 0.272)	− 0.245 (− 0.427, − 0.063)	0.009
Epworth Sleepiness Scale score	96	− 4.375 (− 5.175, − 3.575)	− 1.018 (− 1.204, − 0.832)	< 0.0001
MAP 24 h, mmHg	94	− 0.948 (− 2.226, 0.329)	− 0.153 (− 0.360, 0.053)	0.144
MAP wake, mmHg	94	− 0.990 (− 2.372, 0.393)	− 0.147 (− 0.353, 0.058)	0.158
MAP sleep, mmHg	93	− 0.746 (− 2.371, 0.880)	− 0.097 (− 0.308, 0.114)	0.365
DBP 24 h, mmHg	94	− 1.182 (− 2.331, − 0.033)	− 0.211 (− 0.416, − 0.006)	0.044
DBP wake, mmHg	94	− 1.360 (− 2.608, − 0.112)	− 0.223 (− 0.427, − 0.018)	0.033
DBP sleep, mmHg	93	− 0.578 (− 2.091, 0.934)	− 0.080 (− 0.290, 0.130)	0.450
SBP 24 h, mmHg	94	− 0.371 (− 2.059, 1.318)	− 0.045 (− 0.252, 0.161)	0.664
SBP wake, mmHg	94	− 0.239 (− 2.063, 1.586)	− 0.027 (− 0.232, 0.178)	0.796
SBP sleep, mmHg	93	− 0.658 (− 2.643, 1.326)	− 0.069 (− 0.279, 0.140)	0.512

Models adjusted for baseline AHI, current smoking status, baseline steps, site, BMI, sex, CPAP use, age, race, anti-hypertension meds

† *p* value from the linear mixed model evaluating the statistical significance of the change from baseline

*Standardized difference calculated with respect to unadjusted standard deviation of change score (see Table S.1). *RT*, response time; *RRT*, reciprocal response time; *ESS*, Epworth Sleepiness Scale; *MAP*, mean arterial blood pressure; *DBP*, diastolic blood pressure; *SBP*, systolic blood pressure

Table 4 Adjusted associations between change in ICAM-1 and changes in sleepiness or APBM measurements with CPAP treatment

Outcome	*N*	Adjusted estimate (95% CI)		$p^{\dagger}$
		Observed scale	Standardized*	
Square root-transformed lapses	81	0.068 (− 0.309, 0.445)	0.046 (− 0.210, 0.303)	0.725
Median of correct RT, ms	81	3.918 (− 1.349, 9.186)	0.180 (− 0.062, 0.422)	0.149
Average of fastest 10% RT, ms	81	2.154 (− 1.417, 5.724)	0.160 (− 0.105, 0.424)	0.241
Average of slowest 10% RRT, 1/s	78	0.029 (− 0.081, 0.140)	0.064 (− 0.180, 0.309)	0.608
Total incorrect responses, *n*	81	− 0.250 (− 1.233, 0.734)	− 0.058 (− 0.287, 0.171)	0.621
ESS score	96	0.247 (− 0.616, 1.110)	0.058 (− 0.143, 0.258)	0.576
MAP 24 h, mmHg	94	0.402 (− 1.011, 1.814)	0.065 (− 0.163, 0.293)	0.579
MAP wake, mmHg	94	0.614 (− 0.907, 2.135)	0.091 (− 0.135, 0.318)	0.431
MAP sleep, mmHg	93	− 0.103 (− 1.882, 1.675)	− 0.013 (− 0.244, 0.217)	0.910
DBP 24 h, mmHg	94	0.343 (− 0.936, 1.622)	0.061 (− 0.167, 0.290)	0.601
DBP wake, mmHg	94	0.562 (− 0.819, 1.942)	0.092 (− 0.134, 0.318)	0.427
DBP sleep, mmHg	93	− 0.182 (− 1.833, 1.470)	− 0.025 (− 0.254, 0.204)	0.830
SBP 24 h, mmHg	94	0.232 (− 1.644, 2.108)	0.028 (− 0.201, 0.258)	0.809
SBP wake, mmHg	94	0.196 (− 1.835, 2.227)	0.022 (− 0.207, 0.251)	0.851
SBP sleep, mmHg	93	0.497 (− 1.675, 2.670)	0.052 (− 0.177, 0.282)	0.655

