The relationship between diurnal variation of cytokines and symptom expression in mild obstructive sleep apnea

Hyunju Yang, PhD, RN1; Christopher G. Engeland, PhD2,3; Tonya S. King, PhD4; Amy M. Sawyer, PhD5,6,7
1Chonnam National University, College of Nursing, Gwangju, South Korea; 2The Pennsylvania State University, Department of Biobehavioral Health, University Park, Pennsylvania; 3The Pennsylvania State University, College of Nursing, University Park, Pennsylvania; 4The Pennsylvania State University, College of Medicine, Department of Public Health Sciences, Hershey, Pennsylvania; 5University of Pennsylvania, School of Nursing, Philadelphia, Pennsylvania; 6Corporal Michael J. Crescenz Veterans Affairs Medical Center, Philadelphia, Pennsylvania; 7University of Pennsylvania, Perelman School of Medicine, Center for Sleep & Circadian Neurobiology, Philadelphia, Pennsylvania

Objectives: To identify the relationship between (1) cytokines and everyday symptoms and (2) cytokine diurnal variation and everyday symptoms in mild obstructive sleep apnea (OSA).

Methods: An observational, single-night study of 20 adults with mild to moderate OSA undergoing diagnostic polysomnography. Everyday symptoms included sleepiness measured by Stanford Sleepiness Scale, fatigue and energy levels measured by Lee Fatigue Scale, and cytokine plasma concentrations including interleukin (IL)-1β, IL-6, IL-8, and tumor necrosis factor-α (TNF-α) measured concurrent with symptoms at presleep (8 PM to 10 PM; time 1) and postsleep (5 AM to 6 AM; time 2). Cytokine diurnal variation was calculated as [time 2 − time 1]. Wilcoxon signed-rank tests and Spearman partial rank correlations adjusted for age, body mass index, cardiovascular disease, and type 2 diabetes were used.

Results: Twenty patients (50% male, obese, median age = 51.0 years) with mild OSA (apnea-hypopnea index, AHI; median 9.5 events/h) were evaluated. Evening IL-6 was associated with evening symptoms, including sleepiness (r = .69, P = .002) and energy level (r = −0.68, P = .003); morning IL-8 (r = .73, P = .001), and TNF-α (r = .59, P = .015) were associated with morning fatigue. Only morning IL-8 (r = −0.57, P = .022) and diurnal variations in IL-8 (r = −0.60, P = .014) were associated with morning energy level.

Conclusion: There is scant evidence addressing the diurnal variation of inflammatory biomarkers and the relationship with symptom expression in mild OSA. The present findings provide preliminary mechanistic findings for symptom expression in OSA and contribute insight to mild OSA symptom phenotypes.

Keywords: obstructive sleep apnea, symptom, symptom management, cytokine, inflammatory biomarker


INTRODUCTION

Obstructive sleep apnea (OSA) is a chronic condition characterized by repetitive upper airway obstruction during sleep resulting in repeated blood oxygen desaturation, fragmented sleep, and arousals.1 OSA is increasingly recognized as an independent risk factor for cardiovascular morbidities and mortality. These associated risks are hypothesized to be associated with chronic inflammation as a result of intermittent hypoxia in OSA. Symptoms of OSA may be similarly linked with these underlying physiological pathways. It is therefore important to identify the relationship between inflammatory cytokines, the diurnal rhythm of cytokines, and symptom expression. Inflammatory cytokines in mild OSA have not been examined in relationship to OSA symptoms.

Study Impact: Results suggest IL-6 may be a biological marker of presleep symptoms, and IL-8 may be a biological marker of post-sleep symptoms in mild OSA. The study provides insights for the underlying biological mechanisms of symptom expression in mild OSA.
on the physiological role of cytokines in sleep and sleep-related symptoms.12

The most common daytime manifestation of OSA is excessive daytime sleepiness, but other symptoms—including fatigue and lack of energy—are also commonly reported.13

