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Determinants of sleepiness in obstructive sleep apnea

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Abstract

Study Objectives

Significant interindividual variability in sleepiness is observed in clinical populations with obstructive sleep apnea (OSA). This phenomenon is only partially explained by the apnea–hypopnea index (AHI). Understanding factors that lead to sleepiness is critical to effective management of patients with OSA. We examined demographic and other factors associated with sleepiness in OSA.

Methods

Prospective study of 283 patients with newly diagnosed OSA by polysomnography (AHI ≥ 5 per hour). Subjective sleepiness (Epworth Sleep Scale [ESS] ≥ 11) and objective sleepiness (psychomotor vigilance task [PVT] mean lapse ≥ 2) were assessed.

Results

Participants were classified into four groups (1: sleepy by ESS and PVT, 2: sleepy by PVT only, 3: sleepy by ESS only, and 4: nonsleepy reference group) and compared by generalized logit model. Shorter daily sleep duration by actigraphy and less morningness were associated with higher risk of sleepiness (Odds ratio [OR] = 0.52, 95% confidence interval [CI] 0.33–0.82 and OR = 0.89, CI 0.80–0.98, respectively). African-American race was associated with sleepiness (group 1, OR = 8.8, CI 2.8–27.3; group 2, OR = 16.6, CI 3.3–83.6; and group 3, OR = 3.3, CI 1.0–10.1). IL-6 level was higher in groups 1 and 3 (OR = 1.9, CI 1.0–3.4 and OR 2.0, CI 1.1–3.7, respectively).

Conclusions

African-American race, short sleep duration, chronotype, and increased proinflammatory cytokine IL-6 level were associated with sleepiness in OSA. These findings will inform future investigations determining mechanisms of sleepiness in OSA.

OSA, OSA-clinical assessment, home sleep apnea testing, cytokines, sleepiness, vigilance

Statement of Significance

This study was undertaken to systematically identify mechanisms of interindividual variation in sleepiness in patients with obstructive sleep apnea (OSA). It contributes to and extends the knowledge of OSA by identifying factors beyond polysomnography-based disease severity measures that predict sleepiness in clinical populations with OSA and helps us to better understand the factors that affect presentation of this

symptom. Short daily sleep duration and African-American race independently increase the risk, whereas morning chronotype reduces the risk of sleepiness patients with OSA. Cytokine IL-6 is a biomarker of sleepiness with potential clinical utility in OSA.

Introduction

Daytime sleepiness is a cardinal symptom of obstructive sleep apnea (OSA) and an important factor in treatment acceptance and outcomes [1–5]. However, significant interindividual variability in sleepiness exists in patients with equivalent severity of OSA, and determinants of this variability remain poorly understood [6–8]. OSA severity measures, including apnea–hypopnea index (AHI), correlate modestly with both subjective and objective sleepiness [6, 7, 9–12]. The relationship between AHI and subjective sleepiness by Epworth Sleepiness Scale (ESS) is weaker in community-based cohorts compared with clinical populations [8, 13]. Although the association of Mean Sleep Latency (MSL by Multiple Sleep Latency Test [MSLT]; gold-standard objective measure of sleepiness) with AHI is reportedly superior to ESS, the data regarding this association are conflicting, and AHI appears to explain only a small portion of the variance in MSL [14–16]. Other reported predictors of sleepiness in OSA include younger age, obesity, higher sleep efficiency, frequent respiratory arousals, greater nocturnal hypoxemia on polysomnography (PSG), and possibly inflammatory cytokines [7, 17–20]. Nevertheless, the role of potentially important factors such as chronotype, habitual sleep duration, or use of relevant medications has not been systematically examined.

A fundamental challenge in understanding mediators of sleepiness in patients with OSA is to define sleepiness. In healthy individuals, subjective and objective measures of sleepiness dissociate under conditions of chronic sleep restriction [21] and in the context of interindividual differences [22]. As subjective (ESS) and objective (MSL) sleepiness measures may yield disparate results even in clinical populations with OSA, previous studies have employed a twofold approach of identifying “sleepy” patients based on combined subjective and objective sleepiness [16, 23]. Although the psychomotor vigilance task (PVT) measures neurobehavioral alertness, it is sensitive to sleepiness in populations with OSA and is economical in terms of time and cost compared with MSLT [10, 24]. Lapses in attention on the PVT reflect state instability associated with sleep loss, have high ecological validity with regard to those real-world situations that require high levels of attention, such as driving, and are the most common PVT metric (68%) used in peer-reviewed literature [25]. Two lapses were noted to be the lowest threshold differentiating sleep-deprived from nonsleep-deprived individuals.We identified a priori factors that potentially affect sleepiness in patients with newly diagnosed OSA and prospectively examined the association of these factors within sleepy and nonsleepy phenotypes of OSA. We employed both subjective (ESS $\geq$ 11) and objective (PVT lapse $\geq$ 2 per trial) measures to stratify patients into four groups: group 1 = concordantly sleepy (ESS $\geq$ 11 and PVT lapse $\geq$ 2), group 2 = objectively sleepy (ESS < 11 and PVT lapse $\geq$ 2), group 3 = subjectively sleepy (ESS $\geq$ 11 and PVT lapse < 2), and group 4 = nonsleepy (ESS < 11 and PVT lapse < 2). This approach allowed for the identification of factors mediating concordant sleepiness (subjective sleepiness with neurobehavioral impairment) as well as discordant sleepiness (subjective sleepiness or neurobehavioral impairment only).

Our primary objective was to test whether interindividual differences in sleepiness observed in patients with OSA can be explained by sociodemographic factors (including habitual sleep duration by actigraphy), presence of comorbid medical conditions, use of sedative-hypnotic medications, chronotype (assessed with Basic Language Morningness [BALM] questionnaire), or systemic inflammatory cytokines with somnogenic effects (IL-6 and TNFá) [26], controlling for OSA severity. The aim of this study was to gain a better understanding of daytime sleepiness and its biological underpinnings in OSA. This knowledge is critical to symptom analysis, treatment decisions, outcome evaluation, and intervention development.

