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Authors

Lee, Ellen E
Ancoli-Israel, Sonia
Eyler, Lisa T
et al.

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Sleep Disturbances and Inflammatory Biomarkers in Schizophrenia: Focus on Sex Differences

Ellen E. Lee, MD, Sonia Ancoli-Israel, PhD, Lisa T. Eyler, PhD, Xin M. Tu, PhD, Barton W. Palmer, PhD, Michael R. Irwin, MD, Dilip V. Jeste, MD

Objectives: Persons with schizophrenia, and women in particular, are at high risk for sleep disturbances and inflammatory activation. The sleep-inflammation link has been reported to be stronger in women within the general population. This study sought to examine the sleep-inflammation link in persons with schizophrenia and its relationship with demographic, clinical and cognitive variables. **Design:** Cross-sectional case-control study. **Participants:** Community-dwelling outpatients with schizophrenia (N=144, 46% women) and non-psychiatric comparison (NC) participants (N=134, 52% women), age 26-65 years. **Measurements:** Reported sleep disturbances (sleep quality and duration), and mental and physical health were assessed. Cognitive assessments included executive functioning (Delis-Kaplan Executive Function System) and global cognitive functioning (Telephone Interview for Cognitive Status - modified.) Inflammatory biomarkers included pro-inflammatory cytokines [high sensitivity C-Reactive Protein (hs-CRP), Interleukin (IL)-6, Tumor Necrosis Factor- α (TNF- α)] and an anti-inflammatory cytokine (IL-10). **Results:** The schizophrenia group had longer sleep duration, worse sleep quality, and increased levels of hs-CRP, IL-6, and TNF- α compared to NCs. Women with schizophrenia were less likely to have good sleep quality and had elevated levels of hs-CRP and IL-6 compared to men with schizophrenia. In the schizophrenia group, worse sleep quality and global cognitive functioning were associated with higher hs-CRP and IL-6 levels. Female sex and younger age were also associated with higher hs-CRP levels. **Conclusions:** Sleep disturbances and increased inflammation, which were common in schizophrenia, were associated in persons with schizophrenia. Moreover, women with schizophrenia had worse sleep quality and inflammation than men. Further examination of the

Received July 16, 2018; accepted September 22, 2018. From the Department of Psychiatry, University of California San Diego, La Jolla, CA, United States; Sam and Rose Stein Institute for Research on Aging, University of California San Diego, La Jolla, CA, United States; Department of Medicine, University of California, San Diego, CA, United States; Veterans Affairs San Diego Healthcare System, San Diego, CA, United States; Department of Family Medicine and Public Health, University of California San Diego, La Jolla, CA, United States; Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, CA; and the Department of Neurosciences, University of California, San Diego, CA, United States. Corresponding author: Dilip V. Jeste, MD, Senior Associate Dean for Healthy Aging and Senior Care, Distinguished Professor of Psychiatry and Neurosciences, Estelle and Edgar Levi Memorial Chair in Aging, Director, Sam and Rose Stein Institute for Research on Aging, University of California, San Diego, 9500 Gilman Drive #0664, La Jolla, CA 92023-0664, Fax: (858) 534-5475, Telephone: (858) 534-4020. e-mail: djeste@ucsd.edu

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sleep-inflammation links, their contribution to clinical outcomes, and sex-specific factors is warranted. (Am J Geriatr Psychiatry 2018; 00:1–11)

Keywords: Psychosis, insomnia, hs-CRP, IL-6, sleep quality, cognition

Highlights

- **What is the primary question addressed by this study?**

Persons with schizophrenia are a high-risk group for sleep disturbances and inflammation, relative to the general population. This study examined the relationship of subjective sleep disturbances and inflammation in persons with schizophrenia and non-psychiatric comparison subjects. We also tested the associations of this relationship with respect to age, sex and other clinical variables.