The prevalence of excessive daytime sleepiness in OSA patients is 87.2%,14 compared with 28% in the general population.15 Although excessive daytime sleepiness is recognized as a major threat to public safety,16 the underlying mechanisms between symptom expression and OSA are not clear. Several mechanistic models of the effects of circulating cytokines on daytime sleepiness and fatigue in OSA have been suggested.17–18 TNF-α and IL-1β are cytokines known to regulate sleep,19–21 and circadian IL-6 secretion is associated with both the quantity and quality of sleep.22 The relationship of these same cytokines, specifically their diurnal rhythm, to symptom expression provides an opportunity to phenotype OSA based on molecular signature. Various symptom phenotypes exist in adults with OSA,23,24; therefore, phenotyping approaches (eg, biological markers) are needed to impart knowledge of individual health risks for negative OSA outcomes, such as cardiovascular disease and cardiovascular events. This approach is consistent with the precision health priority wherein individual persons are best matched to treatments of high likelihood for efficacy. To guide precision health approaches to symptom management in OSA, it is critical to understand the biological mechanisms that underlie the OSA symptom phenotypes.

Most cytokine studies in OSA have focused on the effects of continuous positive airway pressure (CPAP) on inflammation in OSA or the relationship between cytokines and moderate to severe OSA.25–27 Considering that the prevalence of mild OSA in the general population (aged 40–65 years) is as high as 20%,28 surprisingly little is known about the relationship between inflammatory cytokines and mild OSA. In addition, relatively few studies have examined the relationship between inflammatory cytokines and symptom expression for any severity of OSA.17–18 To our knowledge, no studies have examined the relationship between diurnal variation of inflammatory cytokines and symptom expression in mild OSA across presleep and postsleep bouts. Given these gaps in the literature, this case series aimed to explore whether inflammatory cytokines (eg, IL-6, IL-8, TNF-α) and the diurnal rhythm of these cytokines are associated with expression of symptoms, including sleepiness, fatigue, and energy, in mild OSA.

**Methods**

A single-night, in-laboratory case series design was used to identify the relationships between inflammatory cytokines and symptom expression in OSA and between diurnal variation of inflammatory cytokines and symptom expression in OSA. Because few studies have examined symptom expression and molecular signature in predominantly mild OSA, a case series design was best suited for exploration of the study aims and hypothesis generation to support subsequent research.

The study period was August 2016 to December 2016. The study was approved by the respective institutional review boards.

**Study participants**

Using convenience sampling, patients with suspected OSA were recruited from a clinical sleep center in the United States. The following inclusion criteria were used: (1) newly diagnosed OSA with apnea-hypopnea index (AHI) 5 to <20 events/h on in-laboratory polysomnography (PSG); (2) males and females ≥18 years of age; and (3) able to read and speak English. Exclusion criteria were (1) participation in a split-night PSG; (2) any treatment history of OSA within the previous one year or any current treatment of OSA; (3) comorbid inflammatory conditions, including current and/or recent acute infections and any preexisting autoimmune disease diagnosed within the past 3 months; (4) use of antibiotics and/or immunosuppressive medication (eg, corticosteroids) within the previous 3 months or current use; (5) concurrent regular use (>3 nights/week) of sedative/hypnotics; (6) catecholamine therapy within 1 month; and (7) diagnosis of another sleep disorder, including insomnia or narcolepsy.

**Procedures**

On the night of diagnostic PSG, participants completed the Berlin Questionnaire to prescreen for the likelihood of OSA. As this study necessitated that participants had OSA by diagnostic PSG (AHI ≥5 events/h), the use of a prediagnosis screening questionnaire reduced the risk of enrolling participants who were not likely to have OSA. With a positive Berlin screen, patients were provided informed consent and enrolled in the study. Participants (n = 20) underwent in-laboratory, full-night PSG (**Figure 1**). As the recommended threshold for split-night studies (AHI 20–40 events/h) was an exclusion criterion for the study, most of the study participants (n = 15, 75%) had mild OSA.

**Phase 1**

After pre-enrollment screening and informed consent, participants completed a demographic questionnaire. Before the full-night diagnostic study (ie, between 8:00 and 10:00 PM), participants completed the Stanford Sleepiness Scale (SSS) and Lee’s Fatigue and Energy Scales and had peripheral blood drawn for cytokine assessment. Blood was transferred to two tubes, one containing ethylenediaminetetraacetic acid and the other containing sodium heparin. Samples were then centrifuged (3,000 rpm for 15 minutes), the supernatant was removed by pipette, and 300 μl of aliquots was stored at −80°C in 1.5-ml Eppendorf tubes. Standard diagnostic PSG procedures29 were then begun at approximately 10:30–11:00 PM.