Methods

Participants

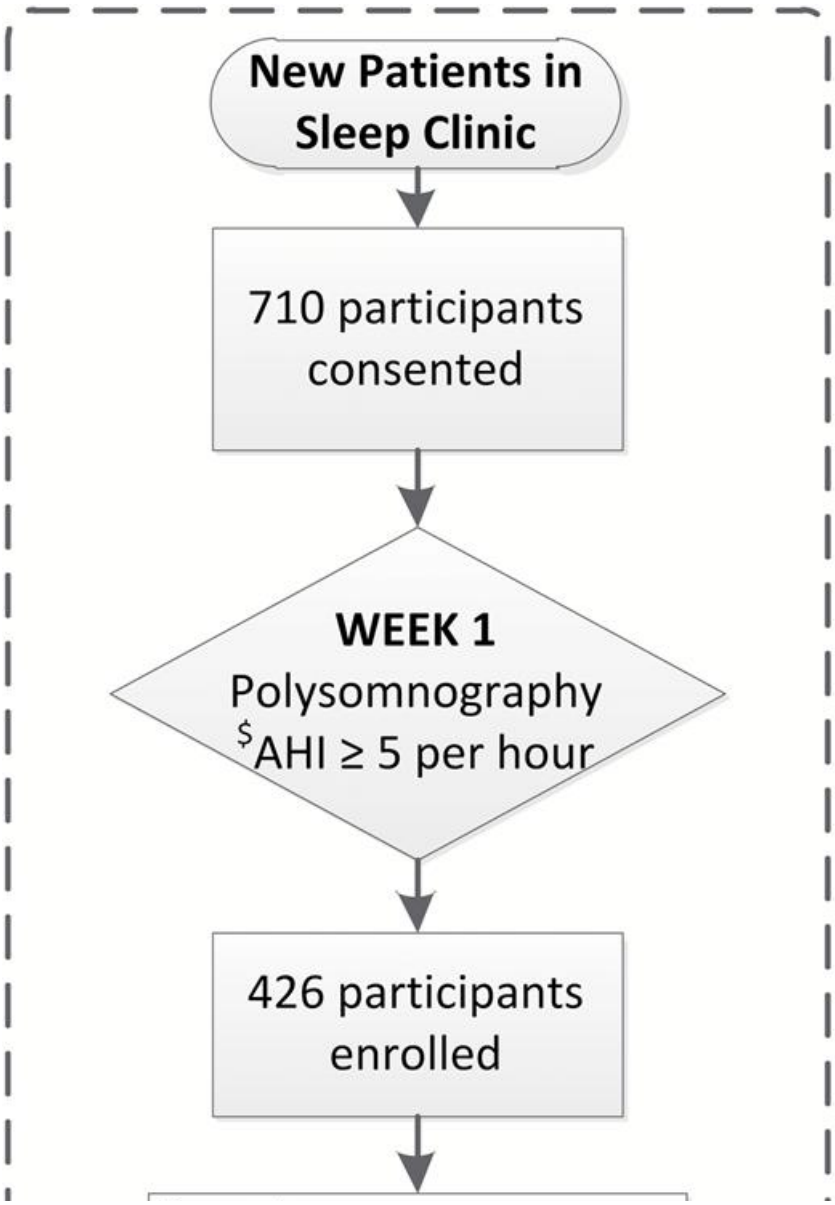
The target population for this study was middle-aged patients with suspected OSA who were referred to the Center for Sleep and Circadian Neurobiology, University of Pennsylvania, Philadelphia. Participants were selected based on the following eligibility criteria: (1) AHI $\geq$ 5 on PSG and (2) 35–60 years of age. These age cutoffs were chosen as patients < 35 years are more likely to have altered sleep schedule (such as phase delay) and patients > 60 years were not enrolled due to increased occurrence of central apneas, the marked reductions in sleep homeostasis that is attributed to the aging process as well as the effects of aging on plasma cytokine levels [27–29]. Exclusion criteria included as follows: (1) diagnosis of another sleep disorder in addition to OSA based on PSG (periodic limb movement disorder, five or more central apneas per hour, insomnia, sleep hypoventilation syndrome, shift-work, or narcolepsy); (2) previous treatment with home oxygen therapy, uvulopalatopharyngoplasty, tracheotomy, or other surgery for OSA; (3) pregnancy; (4) inability to write or read English; and (5) upper extremity motor deficit (e.g. previous stroke or spinal cord

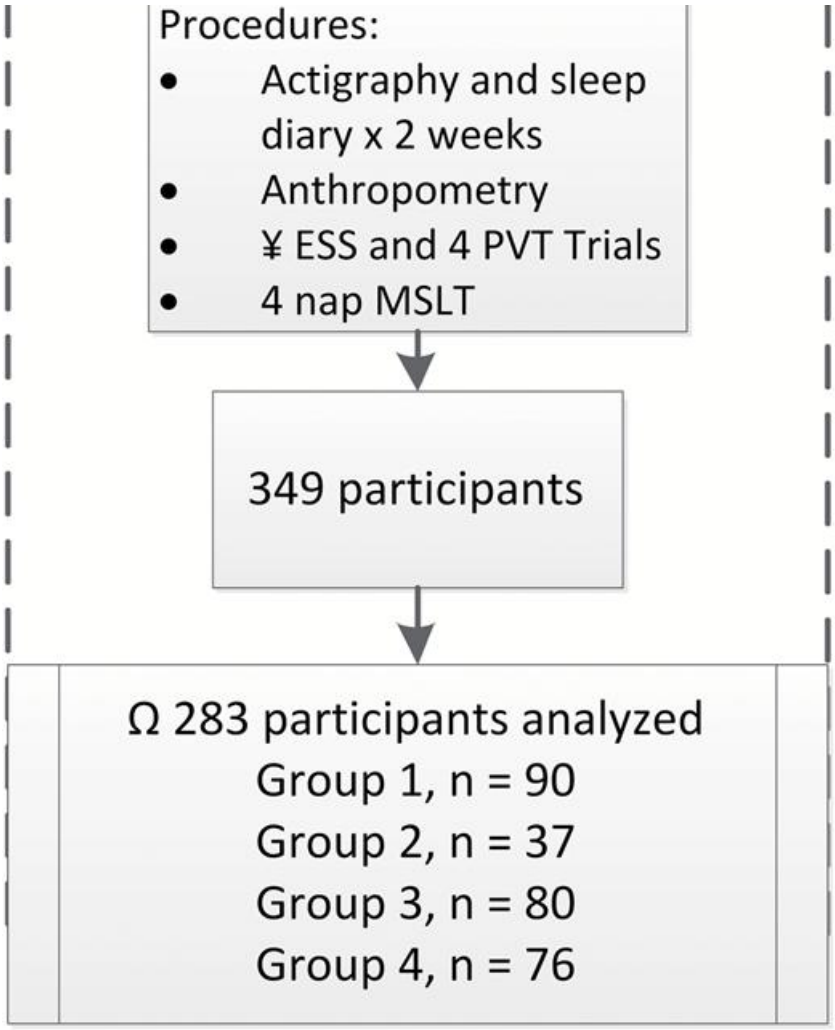
injury). This study was approved by the University of Pennsylvania, Philadelphia, Institutional Review Board.

Study protocol

Details on participant recruitment and procedures are presented in Figure 1. After informed consent, urine pregnancy and drug screening tests were performed. Diagnostic PSG data were acquired using the Sandman system (Elite Sleep System Version 6.1, Natus Medical, Inc., Pleasanton, CA). PSG was scored according to published criteria. Specifically, hypopneas were scored when >50% flow-amplitude reduction or flow reduction accompanied by ≥3% oxygen desaturation or arousal [30]. All participants had sleepiness assessments performed with PVT (Ambulatory Monitoring, Inc., Ardsley, NY) and the ESS. Four 10 min trials of PVT were performed by each participant at 10:00, 12:00, 14:00, and 16:00 hr to account for circadian variation in alertness [31]. Usual sleep time was measured with concurrent actigraphy and sleep diary for 2 weeks. Participants also completed 4-nap MSLT, the gold standard test for physiologic sleepiness [32]. Self-reported medical conditions (comorbidity) and prescription medications as well as over the counter sleep aids and antihistamine use were recorded. Venous blood samples were drawn at 06.30 am after overnight PSG in EDTA tubes and processed within 2 hr of collection. The samples were stored in −70°C freezer before plasma TNFα and IL-6 were measured by enzyme-linked immunosorbant assay (R & D Systems, Minneapolis, MN) [33]. Participants were asked to refrain from use of any anti-inflammatory (steroidal and nonsteroidal) drugs for 1 week prior to blood sample collection. Participants were classified into four groups based on the combined results of ESS and PVT. ESS ≥ 11 was considered sleepy; conversely, <11 was considered nonsleepy [34]. An average PVT lapse (reaction time more than 500 ms) across four trials of ≥2 was used to define sleepy and <2 to define nonsleepy [35]. Thus, the participants were categorized into concordant (objectively and subjectively) and discordant groups in terms of sleepiness. This categorization resulted in the following four groups: group 1 (concordantly sleepy) = PVT lapse ≥ 2 and ESS ≥ 11, group 2 (objectively sleepy) = PVT lapse ≥ 2 and ESS < 11, group 3 (subjectively sleepy) = PVT lapse < 2 and ESS ≥ 11, and group 4 (nonsleepy) = PVT lapse < 2 and ESS < 11.