- **What is the main finding of this study?**

Worse sleep quality was associated with increased levels of pro-inflammatory markers (high-sensitivity C-reactive protein and interleukin-6) in persons with schizophrenia, even when accounting for age, sex, psychopathology, and cognition. Women with schizophrenia had significantly worse sleep disturbances and elevated levels of pro-inflammatory markers compared to men with schizophrenia.

- **What is the meaning of the finding?**

Sleep quality and cognition were significantly associated with inflammation in persons with schizophrenia. Understanding the biological mechanisms of a potentially modifiable target like sleep may help guide future development and assessment of interventions to improve sleep and cognition.

OBJECTIVE

Sleep disturbances are central to many psychiatric disorders, including schizophrenia, with clear implications for cognition, brain health and aging.¹ However, the neurobiological mechanisms connecting sleep and psychopathology are not well understood. Studies have estimated that 30-80% of adults with schizophrenia, compared to 10-30% in the general population, have sleep problems that include sleep initiation difficulties, more frequent disruptions, decreased sleep efficiency, and short/long total sleep time.^{2,3} Many of these sleep issues meet criteria for moderate-severe insomnia disorder^{4,5} in 44-54% of adults with schizophrenia.⁶ While two meta-analyses have reported short sleep duration possibly due to frequent overnight awakenings,^{3,7} one study reported longer sleep duration in persons with schizophrenia, attributed to sedating antipsychotic medications, lack of regular schedules due to unemployment, and depressive symptoms. Sleep abnormalities are present in medication-free patients,³ drug-naïve patients

during their first episode of psychosis⁸ and individuals at high risk for psychosis,⁹ preceding the influence of psychotropic medications and lifestyle habits such as low physical activity and smoking.

Sleep disturbances (e.g., insomnia) are a clinically significant target as they can be effectively treated. Cognitive behavioral therapy for insomnia (CBT-I) is the recommended treatment for insomnia in the general population^{10,11} with further evidence that meditative movement intervention such as t'ai chi and yoga are non-inferior to CBT-I.¹² Some benefits have been reported for relaxation-based therapies¹⁰; other behavioral therapies (excluding cognitive-behavioral therapies¹⁰); and exercise.¹³ Currently, the literature supporting sleep interventions in schizophrenia is limited to a few studies on CBT-I for insomnia,¹⁴ eszopiclone,¹⁵ acupuncture,¹⁶ and music relaxation.¹⁷

Although the precise mechanisms are unclear, sleep disturbances are thought to result in increased inflammation via effects on the hypothalamic-pituitary-adrenal axis and sympathetic nervous system.¹⁸ In turn, inflammatory responses may mediate some clinical outcomes of sleep problems (e.g., cognition, mood,

aging.)^{19,20} In the general population, meta-analyses have reported links between sleep disturbances, long sleep duration (>8 hours/night) and inflammation.^{18,21} Remission of insomnia has been shown to induce decreases in systemic, cellular and genomic markers of inflammation.²² However, there is limited understanding in schizophrenia of how sleep affects inflammatory mechanisms and key outcomes.

While this study focuses on insomnia-type sleep disturbances, obstructive sleep apnea (OSA) may also be important in schizophrenia. Estimates of OSA prevalence among persons with schizophrenia have ranged from 1.6-52% in a few small studies.^{23,24} The studies with higher prevalence rates (>40%) examined older persons (mean age 59.6 years),²⁵ high-risk patients referred to a sleep disorders clinic,²⁶ or included outpatients with other serious mental illnesses,²⁷ while the studies with very low rates included examinations of consecutively admitted inpatients²⁸ and those already diagnosed according to the medical record.²⁹ The large discrepancy in prevalence rates may reflect underdiagnosis and biased study sampling. Even in the general population, adherence to OSA treatment can be as low as 17%³⁰; and untreated OSA is highly associated with inflammation,³¹ increased amyloid production and tau hyperphosphorylation,³² impaired cognition³³ and cognitive decline,³⁴ although associated sociodemographic, medical and inflammatory factors differ from insomnia.³⁵ Both insomnia and respiratory-related sleep disorders may affect inflammation in schizophrenia, though the mechanisms and risk factors may differ.