**Phase 2**

PSG devices were removed between 5:00 and 6:00 AM by a PSG technologist. Participants then completed symptom-related questionnaires, including the Stanford Sleepiness Scale and Lee’s Fatigue and Energy Scales, after an awakening interval of 15–30 minutes. Peripheral blood collection for cytokines was then conducted in the same way as in phase 1. Participants were then debriefed and exited the study.
### Measures

#### Symptom-related questionnaires

**Stanford Sleepiness Scale:** The SSS, which measures sleepiness level at the time of evaluation (ie, the present moment) was used. On a scale of one to seven, a higher score indicates more daytime sleepiness.\(^30\) A cut-point score for sleepiness is ≥ 4.\(^30\) The SSS is the most commonly used instrument for measuring present-moment sleepiness in OSA.\(^31\) The test-retest reliability correlation coefficient is 0.88.\(^32\)

**Lee’s Fatigue and Energy Scales:** Fatigue and energy levels were measured by Lee’s Fatigue and Energy Scales; two subscales include 13 fatigue items and 5 energy items. Individual items are rated 0 to 10 and summed for each subscale. A cut-point score indicating morning fatigue is ≥ 3.2 (ie, indicates fatigue), and evening fatigue is ≥ 5.6 (ie, indicates fatigue); a cut-point score indicating low morning energy is ≤ 6.0 and low evening energy is ≤ 3.5.\(^33\) This instrument was initially developed for adults with sleep disorders,\(^34\) and it measures momentary (ie, present-moment) fatigue and energy levels. The scale has well-established validity and reliability.\(^34\)

#### Cytokine assay

Serum levels of IL-1β, IL-6, IL-8, and TNF-α were measured using a Luminex Human MMP 5-Plex Panel (Invitrogen Corporation, Carlsbad, California).\(^35\) The multiplex assay sensitivity in this study ranged from <0.5 pg/ml to <5 pg/ml. The intra-assay coefficient of variation was <10% with a range of 7%–9.8%.\(^35\) IL-1β had an undetectable value in most samples; IL-1β data are not reported.

#### Polysomnography

All participants underwent overnight, in-laboratory diagnostic PSG using standard techniques.\(^36\) Apnea was defined as a cessation of airflow lasting ≥ 10 seconds; hypopnea was defined as a reduction of airflow by approximately 30% with an associated decrease in blood oxygen saturation (SpO\(_2\)) of at least 4%.\(^36\) During the diagnostic PSG, the participant’s sleep was continuously monitored (24-analog channel and 10-DC channel Aurora TS amplifier system using Gamma software; Grass-Telefactor, West Warwick, Rhode Island). PSG included electroencephalography, electrooculography, submental electromyography, oronasal airflow by an airflow pressure transducer and thermistor, a single-lead electrocardiography, chest and abdominal respiratory effort by plethysmography, SpO\(_2\) by pulse oximetry, and body position.\(^37\)

### Statistical analysis

Sample-size calculations for the present study were based on an estimated level of precision ± 0.3 for a 95% confidence interval around an estimate of partial correlation; a sample size of 28 participants was required. Data were summarized by standard descriptive statistics. Continuous variables were described by median and first and third quartiles (Q1, Q3). Frequencies and percentages were used for categorical data. Because of skewness in the data, even with log transformation, and the small sample size of this study, nonparametric statistical methods were used to evaluate the associations of interest. The changes in inflammatory cytokine levels from morning to evening (ie, diurnal variation) were evaluated using the nonparametric Wilcoxon signed rank test. Spearman partial correlation coefficients were estimated to assess correlation between measures while controlling for potential confounders including age, body mass index (BMI), cardiovascular disease, and type 2 diabetes mellitus (type 2 DM). Statistical significance was defined at \(P < .05\). Data analyses were performed with SAS software V9.4 (SAS Institute Inc., Cary, North Carolina).