Figure 1.





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Study recruitment and procedures. $ AHI = apnea–hypopnea index, ¥ ESS = Epworth sleepiness scale, PVT = psychomotor vigilance test, MSLT = Multiple Sleep Latency Tests, Ω Group 1 = PVT lapse ≥ 2 and ESS ≥ 11, Group 2 = PVT lapse ≥ 2 and ESS < 11, Group 3 = PVT lapse < 2 and ESS ≥ 11, Group 4 = PVT lapse < 2 and ESS < 11.

Statistical analyses

A sample size estimate was performed using the method of Hsieh [36]. This method enables determination of required sample sizes given (1) the probability of being a case when the risk factor value is equal to the mean value and (2) the probability of being a case when the risk factor value is equal to the mean value plus one standard deviation. Together, these values determine the minimum detectable odds ratio (OR) with 80% power. We assumed $\alpha = 0.01$ to adjust for multiple comparisons resulting from the model building strategy described above. In addition, the required sample size depends on the multiple squared correlation of the other variables with a specific risk factor. This value was unknown, so we assumed an R^2=0.50 in sample size determination. Required sample sizes are lower for R^2 values less than 0.50. By design, in our samples, the probability of being a case at the pooled mean of a predictor was 0.50. The probability of being a case increased to 0.71 if the predictor variable value was one standard deviation above mean (equivalent to an OR of 2.5). Under these assumptions, a total sample size of 226 was estimated (113 cases and 113 controls). These values were increased by 15% to be conservative for a total of 130 cases and 130 controls. Data were screened for missing values and appropriate ranges and distributions using descriptive statistics. IL-6 and TNFá were log transformed to improve distribution. Based on distribution, Spearmans or Pearsons correlation coefficients were used. The sleepiness status, determined by both the ESS and PVT and using established clinical cutoffs, was utilized to categorize participants into four groups. This categorical outcome was initially modeled as ordinal in polytomous logistic regression, but since the proportional odds assumption was not met, a generalized logit model was employed. We regressed the sleepiness outcome on demographics of age, race and education, clinical factors including body mass index (BMI), presence of a comorbid health condition (yes/no), BALM scores (chronotype), and OSA and sleep-specific indicators (AHI, average oxygen saturation, sleep efficiency, arousal index, use of sedating medications, and daily sleep duration by actigraphy). All determinants were tested for multicollinearity using tolerance [37]. A separate analysis examined the association of inflammation biomarkers IL-6 and TNFα in addition to the other covariates in a subset of the participants who had these data available. All determinants tested remained in the models regardless of significance. A p-value of $< .05$ was considered significant. All data were analyzed

using SAS 9.3 (SAS Institute, Cary, NC).

Results

Participant characteristics

Table 1 shows the baseline characteristics for the four groups defined by their sleepiness status. Overall, 30% of participants reported use of prescription or over-the-counter medications as sleep aids, and 59% reported comorbid medical conditions. The commonest comorbidities reported were hypertension (32%) and diabetes (28%), followed by bronchitis, emphysema, pulmonary hypertension, heart failure, heart attack, and stroke (at ≤6% each).

Table 1.

Baseline characteristics

Parameter	Group 1 (*n* = 90)[†]	Group 2 (*n* = 37)[†]	Group 3 (*n* = 80)[†]	Group 4 (*n* = 76)[†]	*P**
	Count (%)				
Gender (men)	62 (69)	21 (57)	43 (54)	44 (59)	.20
Race					
European-American	19 (21)	7 (19)	35 (44)	40 (53)	.0002
African-American	63 (70)	26 (70)	40 (50)	29 (38)	
Other	8 (9)	4 (11)	5 (6)	7 (9)	
Use of sedating medications (yes)	34 (38)	11 (30)	29 (36)	23 (30)	.67
Comorbid medical disorders (yes)	57 (63)	21 (56)	41 (51)	49 (64)	.3
Parameter	Mean ± Standard Deviation				*P***
Age (years)	47.5 ± 8.8	46.6 ± 10.0	45.3 ± 7.9	46.4 ± 8.4	.4
Body mass index	40.4 ± 12.4	38.4 ± 10.5	37.6 ± 11.2	36.3 ± 10.4	.13
Education (years after high school)	4.9 ± 0.9	5.1 ± 1.2	5.3 ± 1.2	5.5 ± 1.2	.004
Daily sleep duration (min; actigraphy)[‡]	490 ± 130	541 ± 160	495 ± 111	540 ± 121	.02
BALM score	34 ± 7.6	37 ± 7.3	36 ± 7.5	36 ± 8.2	.08
AHI[§]	33 ± 31	34 ± 32	28 ± 28	28 ± 26	.5
Average oxygen saturation[§]	94 ± 2.7	94 ± 3.7	95 ± 2.5	95 ± 2.3	.5
Nadir oxygen saturation[§]	78 ± 14	77 ± 17	79 ± 18	79 ± 19	.2
Sleep efficiency	78 ± 16	75 ± 17	78 ± 17	87 ± 18	.3
Arousal index	27.9 ± 26	24.9 ± 17	20.3 ± 17	28.2 ± 21	.3
Mean sleep latency[‖]	8.8 ± 4.9	10.1 ± 6.2	10.4 ± 5.2	11.8 ± 5.3	.006
IL-6 (pg/mL)	4.2 ± 3.4	3.7 ± 2.9	3.3 ± 3.4	2.7 ± 2.9	.08
TNFα (pg/mL)	1.3 ± 0.8	1.9 ± 2.0	1.0 ± 0.5	1.3 ± 0.6	.004
Epworth sleepiness scale	15.7 ± 3.1	7.6 ± 2.3	14.9 ± 2.8	6.4 ± 2.6	<.0001
PVT lapses	11.9 ± 15.9	7.6 ± 9.3	0.8 ± 0.5	0.6 ± 0.5	<.0001

AHI = apnea–hypopnea index; BALM = Basic Language Morningness (13–55); ESS = Epworth Sleepiness Scale; PVT = psychomotor vigilance task.

[†]Group 1 = PVT lapse ≥ 2 and ESS ≥ 11, Group 2 = PVT lapse ≥ 2 and ESS < 11, Group 3 = PVT lapse < 2 and ESS ≥ 11, Group 4 = PVT lapse < 2 and ESS < 11.

[‡]Sleep duration by actigraphy.

[§]Derived from polysomnography.

[‖]Derived from Multiple Sleep Latency Tests (MSLT).