Although sex differences in sleep and inflammation have not been extensively examined in persons with schizophrenia, research in the general population has reported that sex differences exist for both sleep and inflammation; and that sex may moderate the sleep-inflammation relationship – though the evidence is modest.²¹ Relative to age-comparable men, older women have worse sleep quality³⁶; greater age-related increases in immune cell and cytokine production³⁷; and increased risk of chronic inflammatory diseases such as Type 2 Diabetes Mellitus, atherosclerosis, and autoimmunity.³⁷ In schizophrenia, women have higher levels of inflammation biomarkers than men.^{38, 39} In studies of animals and the general population, sex influences the relationship between inflammation and sleep.⁴⁰⁻⁴² In women, long sleep duration has been significantly associated with higher C-reactive protein (CRP) levels.⁴⁰ Sleep deprivation has

been found to be associated with increased evening cytokine responses [Interleukin (IL)-6, Tumor Necrosis Factor (TNF)- α] and increased NF- κ B activation in women but not in men.^{41,43} Also, poor sleep quality and increased frequency of sleep disturbances has been found to be associated with elevated levels of morning CRP and IL-6 in women but not in men.⁴²

The above cited literature suggests there may be sex differences in the association of sleep disturbances and inflammation. As both processes are known to be commonly disrupted among persons with schizophrenia, clarification of the nature and magnitude of this association could have important clinical applications for reducing the cognitive and physical comorbidities frequently associated with this disorder. It is also important to consider the influence of sex as a potential moderator of this relationship to guide individualized treatment recommendations.

Our group has previously published on the clinical correlates of inflammatory markers in schizophrenia^{38,39,44,45} and sleep problems in older persons with schizophrenia^{25,46,47}; however, this is our first report examining sleep duration and sleep quality as well as their relationships to levels of inflammatory biomarkers in this study cohort. Based on prior research examining these domains individually, we hypothesized that, relative to non-psychiatric comparison (NC) subjects, persons with schizophrenia would have worse sleep disturbances (short/long sleep duration and worse sleep quality), and elevated levels of pro-inflammatory (hs-CRP, IL-6, TNF- α) and reduced levels of anti-inflammatory (IL-10) biomarkers. We hypothesized that sleep disturbances (duration and quality) would be associated with worse inflammatory marker levels in the schizophrenia and NC groups; while accounting for relevant demographic, clinical, and cognitive variables. We explored the relationships of sleep with levels of an anti-inflammatory cytokine (IL-10.)

METHODS

Study Participants

Participants included 144 persons with schizophrenia or schizoaffective disorder and 134 age- and sex-comparable NCs, age 26-65 years, who were enrolled in an ongoing study of aging in schizophrenia.

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Participants were recruited from the greater San Diego area via outpatient clinical and residential referral networks as well as advertisements.

Inclusion criteria were: diagnosis of schizophrenia/schizoaffective disorder as determined by the Structured Clinical Interview for the DSM-IV-TR (SCID).⁴⁸ The Mini-International Neuropsychiatric Interview (MINI)⁴⁹ was used to screen NCs, who were excluded if they had a past or present diagnosis of a major neuropsychiatric illness. Other exclusion criteria were: 1) other current DSM-IV-TR Axis I diagnoses; 2) alcohol or other non-tobacco substance abuse or dependence within 3 prior months; 3) diagnosis of dementia, intellectual disability disorder, or a major neurological disorder; or 4) medical disability affecting the ability to complete study procedures. The study protocol was approved by the UC San Diego Human Research Protections Program and all participants provided written informed consent prior to participation.

Sociodemographic and Clinical Characteristics

Trained study staff administered standardized assessments for: psychopathology [Patient Health Questionnaire-9 (PHQ-9) for depression,⁵⁰ Scales for the Assessment of Positive and Negative Symptoms (SAPS and SANS, respectively^{51,52})], mental well-being and physical well-being [Medical Outcomes Survey - Short Form 36 (SF-36)],⁵³ and medical comorbidity (Cumulative Illness Rating Scale).⁵⁴ Height and waist circumference and weight was measured using standard protocols. BMI was calculated from the height and weight based on standard formulas.