### RESULTS

#### Sample characteristics

The number of participants enrolled was 66. There were no withdrawals over the study period; however, 69.7% of enrolled...
Study participants either did not have OSA or underwent a split-night PSG study resulting in a final sample size of 20 adults with sleep apnea comprising both male and female adults, median age 51 years, who were overweight or obese, predominantly non-Hispanic whites (Table 1). Reasons for referral to the sleep clinic included snoring (75.0%), daytime sleepiness (60.0%) and/or restless sleep (60.0%). Fewer than half of the study participants were full-time workers (30.0%). The most prevalent comorbidities were cardiovascular disease (50.0%) (i.e., hypertension, cardiac arrhythmias, heart failure) and type 2 diabetes mellitus (10.0%), confirmed by electronic medical record diagnosis codes.

### Polysomnography variables in OSA

Study participants had mild OSA, with median AHI of 9.5 events/h and 4% ODI of 11.1 events/h (Table 2). Median apnea index and hypopnea index were 2.4 events/h and 7.6 events/h, respectively. Median total sleep time was 380.2 minutes, and median arousal index was 19.6 events/h. Median respiratory effort-related arousal index (RERA index) was 1.6 events/h. The SpO2 nadir median was 83.5%; the total sleep-time SpO2 median was 93.3%.

### Research variable description: inflammatory cytokines and symptoms

The only inflammatory cytokine with a significant change in levels from presleep (median 1.42 [interquartile range, IQR 1.08, 2.37]) to postsleep (median 1.97 [IQR 1.46, 2.62]) was TNF-α (P = .005). Although other inflammatory cytokines demonstrated variations between presleep and postsleep, study participants either did not have OSA or underwent a split-night PSG study resulting in a final sample size of 20 adults with sleep apnea comprising both male and female adults, median age 51 years, who were overweight or obese, predominantly non-Hispanic whites (Table 1). Reasons for referral to the sleep clinic included snoring (75.0%), daytime sleepiness (60.0%) and/or restless sleep (60.0%). Fewer than half of the study participants were full-time workers (30.0%). The most prevalent comorbidities were cardiovascular disease (50.0%) (i.e., hypertension, cardiac arrhythmias, heart failure) and type 2 diabetes mellitus (10.0%), confirmed by electronic medical record diagnosis codes.

### Polysomnography variables in OSA

Study participants had mild OSA, with median AHI of 9.5 events/h and 4% ODI of 11.1 events/h (Table 2). Median apnea index and hypopnea index were 2.4 events/h and 7.6 events/h, respectively. Median total sleep time was 380.2 minutes, and median arousal index was 19.6 events/h. Median respiratory effort-related arousal index (RERA index) was 1.6 events/h. The SpO2 nadir median was 83.5%; the total sleep-time SpO2 median was 93.3%.

### Research variable description: inflammatory cytokines and symptoms

The only inflammatory cytokine with a significant change in levels from presleep (median 1.42 [interquartile range, IQR 1.08, 2.37]) to postsleep (median 1.97 [IQR 1.46, 2.62]) was TNF-α (P = .005). Although other inflammatory cytokines demonstrated variations between presleep and postsleep,
Figure 2—Distribution of symptom variables.

Sleepiness measured by Stanford Sleepiness Scale; fatigue and energy measured by Lee Fatigue and Energy Scale. Hashed lines indicate cut-point scores for sleepiness (≥4), evening fatigue (≥5.6), morning fatigue (≥3.2), evening energy (≤3.5, indicating low levels of energy), and morning energy (≤6.0, indicating low levels of energy). E = evening, M = morning.

there were no statistically significant differences: (1) median pre-IL6 of 0.62 (IQR 0.56, 1.08) and median post-IL6 of 0.56 (IQR 0.42, 1.11) \((P = .940)\) and (2) between median pre-IL8 of 2.96 [IQR 2.23, 4.52] and median post-IL8 of 3.69 [IQR 2.40, 4.77] \((P = .204)\). Median postsleep sleepiness (3.0) was not different from presleep sleepiness (3.0), but both presleep and postsleep sleepiness levels were lower than the established sleepiness threshold of 4.0 (Figure 2). Median postsleep fatigue (4.89) was greater than the established fatigue threshold of 3.2. Median postsleep energy (4.00) was lower than the established energy threshold of 6.0.\(^3\) None of the symptoms improved overnight (Figure 2).