**p*-value = chi-square; ***p*-value = ANOVA or Kruskal–Wallis test.

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Although this sample was generally a highly educated group, the number of years of college education increased across groups 1 through 4, with group 1 (concordantly sleepy) reporting fewer years of college education ($p = .004$). Group 1 was also different from other groups as it had the shortest daily sleep duration by actigraphy and there was a greater proportion of African Americans ($p = .02$ and .0002, respectively). Participants that completed cytokine sampling were not different from those that did not have cytokine sampling with respect to the outcomes of sleepiness or any of the covariates (all $p > .1$). TNFα, inflammatory cytokine level, was significantly different between the groups. Notably, MSL decreased and IL-6 increased monotonically from group 4 (nonsleepy) to group 1 (concordantly sleepy). This trend failed to achieve statistical significance for IL-6 ($p = .08$). By MSL-defined sleepiness (≤8 min), 47/90; 52% of group 1, 15/37; 40% of group 2, 30/80; 37% of group 3, and 21/76; 27% of group 4 were sleepy. MSL was significantly shorter in group 1 vs. group 4 ($p = .006$) and the OR (1.9, 1.2–3.1) of MSL ≤ 8 min was significantly higher in those with PVT lapses ≥ 2 compared with PVT lapses < 2. A significant correlation was observed between MSL and PVT lapses ($r = −0.20$, $p = .0006$) as well as MSL and ESS ($r = −0.20$, $p = .0002$). MSL was not significantly correlated to cytokines (lnIL6; $r = −0.06$, $p = .3$, lnTNFα; $r = 0.01$, $p = .8$). None of the sleepiness measures (MSL, ESS, and PVT lapses) were associated with self-reported hypertension (t-statistic 1.1, $p = .3$; t-statistic 1.9, $p = .1$; t-statistic 0.17, $p = .7$, respectively). Models using MSL (≤8 vs. >8) as the outcome did not show an omnibus race effect, but in the logistic model, the association of African-American race with MSL ≤ 8 was significant (chi-square 6.24, $p = .04$). In exploratory multivariable linear regression analysis to examine the association of MSL with determinants described above, only sleep duration and male sex were significantly associated with short MSL ($p = .0004$ and .006, respectively).

Determinants of sleepiness

In the initial multivariable regression model of the larger dataset without cytokines, race ($p = .007$), lower BALM score ($p = .02$), arousal index ($p = .02$), and shorter habitual sleep duration ($p = .02$) were found to be significant determinants of sleepiness in OSA (Table 2, $n = 283$). The first three determinants, race, BALM score, and arousal index, were significantly associated with sleepiness in the second multivariable model using a smaller dataset including cytokines: IL-6 and TNFá (Table 3, $n = 211$). In this model, sleep duration was no longer significant. A priori comparisons were made among groups 1, 2, and 3 individually to reference group 4 for the significant predictor's of concordant and discordant sleepiness (Tables 4 and 5).

Table 2.

Predictors of sleepiness: model without cytokines ($n = 283$)

Parameter	Wald chi square†	*P*
Age	4.36	.2
Gender (men)	1.52	.7
BMI	0.97	.8
Race	17.7	**.007**
Education (years of college)	2.62	.4
BALM score	9.35	**.02**
Sedating medication (yes/no)	0.59	.9
Comorbidity (yes/no)	2.07	.5
Daily sleep duration (actigraphy)	9.93	**.02**
AHI	0.64	.6
Average oxygen saturation	3.33	.3
Sleep efficiency	1.88	.6
Arousal index	9.62	**.02**

One hundred fifteen observations were deleted due to missing values for the predictors or outcome variables in the full model. Group 4 (nonsleepy) is reference group vs. other groups.

BMI = body mass index; BALM = Basic Language Morningness questionnaire; AHI = apnea–hypopnea index.

[†]Generalized Logit Type 3 Analysis of Effects, Degrees of Freedom = 3.

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Table 3.

Predictors of sleepiness: model with cytokines (*n* = 211)

Parameter	Wald chi square[†]	*P*
Age	5.82	.1
Gender (men)	2.94	.4
BMI	2.11	.5
Race	21.01	**.001**
Education (years of college)	0.78	.8
BALM score	10.32	**.01**
Sedating medication (yes/no)	0.46	.9
Comorbidity (yes/no)	3.46	.3
Daily sleep duration (actigraphy)	4.95	.1
AHI	3.53	.3
Average oxygen saturation	1.27	.73
Sleep efficiency	3.26	.3
Arousal index	13.43	**.003**
*lnIL-6	6.25	.09
**lnTNFα*	7.14	.06

One hundred fifteen observations were deleted due to missing values for the predictors or outcome variables in the full model. Group 4 (nonsleepy) is reference group vs. other groups.

BMI = body mass index; BALM = Basic Language Morningness questionnaire; AHI = apnea–hypopnea index; *ln = log normal transformation.

[†]Generalized Logit Type 3 Analysis of Effects, Degrees of Freedom = 3.

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Table 4.

Predictors of objective and subjective sleepiness: model without cytokines (*n* = 283)

Parameter[†]	Group 1 (n = 90)[‡]		Group 2 (n = 37)[‡]		Group 3 (n = 80)[‡]	
	Estimate	*P*	Estimate	*P*	Estimate	*P*
Age	0.04	.06	0.01	.6	0.003	.8
Gender (men)	0.29	.4	−0.09	.8	−0.15	.7
BMI	0.008	.6	−0.01	.6	0.005	.7
Race[§]						
African American	1.39	.002	1.92	.001	0.43	.3
Other	0.97	.1	1.29	.1	−0.40	.5
Education (years of college)	−0.24	.1	−0.00	.9	−0.06	.7
BALM score	−0.41	.02	0.14	.5	0.04	.8
Sedating medication (yes/no)	0.24	.5	0.10	.8	0.25	.5
Comorbidity (yes/no)	−0.26	.4	−0.33	.4	−0.52	.1
Daily sleep duration (actigraphy)	−0.11	.01	0.006	.8	−0.09	.03
AHI	0.005	.5	0.007	.5	0.007	.4
Average oxygen saturation	−0.12	.1	−0.17	.08	−0.10	.2
Sleep efficiency	−0.002	.3	−0.01	.3	−0.006	.4
Arousal index	−0.01	.2	−0.02	.08	−0.03	.003

One hundred fifteen observations were deleted due to missing values for the predictors or outcome variables.

BMI = body mass index; BALM = Basic Language Morningness (range 13–55); AHI = apnea–hypopnea index.

[†]Generalized Logit Type 3 Analysis of Effects, Degrees of Freedom = 3.

[‡]Group 1 = PVT lapse ≥ 2 and ESS ≥ 11, Group 2 = PVT lapse ≥ 2 and ESS < 11, Group 3 = PVT lapse < 2 and ESS ≥ 11, Group 4 = PVT lapse < 2 and ESS < 11. Group 4 (nonsleepy) = Reference; n = 76.

[§]Reference race was European American.

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Table 5.

Predictors of objective and subjective sleepiness: model with cytokines (n = 211)

Parameter[†]	Group 1 (n = 71)[‡]		Group 2 (n = 24)[‡]		Group 3 (n = 61)‡	
	Estimate	*P*	Estimate	*P*	Estimate	*P*
Age	0.06	.03	0.00	.9	0.02	.4
Gender (men)	0.24	.5	−0.20	.6	−0.24	.5
BMI	−0.00	.7	−0.03	.3	−0.03	.2
Race[§]						
African American	2.17	.0002	2.81	.0006	1.20	.03
Other	1.16	.1	1.17	.3	−0.34	.6
Education (years of college)	0.06	.7	0.15	.5	0.17	.4
BALM score	−0.65	.005	−0.13	.6	−0.04	.8
Sedating Medication (yes/no)	0.11	.8	−0.21	.7	0.13	.8
Comorbidity (yes/no)	−0.61	.2	−0.78	.2	−0.86	.07
Daily Sleep Duration (actigraphy)	−0.11	.02	−0.05	.3	−0.06	.2
AHI	0.01	.4	0.01	.2	0.02	.07
Average oxygen saturation	−0.07	.5	−0.10	.4	−0.00	.9
Sleep Efficiency	0.01	.1	−0.001	.9	0.003	.8
Arousal Index	−0.02	.1	−0.03	.06	−0.05	.0003
*lnIL-6	0.65	.03	0.45	.2	0.71	.02
*lnTNFα	−0.07	.8	0.59	.2	−0.81	.09

One hundred eighty-seven observations were deleted due to missing values for the predictors or outcome variables.