Sleep Variables

Participants were interviewed as to whether they had a current or past diagnosis of OSA.

Participants were asked to quantify the number of hours/night they slept. Sleep duration subgroups were defined as short (<7 hours/night), optimal (7-8 hours/night) and long (>8 hours/night) based on the literature²¹. Participants were also interviewed as to whether they had a current or past diagnosis of OSA.

Participants also completed four Likert-scale ratings (1 = "every night" to 5 = "never") regarding frequency of problems with falling asleep, overnight awakening, waking too early, and waking feeling

unrefreshed. Sleep quality composite and subgroups measures were derived from these items. The sleep quality composite measure combined the four items (scores ranging from 4 to 20), such that higher scores reflected worse sleep disturbances overall. The four items had high internal consistency (Cronbach's $\alpha=0.82$.) The poor quality sleep group included persons who reported the following symptoms every or a few nights per week: **either** difficulty falling asleep, frequent/long periods of awakening overnight, **or** waking too early; **and** waking feeling unrefreshed. Participants who reported sleep disturbances occurred rarely/never were categorized as having good quality sleep. The remainder of participants were categorized as having moderate quality sleep. Overall, the composite sleep quality measure was consistent with the sleep quality subgroups, thus we examined sleep quality as a continuous variable for the analyses.

Cognitive Measures

Standardized cognitive assessments included the Delis-Kaplan Executive Function System for executive functioning⁵⁵ and the Telephone Interview for Cognitive Status or TICS (modified) for global cognitive functioning.⁵⁶

Inflammatory Biomarker Assays

All assays were run from a baseline fasting blood draw. Based on prior empirical literature,⁴¹⁻⁴³ we chose to focus on three pro-inflammatory markers that have been observed to be linked to sleep disturbances (high-sensitive CRP or hs-CRP, TNF- α , and IL-6) and explored the relationships with an anti-inflammatory cytokine (IL-10) that has not been previously examined in reference to sleep disturbance in schizophrenia.

Plasma hs-CRP levels were obtained with a commercially available (MSD, Rockville, MD) enzyme-linked immunosorbent assay (ELISA) at the UC San Diego Clinical and Translational Research Institute (CTRI) lab, from whole blood samples. To obtain Plasma TNF- α , IL-6, and IL-10 levels, we used Meso Scale Discovery MULTI-SPOT[®] Assay System on a SECTOR Imager 2400 instrument (Rockville, MD, USA). Levels were measured with V-PLEX Human Biomarker panels (Catalog # K151A0H-2).

Statistical Analyses

Continuous variables were assessed for violation of distribution assumptions (skew and kurtosis) and were log-transformed as necessary. Biomarker levels were log-transformed for all analyses. Ratios of IL-6 to IL-10 and TNF- α to IL-10 were calculated to assess the balance between pro- and anti-inflammatory markers. Independent sample t-tests or Chi-square tests were used to assess differences in sample characteristics, mental health measures, cognitive scores, physical health measures, sleep variables, and inflammatory marker levels between different subgroups (by diagnosis and sex).

To examine the influence of other clinical predictors on inflammatory marker levels, we first examined the multicollinearity of these factors using Variance Inflation Factors (VIFs)⁵⁷ and conducted general linear models that included: age, sex, positive symptoms, negative symptoms, depressive symptoms, daily antipsychotic dose, executive functioning, overall cognitive functioning, and the composite sleep quality measure. We used backward elimination approach to trim models for all factors, except for sleep quality which was included in each model. This approach yields less biased estimates than the forward selection method.⁵⁸

To examine the moderating effect of sex, we compared the sex groups and ran general linear models of inflammatory markers including: 1) sleep quality and gender as main effects and 2) sleep quality, gender and sleep quality $\times$ gender.