Models adjusted for baseline AHI, current smoking status, baseline steps, site, BMI, sex, CPAP use, age, race, anti-HTN meds

† *p* value from linear regression evaluating the significance of the association between ICAM-1 change and change in outcome

*Standardized estimate equal to expected SD change in outcome for 1 SD increase in ICAM-1 change. *RT*, response time; *RRT*, reciprocal response time; *ESS*, Epworth Sleepiness Scale; *MAP*, mean arterial blood pressure; *DBP*, diastolic blood pressure; *SBP*, systolic blood pressure

inflammatory cytokine IL-6 levels are associated with sleepiness in OSA [24]. This association with IL-6 was demonstrated in individuals who were found to be sleepy according to both PVT and ESS cutoffs (PVT lapse ≥ 2 and ESS ≥ 11) and those found to be subjectively sleepy (PVT lapse < 2 and ESS ≥ 11) but not those objectively sleepy (PVT lapse ≥ 2 and ESS < 11) [24]. We did not see significant associations on differences in ICAM-1 based on these sleepiness thresholds in our supplementary analyses. Previous work has found that objective sleepiness measured by multiple sleep latency tests was associated with elevated 24-h daytime and nighttime IL-6 levels and decreased daytime cortisol levels, while subjective sleepiness (ESS) was not [25]. In a study of 58 adults with untreated OSA, the number of PVT lapses, lower values of 1/RT, and slowest 10% RTs was associated with ESS scores but not inflammation (IL-6 levels) [26]. In the present study, we found that objective measures of sleepiness from PVT and subjective sleepiness, but not ICAM-1 or ABPM measures, significantly improved on average after four months of CPAP adherence. Thus, further work is needed to identify relevant biomarkers associated with changes in comprehensively assessed sleepiness with CPAP.

Although significant reductions in blood pressure measurements are reported in response to CPAP treatment, effect sizes remain low. A meta-analysis of 28 studies showed that individuals who were younger, sleepier, had more severe OSA, and had greater PAP adherence generally exhibited statistically significant reductions in BP [28]. A smaller meta-analysis and meta-regression showed that CPAP adherence, age, and baseline SBP were positively correlated with a decrease in 24-h DBP but not a reduction in 24-h SBP [29]. This finding supports our result showing nominal reductions in diastolic BP over 24 h but not systolic BP.

In our prior study examining whether CPAP results in changes in ICAM-1 after 2 years, we found that non-users had increased ICAM-1 compared to decreased levels in full users (≥ 4 h/night and use on ≥ 20 of last 28 nights) and the changes were the largest in the most obese [7]. Our prior study, however, did not examine the underlying drivers of the changes in sleepiness or blood pressure with CPAP treatment. In contrast, we did not see a significant reduction in ICAM-1 after 4 months of CPAP treatment in the current study. It is possible the treatment duration was insufficient to provide the level of effect hypothesized. This may also explain the lack of association between changes in ICAM-1 and blood pressure after 4 months; while there was variability in change scores, neither measure changed significantly from baseline on average. Future studies should consider longer treatment periods when examining these associations.

The strengths of this study include the comprehensive measures of daytime functioning (PVT, ESS), ICAM-1, and 24-h blood pressure measures at baseline and follow-up and objective CPAP monitoring. Our comprehensive measures of sleepiness are particularly important to note as sleepiness has more dimensions than the likelihood of falling asleep and more instruments in addition to ESS are needed when evaluating daytime sleepiness [30]. A limitation of our study is the low number of women included in our sample, which limits generalizability. Furthermore, we did not systematically include individuals who did not adhere to therapy, as the goal of this study was to evaluate the association of our variables of interest following adherence to CPAP treatment.

In conclusion, our study showed reductions in sleepiness-related measurements, although no significant changes in ICAM-1 or ABPM measures, with 4 months of CPAP treatment. We found no evidence to suggest that changes in ICAM-1 are associated with changes in sleepiness or ABPM measures following CPAP treatment of adults with OSA. It will be important for future studies to explore the relationship between other novel biomarkers and changes in sleepiness and blood pressure with CPAP treatment.

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Availability of data and material (data transparency) Available upon request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent The protocol was approved by the Institutional Review Boards at the respective sites and written consent was obtained from all participants.

Code availability Available upon request.

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