BMI = body mass index; BALM = Basic Language Morningness (range 13–55); AHI = apnea–hypopnea index; *ln = log normal transformation.

[†]Generalized Logit Type 3 Analysis of Effects, Degrees of Freedom = 3.

[‡]Group 1 = PVT lapse ≥ 2 and ESS ≥ 11, Group 2 = PVT lapse ≥ 2 and ESS < 11, Group 3 = PVT lapse < 2 and ESS ≥ 11, Group 4 = PVT lapse < 2 and ESS < 11. Group 4 (nonsleepy) = Reference; n = 55.

[§]Reference race was European American.

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Due to the persistent observed association of race with sleepiness, we first analyzed race without sociodemographic covariates (univariate analysis). The African-American race was significantly associated with risk of concordant sleepiness (group 1 vs. 4; OR = 3.8, 95% confidence interval [CI] 2.0–7.3) and objective sleepiness (group 2 vs. 4; OR = 4.0, CI 1.7–9.6), but not with subjective sleepiness (group 3 vs. 4; OR = 1.2, CI 0.6–2.2). The association of the African-American race with concordant sleepiness (group 1) in the multivariate models remained significant (with and without cytokines, OR = 8.8, CI 2.8–27.3 and OR = 4.0, CI 1.6–9.8, respectively). In contrast, the association of the African-American race with objective sleepiness (group 2) was stronger in the multivariate models (with and without cytokines, OR = 16.6, CI 3.3–83.6 and OR = 7.18, CI 2.2–22.9, respectively). The African-American race was associated with subjective sleepiness only in the multivariate model with cytokines (group 3 vs. 4, OR = 3.3, CI 1.0–10.1). Other race (not African-American or European-American) was a smaller sample of 29 participants and showed a trend towards higher odds of objective sleepiness that failed to achieve statistical significance (Table 4, OR = 4.5, CI 0.9–22.4).

Higher BALM score (morning chronotype) and longer habitual sleep duration were protective for concordant sleepiness in models with and without

cytokines (BALM: group 1 vs. 4; OR = 0.52, CI 0.33–0.82 and OR = 0.65, CI 0.48–0.93, respectively, and sleep duration: group 1 vs. 4; OR = 0.89, CI 0.81–0.99 and OR = 0.89, CI 0.80–0.98, respectively). Neither chronotype nor habitual sleep duration was associated with risk of objective or subjective sleepiness alone (group's 2 or 3 vs. group 4). Older age was associated with concordant sleepiness only in the model with cytokines (OR = 1.06, CI 1.0–1.1). PSG-derived sleep and respiration variables were not significant determinants of sleepiness with the exception of arousal index. A high arousal index was associated with lower risk of subjective sleepiness in models with and without cytokines (OR = 0.94, CI 0.91−0.97 and OR = 0.96, CI 0.94−0.98).

Although group 1 had fewer years of college education (Table 1), this was not associated with the outcome of sleepiness in the multivariable models. Finally, with respect to the association of cytokines with sleepiness in the final model (Table 5), higher IL-6 levels were associated with risk of concordant and subjective sleepiness (group 1 vs. 4; OR = 1.91, CI 1.0–3.4 and group 3 vs. 4; OR 2.0, CI 1.1–3.7). As increases in IL-6 levels have previously been reported with obesity, sleepiness, and OSA [38–41], we added interaction term BMI × lnIL-6 to the final multivariable model and found no significant interaction (p-value = .99). When BMI was considered in categories, we saw a similar p-value = .87 for the joint test of the interaction. This suggests that the relationship of IL-6 to the outcome of sleepiness did not differ by BMI.

Although sedating medications were included as covariates, we explored the effect of sedatives on sleepiness by repeating the multivariate analyses in participants without self-reported sedative use (n = 186; group 1 = 56, group 2 = 26, group 3 = 51, group 4 = 53). The smaller sample size limited statistical power, but similar trends were seen with respect to determinants of sleepiness. Daily sleep duration by actigraphy and race showed trend towards association with sleepiness (type 3 ANOVA, p = .06 for each). The analysis of maximum likelihood estimates showed sleep duration trended to lower values in groups 1 and 3 compared with group 4 (−.09, p = .05 and −.1, p = .05, respectively). African-American race was associated with groups 1 and 2 compared with group 4 (1.35, p = .02 and 1.57, p = .03, respectively). Lower education level was associated with group 1 vs. group 4 (−.44, p = .04) and a lower arousal index was associated with group 3 vs. group 4 (−.03, p = .03).

Discussion

Excessive daytime sleepiness is a hallmark of clinically significant OSA and leads to impaired function, reduced quality of life, and possibly poorer cardiovascular outcomes [41–45]. Sleepiness increases healthcare utilization in populations at risk of OSA [46]. This study prospectively examined determinants of objective and subjective sleepiness in a cohort with treatment-naïve OSA. We report a positive association of the self-identified African-American race and a negative association of morning chronotype with concordant objective and subjective sleepiness in OSA. In addition, elevated IL-6, a proinflammatory cytokine, was predictive of concordant sleepiness. Our finding of short sleep duration being a significant predictor of concordant sleepiness is consistent with previous reports in OSA [13, 47]. As noted above, sleepiness appears to be a phenotypic marker of increased risk of adverse health outcomes in OSA, but its manifestation does not hinge on the severity of OSA. Understanding the sociodemographic and biological characteristics that lead to sleepiness will aid the development of personalized treatment approaches and goals for individuals with OSA.

The role of race in the manifestation of sleepiness in OSA has been unclear. Studies in general sleep clinic populations and epidemiological cohorts report 1–2 points greater ESS scores in African Americans compared with European Americans [48, 49]. In a subset analysis, after adjusting for age, gender, BMI, education, sleep duration, depression, and AHI, ESS remained numerically higher in African Americans by 0.85 points [49]. This study also noted that higher ESS scores in African Americans stemmed from two out of eight questions. Another report of racial differences in subjective sleepiness within an epidemiological cohort found less frequent sleepiness, but a 1.5-fold higher prevalence of increased ESS score in African Americans after adjusting for demographics, sleep duration, OSA, insomnia, medication use, depression, and social support [50]. Few studies have specifically examined the role of race in sleepiness in clinical populations with OSA. Scharf et al. performed a retrospective analyses of racial differences in clinical populations with OSA and found higher ESS scores in univariate analyses among African Americans [51]. A recent study by Eliasson et al. examined the effects of gender and race on ESS in European-American and African-American adults at high risk for OSA [52]. This study reported a greater ESS in African-American men with OSA, but this association was not significant when adjusted for age, gender, BMI, perceived stress, and self-reported sleep duration. Another study of patients with severe OSA (AHI > 30 per hour) and more than 60% of the sample represented by African Americans found no association of ESS with race, but did report depression and oxygen desaturation index as determinants of increased ESS [53]. In aggregate, these findings suggest greater subjective sleepiness in African Americans with OSA, but highlight the potential impact of variations on perception and cultural interpretation, limiting the utility of subjective sleepiness in measuring the health effects of sleepiness. To the best of our knowledge, this is the first study to demonstrate a significant association of African-American race with both objective and subjective sleepiness, independent of confounders. Multivariate models with and without inflammatory cytokines showed that the African-American race was predictive of concordant and objective sleepiness. In the second model, after adjustment for cytokines, the African-American race was associated with higher risk of concordant, objective, and subjective sleepiness (approximately 7-, 16-, and 3-fold increased risk, respectively). Notably, the association of sleepiness with African-American race was stronger in categories including objective sleepiness (groups 1 and 2) and roughly

doubled with the inclusion of inflammatory cytokines in the model. Similarly, inclusion of education, a socioeconomic status proxy, failed to mitigate this relationship. Furthermore, sleepiness indicated by MSL, which is less affected by mood, was also associated with African-American race [54]. Overall, these associations indicate that the African-American race is a risk factor for sleepiness in OSA.