**Inflammatory cytokines and symptoms relationships**
Evening IL-6 level was positively correlated with evening sleepiness \((r = .69, 95\% \text{ CI} = [.29, .88], P = .002)\) and negatively correlated with evening energy \((r = −.68, 95\% \text{ CI} = [−.88, −.28], P = .003)\) (Figure 3A). After removing an outlier, there was still significant positive correlation between evening IL-6 level and evening sleepiness \((r = .69, 95\% \text{ CI} = [.28, .88], P = .003)\) (data not shown). No other relationships were statistically significant among evening biomarkers and symptoms. Morning fatigue was positively correlated with morning IL-8 \((r = .73, 95\% \text{ CI} = [.37, .90], P = .001)\) and morning TNF-\(\alpha\) \((r = .59, 95\% \text{ CI} = [.13, .84], P = .015)\) (Figure 3B), and these two cytokines were correlated. Morning IL-8 \((r = −.57, 95\% \text{ CI} = [.82, .09], P = .022)\) and the diurnal variation of IL-8 \((r = −.60, 95\% \text{ CI} = [−.84, −.15], P = .014)\) were negatively associated with morning energy and were correlated with each other by definition.

**DISCUSSION**
This study is the first to examine the relationship between the diurnal variation of inflammatory biomarkers and symptom expression in mild OSA. The major findings of our study indicate that higher evening IL-6 in an adult sample of mild OSA was significantly associated with evening symptoms, including greater sleepiness and lower energy. We also identified that higher morning IL-8 levels and greater diurnal variation of IL-8 were associated with higher morning fatigue and lower morning energy levels.

Most study participants had mild OSA (75.0%), defined by AHI 5 to <15 events/h. Previous studies have suggested that mild OSA, per se, is a risk factor for systemic inflammation and cardiovascular consequences wherein the odds ratio (OR) for developing an incident nondipping blood pressure in adults with mild OSA was 3.1 (95% CI, 1.3–7.7) compared with non-OSA even after adjustment for age, sex, and BMI.\(^3\) Likewise, a longitudinal study identified the incident hypertension in mild OSA OR was 2.03 (95% CI 1.29, 3.17) compared with an OR of 1.42 (95% CI, 1.14, 1.78) in non-OSA (as defined by AHI of 0.1–4.9 events/h).\(^4\) Duchna and colleagues\(^1\) demonstrated that vascular endothelial dysfunction is markedly worse in mild OSA compared with that in healthy adults, which suggests adverse cardiovascular consequences and at least local, and possibly systemic inflammation exist in mild OSA. In the same study, CPAP treatment in mild OSA improved vasodilatory capacity. In prior studies, proinflammatory cytokines such as TNF-\(\alpha\) and IL-1\(\beta\) were higher in mild OSA compared with non-OSA even after controlling for the effects of confounding variables, including age, BMI, and comorbidities.\(^4\) The accumulating findings, including the results reported herein, suggest there may be clinical importance for early detection, intervention, and treatment of mild OSA; however, more definitive evidence on the effect of early detection and management of mild OSA is required as there is limited, and conflicting, evidence with regard to mild OSA and cardiovascular outcomes.

This is in addition to TNF-\(\alpha\), which has been identified in previous OSA studies to be an important biomarker and exhibited value here as well. The present study identified a significant rise in TNF-\(\alpha\) in predominantly mild OSA over the sleep period, suggesting that TNF-\(\alpha\) may play a role in the pathophysiologic sequela of OSA and may contribute to daytime somnolence. Different circadian rhythms of TNF-\(\alpha\) release have been identified between healthy adults and adults with OSA.\(^4\) In healthy adults, TNF-\(\alpha\) levels surge in the late evening.
and peak during early sleep, and its lowest level occurs in the morning, suggesting that TNF-α may be involved in sleep regulation by promoting slow-wave sleep. Conversely, in OSA, there was a shift in the circadian rhythm of TNF-α wherein peak levels occurred at noon and the lowest levels were observed in the evening (ie, before bedtime). Additional study found that hypoxic stress during sleep, defined as percentage of time with SaO₂ < 90%, was the strongest predictor of TNF-α production (P = .001) and increased TNF-α was positively correlated to excessive daytime sleepiness (r = .68, P = .0003). In the same study, treatment with CPAP for one month significantly decreased TNF-α levels and excessive daytime sleepiness...
study did not change significantly. These findings suggest that sleep deprivation may be a useful target for evaluating therapeutic effectiveness in OSA.