We present effect sizes and p-values for all of these statistical tests, and interpret greater than medium effect sizes (i.e., Cohen's $d \geq .45$ or $r \geq .30$) as meaningful. Significance was defined as Type I error $\alpha = 0.05$ (two-tailed) for all analyses, and False Discovery Rate (FDR) was used to account for multiple comparisons to ensure overall Type I error = 0.05.

RESULTS

Sociodemographic and Clinical Characteristics

There were no significant group differences in age, sex, or ethnic background between the NC and schizophrenia groups (Table 1). The schizophrenia group had significantly fewer mean years of education. The schizophrenia group reported significantly

longer sleep duration and worse sleep quality. Persons with schizophrenia also had higher mean levels of hs-CRP, IL-6, and TNF- α than NCs as well as worse executive functioning scores and worse global cognitive functioning, consistent with previous reports on a subsample of these participants.^{38,39}

Overall, 3.4% of the schizophrenia group reported a current diagnosis of OSA, compared to 1.4% of the NCs ($\chi^2=0.68$, $df=1$, $p=0.41$). A significantly greater proportion of schizophrenia participants reported a past diagnosis of OSA compared to the NC group (13.6% versus 4.2%, $\chi^2=4.3$, $df=1$, $p=0.04$).

Analyses of the Relationship Between Sleep and Inflammation

Subgroups with optimal, short, and long sleep duration were compared in both the NC and schizophrenia groups. No significant differences in any clinical, cognitive, or inflammatory measures were observed in the NC subgroups of sleep duration (data not shown). In the schizophrenia group, the short sleepers had worse mean scores of mental well-being and negative symptoms compared to the optimal sleep group: [38.8 (SD=11.3) versus 38.8 (SD=10.8), $t_{98}=-2.3$, $p=0.02$, $d=-0.48$; and 8.7 (SD=5.2) versus 6.7 (SD=4.0), $t_{98}=2.2$, $p=0.03$, $d=0.44$; respectively.) Also, the long sleepers with schizophrenia had more years of education (13.0 (SD=2.0) versus 12.0 (SD=2.4), $t_{105}=2.2$, $p=0.03$, $d=0.44$), better executive functioning scores (-0.34 (SD=0.75) versus -0.64 (SD=0.61), $t_{105}=-2.3$, $p=0.02$, $d=-0.45$), and shorter mean duration of illness (21.1yr (SD=11.0) versus 27.8 (SD=11.5), $t_{102}=3.0$, $p=0.003$, $d=0.60$) than those with optimal sleep. Among the participants with schizophrenia, sleep duration groups did not differ on levels of any inflammatory markers.

To examine the contribution of sleep quality to elevated hs-CRP and IL-6 levels in the schizophrenia group, we conducted general linear models that included factors that have been associated with inflammation and sleep. General linear models of inflammation (hs-CRP and IL-6) and sleep also included demographic, clinical, and cognitive variables. Backwards elimination was used to determine the additional factors to include in the models of inflammation and sleep. The final models are shown in Table 2. Sex, age, global cognitive functioning, and sleep quality were significantly associated with

*Sleep Disturbances and Inflammatory Biomarkers in Schizophrenia: Focus on Sex Differences***TABLE 1. Comparison of Study Participants With and Without Schizophrenia**