The effect of chronotype on sleepiness in OSA has not been systematically studied. Morningness and eveningness have been associated with higher AHI compared with populations with intermediate chronotype in obese adults with OSA [55]. In contrast, higher prevalence of OSA and higher levels of stress hormones have been reported in evening chronotype [56]. Stelmach-Mardas et al. reported positive effects of morning chronotype on quality of life in OSA, particularly in the physical health and social relationship domains. This study assessed the relationship of depression and cardiometabolic markers (including blood pressure) with quality of life, but did not measure sleepiness [57]. More recently, in a genome-wide association study of self-reported morningness, the authors found no association of morningness with "self-reported sleep phenotypes" including insomnia and sleep apnea. This study also reported an association of morningness with lower rates of depression and obesity [58]. Taken together, these studies suggest that the relationship of chronotype with OSA is complex and confounded by obesity and mood. The protective effect, albeit a modest one (Cohen's d effect size = 0.2), of morning chronotype on sleepiness in OSA is an important finding, and vulnerability to adverse health outcomes in OSA imparted by chronotype needs to be examined in future studies.

Similar to the largest study on the association of subjective sleepiness with short self-reported sleep duration [13], we found that the group with concordant sleepiness slept an average of 49 min less per night by actigraphy compared with nonsleepy group. Not surprisingly, sleep duration had a large effect on concordant sleepiness (effect size = 0.7). Objective and subjectively sleepiness alone was also associated with a trend to shorter sleep duration that failed to achieve statistical significance. Sleep deprivation is the commonest cause of sleepiness in the general population and is associated with adverse cardiometabolic outcomes [59, 60]. More recently, sleep deprivation–related exacerbation of oxidative stress, inflammation, and risk for hypertension in OSA has been reported [61, 62]. However, it is unclear whether the adverse impact of sleep loss is further heightened by OSA. Nevertheless, our findings underscore the importance of sleep extension counseling and intervention as integral components of management of symptomatic OSA.

There are conflicting reports on the somnogenic effects of proinflammatory cytokine IL-6 in OSA [63]. Bravo et al. identified objective and subjective sleepiness by ESS and MSLT in a clinical sample of men with severe OSA compared with matched controls. OSA patients had higher levels of IL-6 compared with controls, but this was not different between OSA with and without sleepiness [19]. A similar approach to identifying sleepiness by ESS and MSLT in OSA was taken in a recent report that found a significant relationship between objective sleepiness and elevated IL-6 levels but no association between severe subjective sleepiness and IL-6 [20]. Our results replicate and extend these findings by showing a similar association of IL-6 levels with concordant sleepiness identified by PVT and ESS and with subjective sleepiness. This study failed to show an association with PVT-measured sleepiness alone, likely due to the small sample size. Notable differences that may account for the discrepant findings with respect to subjective sleepiness are a smaller sample size and a lack of objectively measured habitual sleep duration in the study by Li et al. Although IL-6 levels do not appear to improve with continuous positive airway pressure (CPAP) treatment of OSA in unselected populations [64], it is unclear whether this may yet prove to be a useful biomarker of CPAP treatment response or lack thereof in sleepy OSA populations. The potential utility of IL-6 as a biomarker of physiological sleepiness and residual sleepiness in treated OSA, independent of obesity, sleep duration, and other confounders, needs to be further explored [63, 65].

TNFá level was not associated with sleepiness. There are conflicting reports regarding elevated TNFá levels and its association with sleepiness in children with OSA [66, 67]. The role of TNFá, if any, as a biomarker of sleepiness in OSA remains to be clarified. Unlike previous reports, the lack of association of sleepiness with OSA severity in this study is likely due to the overall modest severity of OSA [68]. A lower arousal index was noted in the subjectively sleepy group, similar to another report of longer and deeper sleep noted in patients with moderate OSA with subjective sleepiness [7]. This finding suggests that subjective sleepiness alone may reflect homeostatic sleep drive in moderate OSA. As respiratory arousals were not separately assessed in this study, it is difficult to ascertain the significance of this finding with respect to OSA.

There is limited data regarding the role of age, obesity, and gender in pathogenesis of objective sleepiness in OSA. Similar to the previous report by Kapur et al., we did not find age to be associated with subjective sleepiness [13], but older age increased the risk of concordant sleepiness, when inflammation was taken into account. Unlike the previous report, this study included a middle-aged relatively healthy sample with a low prevalence of serious medical conditions such as chronic cardiopulmonary disease (<6% vs. 10%–24%). It is plausible that aging in this sleepy OSA population increases vulnerability to functional impairment. This finding needs replication and further validation. In this study, PVT, a brief objective measure of sleepiness that is easily deployable in the clinic, has shown sensitivity to short MSL, chronic sleep deprivation, chronotype, and inflammation in OSA. This adds to the evidence that suggests that PVT is an underutilized objective tool for assessment of sleepiness in OSA [69–71]. Larger studies examining IL-6 as a biomarker of sleepiness in treated and untreated OSA are needed to understand its utility in predicting occupational and health risks attributable to OSA. Additional novel pathways and tools that can improve our understanding of the pathogenesis of sleepiness in OSA include metabolic pathways and advanced neuroimaging [72, 73]. Finally, a parsimonious combination of physiological and biochemical biomarkers may be

more valuable than any single measure of sleepiness [74].

The strengths of this study include a diverse, well-characterized sample of treatment naïve OSA, objective assessment of sleepiness, and usual sleep duration. Important confounders, such as other primary sleep disorders, were excluded. Medical and psychiatric disorders as well as use of medications were considered in the final analyses. In this context, it is important to note that subjective sleepiness has been studied more widely than objective sleepiness, and factors important in its regulation include mood [53, 75]. A notable limitation of this study is that mood and psychosocial stress or support were not measured as potential confounders in participants. This is important given the association of self-identified African-American race and chronotype with sleepiness. Adequately powered studies are needed to address the association of chronotype and race with sleepiness, independent of mood and psychosocial stress. This is relevant to designing effective therapeutic interventions and is an important area of future investigation. Another limitation of this study that may affect the generalizability of our findings includes lack of young and older adults, precluding conclusions regarding the effect of aging on sleepiness.

In summary, this study highlights known and novel factors that are important in the pathogenesis of sleepiness in OSA, namely, chronic sleep deprivation, chronotype, African-American race, and inflammation. An important next step is to understand the extent and mechanisms by which these factors mediate sleepiness and identify sleepiness measures that are valid biomarkers of adverse health outcomes in OSA.