No other biomarkers demonstrated significant change over the sleep bout in the current study. IL-6 is known to have a distinct circadian pattern and to contribute to the circadian regulation of sleepiness. Vgontzas and colleagues found that healthy adults have a biphasic circadian pattern of IL-6 wherein the peak levels of IL-6 occurred at 7:00 PM and 5:00 AM and the nadir levels of IL-6 occurred at 8:00 AM and 9:00 PM. In the same study, they found that sleep deprivation affected IL-6 circadian rhythmicity. After sleep restriction for one week, the mean level of IL-6 during daytime (8:00 AM to 10:00 PM) was significantly higher (P < .05), whereas the mean level of IL-6 during the nighttime (10:00 PM to 6:00 AM) was lower than baseline levels. Although the present study did not measure IL-6 every hour, the levels measured at presleep (between 8:00 and 10:00 PM) and postsleep (between 5:00 and 6:00 AM) showed results similar to those of Vgontzas and colleagues. The difference, however, or diurnal variation, was not statistically significant. Similarly, IL-8 levels in the present study did not change significantly from presleep to postsleep; however, mean levels increased across the night. These findings suggest that sleep apnea influences the natural change of inflammatory cytokines across sleep; hence, it appears important to examine predisposing factors that contribute to the circadian patterns of inflammatory cytokines and shifts in mild OSA (eg, arousals, hypoxic events, etc.).

This study is the first to concurrently examine OSA symptoms and the diurnal variation of cytokines in predominantly mild OSA. This study identified a significant association between higher IL-6 levels and both higher sleepiness and lower energy levels, all measured in the evening; IL-6 expression potentially underlies the biological mechanism of these common OSA symptoms. In OSA, repetitive upper airway collapses during sleep induce chronic intermittent hypoxia, leading to inflammatory responses. IL-6, which is a proinflammatory cytokine with somnogenic effects, increases in response to local and systemic inflammation. Entian and colleagues found that peak levels of IL-6 in OSA occur at approximately 9:00 PM, suggesting that higher concentrations of IL-6 in OSA may play a role in mediating sleepiness and lower energy. A recent study found that both self-reported and objective sleepiness were associated with increased IL-6 levels in severe OSA (mean AH1 33 ± 31 events/h). These findings suggest that IL-6 is implicated in the causal mechanism underlying the relationship between sleepiness and IL-6, particularly the variability of this relationship across the OSA severity spectrum. One of the points of this article might be that even in predominantly mild OSA, there is a relationship between cytokine levels and OSA symptom expression, with IL-6 and IL-8 being standouts as good potential biomarkers for future OSA research.

This study is also the first to examine the relationships between the levels of IL-8, diurnal variation of IL-8, and everyday symptoms in mild OSA. This study found a positive correlation between morning fatigue and both IL-8 measured in the morning and the diurnal variation of IL-8. Several studies in non-OSA adult populations have similarly identified a relationship between IL-8 and fatigue. Natelson and colleagues found increased levels of IL-8 in cerebrospinal fluid of individuals with chronic fatigue syndrome. Another recent study identifying biological mechanisms of multiple symptoms in patients with non–small-cell lung cancer found that among 55 single nucleotide polymorphisms (SNPs) in 37 genes, interleukin genotype IL8-T251A was the most relevant genetic factor for the symptom of fatigue (OR = 2.07, 95% CI = 1.16–3.70). To address more accurately the relationship between IL-8 and fatigue in OSA and determine whether this relationship is consistent across the spectrum of OSA severity, a case-control study with a larger number of study participants with variations in OSA severity is necessary.