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Notes

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References

1. Rauscher H et al. Acceptance of CPAP therapy for sleep apnea. *Chest* 1991;100(4):1019–1023.
   Google Scholar Crossref PubMed

2. Weaver TE et al. Continuous positive airway pressure treatment of sleepy patients with milder obstructive sleep apnea: results of the CPAP Apnea Trial North American Program (CATNAP) randomized clinical trial. *Am J Respir Crit Care Med* 2012;186(7):677–683.
   Google Scholar Crossref PubMed

3. Huang JF et al. The relationship between excessive daytime sleepiness and metabolic syndrome in severe obstructive sleep apnea syndrome. *Clin Respir J* 2016;10(6):714–721.
   Google Scholar Crossref PubMed

4. Guglielmi O et al. Job stress, burnout, and job satisfaction in sleep apnea patients. *Sleep Med* 2014;15(9):1025–1030.
   Google Scholar Crossref PubMed

5. Ward KL et al. Excessive daytime sleepiness increases the risk of motor vehicle crash in obstructive sleep apnea. *J*

Clin Sleep Med 2013;9(10):1013–1021.
Google Scholar PubMed

6. Vgontzas AN . Excessive daytime sleepiness in sleep apnea: it is not just apnea hypopnea index. *Sleep Med* 2008;9(7):712–714.
Google Scholar Crossref PubMed

7. Roure N et al. Daytime sleepiness and polysomnography in obstructive sleep apnea patients. *Sleep Med* 2008;9(7):727–731.
Google Scholar Crossref PubMed

8. Bixler EO et al. Effects of age on sleep apnea in men: I. Prevalence and severity. *Am J Respir Crit Care Med* 1998;157(1):144–148.
Google Scholar Crossref PubMed

9. Punjabi NM et al. Modeling hypersomnolence in sleep-disordered breathing. A novel approach using survival analysis. *Am J Respir Crit Care Med* 1999;159(6):1703–1709.
Google Scholar Crossref PubMed

10. Batool-Anwar S et al. Obstructive sleep apnea and psychomotor vigilance task performance. *Nat Sci Sleep* 2014;6:65–71.
Google Scholar Crossref PubMed

11. Lee IS et al. Number of lapses during the psychomotor vigilance task as an objective measure of fatigue. *J Clin Sleep Med* 2010;6(2):163–168.
Google Scholar PubMed

12. Sharkey KM et al. Subjective sleepiness and daytime functioning in bariatric patients with obstructive sleep apnea. *Sleep Breath* 2013;17(1):267–274.
Google Scholar Crossref PubMed

13. Kapur VK et al. Sleepiness in patients with moderate to severe sleep-disordered breathing. *Sleep* 2005;28(4):472–477.
Google Scholar Crossref PubMed

14. Fong SY et al. Comparing MSLT and ESS in the measurement of excessive daytime sleepiness in obstructive sleep apnoea syndrome. *J Psychosom Res* 2005;58(1):55–60.
Google Scholar Crossref PubMed

15. Guilleminault C et al. Determinants of daytime sleepiness in obstructive sleep apnea. *Chest* 1988;94(1):32–37.
Google Scholar Crossref PubMed

16. Olson LG et al. Correlations among Epworth Sleepiness Scale scores, multiple sleep latency tests and psychological symptoms. *J Sleep Res* 1998;7(4):248–253.
Google Scholar Crossref PubMed

17. Slater G et al. Obesity as an independent predictor of subjective excessive daytime sleepiness. *Respir Med* 2013;107(2):305–309.
Google Scholar Crossref PubMed

18. Gozal D et al. Sleep measures and morning plasma TNF-alpha levels in children with sleep-disordered breathing. *Sleep* 2010;33(3):319–325.
Google Scholar Crossref PubMed

19. Bravo Mde L et al. Inflammatory proteins in patients with obstructive sleep apnea with and without daytime sleepiness. *Sleep Breath* 2007;11(3):177–185.
Google Scholar Crossref PubMed

20. Li Y et al. Objective, but not subjective, sleepiness is associated with inflammation in sleep apnea. *Sleep* 2017;40:zsw033.

21. Van Dongen HP et al. The cumulative cost of additional wakefulness: dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. *Sleep* 2003;26(2):117–126.
Google Scholar Crossref PubMed

22. Van Dongen HP et al. Systematic interindividual differences in neurobehavioral impairment from sleep loss: evidence of trait-like differential vulnerability. *Sleep* 2004;27(3):423–433.
Google Scholar PubMed

23. Kritikou I et al. Sleep apnoea, sleepiness, inflammation and insulin resistance in middle-aged males and females. *Eur Respir J* 2014;43(1):145–155.
Google Scholar Crossref PubMed

24. Kim H et al. Sleep-disordered breathing and psychomotor vigilance in a community-based sample. *Sleep* 2007;30(10):1309–1316.
Google Scholar Crossref PubMed

25. Basner M et al. Maximizing sensitivity of the psychomotor vigilance test (PVT) to sleep loss. *Sleep* 2011;34(5):581–591.
Google Scholar Crossref PubMed

26. Shearer WT et al. Soluble TNF-alpha receptor 1 and IL-6 plasma levels in humans subjected to the sleep deprivation model of spaceflight. *J Allergy Clin Immunol* 2001;107(1):165–170.
Google Scholar Crossref PubMed

27. Chang AM et al. Sleep timing and circadian phase in delayed sleep phase syndrome. *J Biol Rhythms* 2009;24(4):313–321.
Google Scholar Crossref PubMed

28. Dijk DJ et al. Contribution of circadian physiology and sleep homeostasis to age-related changes in human sleep. *Chronobiol Int* 2000;17(3):285–311.
Google Scholar Crossref PubMed

29. de Gonzalo-Calvo D et al. Differential inflammatory responses in aging and disease: TNF-alpha and IL-6 as possible biomarkers. *Free Radic Biol Med* 2010;49(5):733–737.
Google Scholar Crossref PubMed

30. Task Force. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. *Sleep* 1999;22:667–689.

Crossref PubMed

31. Van Dongen HP et al. Investigating the interaction between the homeostatic and circadian processes of sleep-wake regulation for the prediction of waking neurobehavioural performance. *J Sleep Res* 2003;12(3):181–187.
Google Scholar Crossref PubMed

32. Littner MR et al. Practice parameters for clinical use of the multiple sleep latency test and the maintenance of wakefulness test. *Sleep* 2005;28:113–121.
Google Scholar Crossref PubMed

33. Nadeem R et al. Serum inflammatory markers in obstructive sleep apnea: a meta-analysis. *J Clin Sleep Med* 2013;9(10):1003–1012.
Google Scholar PubMed

34. Johns MW . Sleepiness in different situations measured by the Epworth Sleepiness Scale. *Sleep* 1994;17(8):703–710.
Google Scholar Crossref PubMed

35. Almendros I et al. Tumor cell malignant properties are enhanced by circulating exosomes in sleep apnea. *Chest* 2016;150(5):1030–1041.
Google Scholar Crossref PubMed

36. Hsieh FY . Sample size tables for logistic regression. *Stat Med* 1989;8(7):795–802.
Google Scholar Crossref PubMed

37. Belsley D.A. KE et al. *Regression Diagnostics: Identifying Influential Data and Sources of Collinearity* . New York: Wiley; 1980.
Google Scholar Crossref

38. Eder K et al. The major inflammatory mediator interleukin-6 and obesity. *Inflamm Res* 2009;58(11):727–736.
Google Scholar Crossref PubMed

39. Tanaka S et al. Increased plasma IL-6, IL-8, TNF-alpha, and G-CSF in Japanese narcolepsy. *Hum Immunol* 2014;75(8):940–944.
Google Scholar Crossref PubMed

40. Pejovic S et al. Effects of recovery sleep after one work week of mild sleep restriction on interleukin-6 and cortisol secretion and daytime sleepiness and performance. *Am J Physiol Endocrinol Metab* 2013;305(7):E890–E896.
Google Scholar Crossref PubMed

41. Silva GE et al. Obstructive sleep apnea and quality of life: comparison of the SAQLI, FOSQ, and SF-36 questionnaires. *Southwest J Pulm Crit Care* 2016;13(3):137–149.
Google Scholar Crossref PubMed

42. Robinson GV et al. Predictors of blood pressure fall with continuous positive airway pressure (CPAP) treatment of obstructive sleep apnoea (OSA). *Thorax* 2008;63(10):855–859.
Google Scholar Crossref PubMed

43. Lindberg E et al. Role of snoring and daytime sleepiness in occupational accidents. *Am J Respir Crit Care Med* 2001;164(11):2031–2035.

Google Scholar Crossref PubMed

44. Kapur VK et al. ; Sleep Heart Health Study Group. Sleep disordered breathing and hypertension: does self-reported sleepiness modify the association?*Sleep* 2008;31(8):1127–1132.
Google Scholar PubMed

45. Ronksley PE et al. Obstructive sleep apnoea is associated with diabetes in sleepy subjects. *Thorax* 2009;64(10):834–839.
Google Scholar Crossref PubMed

46. Ronksley PE et al. Excessive daytime sleepiness is associated with increased health care utilization among patients referred for assessment of OSA. *Sleep* 2011;34(3):363–370.
Google Scholar Crossref PubMed

47. Miliauskas S et al. Obstructive sleep apnea: factors important for severe daytime sleepiness. *Medicina (Kaunas)* 2003;39(3):232–236.
Google Scholar PubMed

48. Knutson KL et al. Stability of the Pittsburgh sleep quality index and the epworth sleepiness questionnaires over 1 year in early middle-aged adults: the CARDIA study. *Sleep* 2006;29(11):1503–1506.
Google Scholar Crossref PubMed

49. Hayes AL et al. The Epworth score in African American populations. *J Clin Sleep Med* 2009;5(4):344–348.
Google Scholar PubMed

50. Baron KG et al. Race and ethnic variation in excessive daytime sleepiness: the multi-ethnic study of atherosclerosis. *Behav Sleep Med* 2010;8(4):231–245.
Google Scholar Crossref PubMed

51. Scharf SM et al. Racial differences in clinical presentation of patients with sleep-disordered breathing. *Sleep Breath* 2004;8(4):173–183.
Google Scholar Crossref PubMed

52. Eliasson AH et al. ; Integrative Cardiac Health Project Registry. Fatigued on Venus, sleepy on Mars-gender and racial differences in symptoms of sleep apnea. *Sleep Breath* 2015;19(1):99–107.
Google Scholar Crossref PubMed

53. Jacobsen JH et al. Factors associated with excessive daytime sleepiness in patients with severe obstructive sleep apnea. *Sleep Breath* 2013;17(2):629–635.
Google Scholar Crossref PubMed

54. Barateau L et al. Hypersomnolence, hypersomnia, and mood disorders. *Curr Psychiatry Rep* 2017;19(2):13.
Google Scholar Crossref PubMed

55. Kim LJ et al. Is the chronotype associated with obstructive sleep apnea?*Sleep Breath* 2015;19(2):645–651.
Google Scholar Crossref PubMed

56. Lucassen EA et al. Evening chronotype is associated with changes in eating behavior, more sleep apnea, and increased stress hormones in short sleeping obese individuals. *PLoS One* 2013;8:e56519.
Google Scholar Crossref PubMed

57. Stelmach-Mardas M et al. Quality of life, depression and dietary intake in obstructive sleep apnea patients. *Health Qual Life Outcomes* 2016;14(1):111.
Google Scholar Crossref PubMed

58. Hu Y et al. GWAS of 89283 individuals identifies genetic variants associated with self-reporting of being a morning person. *Nat Commun* 2016;7:10448.
Google Scholar Crossref PubMed

59. Gottlieb DJ et al. Association of usual sleep duration with hypertension: the Sleep Heart Health Study. *Sleep* 2006;29(8):1009–1014.
Google Scholar Crossref PubMed

60. Gangwisch JE et al. Sleep duration as a risk factor for diabetes incidence in a large U.S. sample. *Sleep* 2007;30(12):1667–1673.
Google Scholar Crossref PubMed

61. DeMartino T et al. Oxidative stress and inflammation differentially elevated in objective versus habitual subjective reduced sleep duration in obstructive sleep apnea. *Sleep* 2016;39(7):1361–1369.
Google Scholar Crossref PubMed

62. Priou P et al. Cumulative association of obstructive sleep apnea severity and short sleep duration with the risk for hypertension. *PLoS One* 2014;9:e115666.
Google Scholar Crossref PubMed

63. Vgontzas AN et al. IL-6 and its circadian secretion in humans. *Neuroimmunomodulation* 2005;12(3):131–140.
Google Scholar Crossref PubMed

64. Paz Y Mar HL et al. Effect of continuous positive airway pressure on cardiovascular biomarkers: the sleep apnea stress randomized controlled trial. *Chest* 2016;150(1):80–90.
Google Scholar Crossref PubMed

65. Arnardottir ES et al. The interaction of obstructive sleep apnea and obesity on the inflammatory markers C-reactive protein and interleukin-6: the Icelandic Sleep Apnea Cohort. *Sleep* 2012;35(7):921–932.
Google Scholar PubMed

66. Alexopoulos EI et al. Obstructive sleep apnea, excessive daytime sleepiness, and morning plasma TNF-α levels in Greek children. *Sleep* 2013;36(11):1633–1638.
Google Scholar PubMed

67. Khalyfa A et al. TNF-α gene polymorphisms and excessive daytime sleepiness in pediatric obstructive sleep apnea. *J Pediatr* 2011;158(1):77–82.
Google Scholar Crossref PubMed

68. Uysal A et al. Nocturnal hypoxemia biomarker predicts sleepiness in patients with severe obstructive sleep apnea. *Sleep Breath* 2014;18(1):77–84.
Google Scholar Crossref PubMed

69. Sunwoo BY et al. Reliability of a single objective measure in assessing sleepiness. *Sleep* 2012;35(1):149–158.
Google Scholar Crossref PubMed

70. Zhang C et al. Psychomotor vigilance testing of professional drivers in the occupational health clinic: a potential objective screen for daytime sleepiness. *J Occup Environ Med* 2012;54(3):296–302.
Google Scholar Crossref PubMed

71. Luz GP et al. Impaired sustained attention and lapses are present in patients with mild obstructive sleep apnea. *Sleep Breath* 2016;20(2):681–687.
Google Scholar Crossref PubMed

72. Sanchez-de-la-Torre M et al. Plasma levels of neuropeptides and metabolic hormones, and sleepiness in obstructive sleep apnea. *Respir Med* 2011;105:1954–60.
Google Scholar Crossref PubMed

73. Xiong Y et al. Brain white matter changes in CPAP-treated obstructive sleep apnea patients with residual sleepiness. *J Magn Reson Imaging* 2017;45(5):1371–1378.
Google Scholar Crossref PubMed

74. Fleming WE et al. Blood biomarkers of endocrine, immune, inflammatory, and metabolic systems in obstructive sleep apnea. *Clin Biochem* 2016;49(12):854–861.
Google Scholar Crossref PubMed

75. Pamidi S et al. Depressive symptoms and obesity as predictors of sleepiness and quality of life in patients with REM-related obstructive sleep apnea: cross-sectional analysis of a large clinical population. *Sleep Med* 2011;12(9):827–831.
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