This study has several limitations, and the results should be interpreted with caution as the study may not provide sufficient power to detect statistically significant differences based on the a priori sample size estimate (n = 28) and the final study sample size (n = 20). Second, this exploratory study was designed to measure inflammatory cytokines at presleep and postsleep to address diurnal variability of symptoms and cytokines; diurnal variability was therefore extrapolated from the two biomarker measurements. Hence, the circadian rhythmicity of inflammatory cytokines was not fully determined. Third, there was no non-OSA comparison group, and normal cytokine patterns across sleep are inferred from the literature. Fourth, this study applied a 4% rule for hypopnea, whereas several cited studies defined hypopnea as an oxyhemoglobin desaturation of at least 3% or an arousal. The different applied hypopnea definitions lead to variations in AHI and may affect the findings of studies investigating the relationship between cytokines and OSA. Lastly, the cytokine levels observed in a laboratory setting during a single-night study are not necessarily representative of within-individual cytokine expression owing to an altered sleep schedule, which may influence a participant’s circadian rhythm. A larger, longitudinal cohort study, or case-control study with one to three nights run in (ie, adjustment nights) conducted in the laboratory is necessary to clarify the relationship between inflammatory cytokines and symptom expression in adults with OSA.

This exploratory study, using a novel approach to symptom expression and phenotypes, suggests that inflammation is associated with symptom expression in OSA. Evening IL-6 levels were significantly associated with evening symptoms, including sleepiness and lower energy; morning IL-8 levels were associated with morning fatigue and energy levels. Ideally, future studies should include comparators of non-OSA with asymptomatic OSA and symptomatic OSA of all severity levels to address rigorously the biological mechanisms that underlie OSA symptom phenotypes. This line of inquiry will afford researchers better insight into the relationship between OSA and inflammation and will inform precision health approaches to symptom management in adults with OSA.
H Yang, CG Engeland, TS King, et al.

Cytokines and symptom expression in OSA

ABBREVIATIONS

AHI, apnea-hypopnea index
BMI, body mass index
CI, confidence interval
CPAP, continuous positive airway pressure
ESS, Epworth Sleepiness Scale
IL-1β, interleukin-1β
IL-6, interleukin-6
IL-8, interleukin-8
N1, stage non-rapid eye movement (NREM) 1 sleep
N2, stage non-rapid eye movement (NREM) 2 sleep
ODI4, 4% oxygen desaturation index
OR, odds ratio
OSA, obstructive sleep apnea
PSG, polysomnography
REM, rapid eye movement sleep
RERA Index, Respiratory Effort Related Arousal Index
SNPs, single nucleotide polymorphisms
SpO₂, blood oxygen saturation
SSS, Stanford Sleepiness Scale
SWS, slow-wave sleep or stage non-rapid eye movement (NREM) 3 sleep
TNF-α, tumor necrosis factor-α
TST, total sleep time
Type 2 DM, type 2 diabetes mellitus
W, stage wake sleep

REFERENCES


ACKNOWLEDGMENTS

Hyunju Yang contributed to conception and design and analysis and interpretation of data; drafted the manuscript; critically revised the manuscript; gave final approval. Christopher G. Engeland contributed to specimen preparation, collection, and interpretation, analysis, and interpretation of data; drafted the manuscript; critically revised the manuscript; gave final approval. Tonya S. King contributed to analysis, and interpretation of statistical data; critically revised the manuscript; gave final approval; Amy M. Sawyer contributed to conception and design, analysis, and interpretation; drafted the manuscript; critically revised the manuscript; and gave final approval.

DISCLOSURE STATEMENT

The author(s) declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. The work was performed at the Penn State Hershey Medical Center in Hershey, Pennsylvania. The ideas and opinions expressed in this article are those of the authors and endorsement of those opinions by the funding agency, or Veterans Affairs, is not intended nor inferred. The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: American Nurses Foundation (ANF) (no. 189415), Williamson Endowment Graduate Award, 2016 Beta Sigma Research Grant, NLN Foundation for Nursing Education Scholarship Awards (H. Yang, Principal Investigator).