	Non-psychiatric Comparison (N = 134)			Schizophrenia (N = 144)			<i>t</i> or <i>X</i> ²	<i>p</i>	<i>Cohen's d</i>
	N	Mean / %	SD	N	Mean / %	SD			
Demographic Factors									
Age (years)	134	48.2	11.6	144	48.2	10.6	0.03	0.97	<0.01
Sex (% women)		52			46		1.14	0.29	
Race (%)							5.5	0.07	
Non-Hispanic Caucasian		59			45				
Hispanic		22			32				
Other		19			23				
Education (years)	134	14.6	2.2	144	12.4	2.3	8.25	< 0.001	0.99
Psychopathology									
Duration of illness (years)	—	—	—	140	25.3	11.8			
Antipsychotic dose ¹	—	—	—	144	1.8	1.6			
Positive symptoms ²	—	—	—	144	6.7	4.2			
Negative symptoms ³	—	—	—	144	7.2	4.4			
Depressive symptoms ⁴	—	—	—	140	7.6	6.5			
Mental well-being ⁵	134	54.5	6.1	144	42.9	11.3	10.5	< 0.001	1.28
Executive function ⁶	134	0.41	0.59	144	-0.54	0.72	12.0	< 0.001	1.45
Global cognitive functioning ⁷	132	37.5	4.2	140	31.1	5.8	10.5	< 0.001	1.28
Physical Health									
Physical well-being ⁸	134	51.3	9.2	144	42.6	10.1	7.4	< 0.001	0.89
Physical comorbidity ⁹	132	2.98	3.37	144	6.61	4.78	-7.2	< 0.001	-0.88
BMI (Kg/m ²)	133	27.8	6.68	142	32.1	7.26	-5.1	< 0.001	-0.61
Sleep									
Hours/night	132	6.88	1.15	132	8.04	2.07	-5.6	< 0.001	-0.69
Duration (subgroups)							27.6	< 0.001	
% short (< 7hrs)		36			26				
% optimal (7 – 8 hrs)		58			44				
% long (> 8 hrs)		6			31				
Quality (composite)	133	14.5	3.5	138	12.7	4.1	4.1	< 0.001	0.49
Quality (subgroups)							22.6	< 0.001	
% Poor		34			62				
% Moderate		19			9				
% Good		47			30				
Pro-Inflammatory biomarkers									
hs-CRP (mg/L)	131	2.13	3.35	144	4.89	8.45	-5.6	< 0.001	-0.71
Interleukin-6 (pg/mL)	115	0.88	1.46	135	1.19	1.18	-4.3	< 0.001	-0.55
TNF-α (pg/mL)	115	2.55	0.81	135	3.14	1.29	-4.5	< 0.001	-0.57
Anti-Inflammatory biomarkers									
Interleukin-10 (pg/mL)	114	0.40	0.65	133	0.44	0.41	-1.7	0.10	-0.21

¹ Antipsychotic medication daily dosages were converted to WHO average daily doses based on published standards [WHO: Guidelines for ATC classification and DDD assignment, 2010 and WHO: Introduction to Drug Utilization Research, 2009]

² As assessed by the Scale for the Assessment of Positive Symptoms (SAPS) total score

³ As assessed by the Scale for the Assessment of Negative Symptoms (SANS) total score

⁴ As assessed by the Patient Health Questionnaire-9 (PHQ-9) total score.

⁵ AS assessed by the Short Form Health Survey (SF-36) Mental Composite score

⁶ As assessed by the Delis-Kaplan Executive Function System

⁷ As assessed by the Modified Telephone Interview for Cognitive Status (TICS-M).

⁸ As assessed by the Short Form Health Survey (SF-36) Physical Composite score

⁹ As assessed by the Cumulative Illness Rating total score.

BMI = body mass index, hs-CRP = high sensitivity C-Reactive Protein, pg/mL = picograms per milliliter, TNF = Tumor Necrosis Factor. For all measures, lower scores suggest worse functioning.

hs-CRP levels. Executive functioning and sleep quality were significantly associated with IL-6 levels.

Sex Differences in Sleep and Inflammation

To further examine the influence of sex on sleep and inflammation, we first compared the sleep,

inflammatory and other health measures between the sexes. Among NCs, men and women did not differ in any measure of sleep, mental health/cognition, physical health, or inflammation. However within the schizophrenia group, there were significant differences between women and men ([Supplemental Table 1](#)). Though the sleep quality composite scores did not

TABLE 2. General Linear Models of Inflammatory markers, demographic, and clinical variables in the schizophrenia group (N = 144)

	Factors	B [95% CI]	F	dfs	FDR-adjusted p	η_p^2
hs-CRP	Sex	0.26 [0.09, 0.44]	9.07	1, 129	0.012	0.066
	Age	-0.009 [-0.02, -0.001]	5.06	1, 129	0.03	0.038
	Global cognitive functioning	-0.02 [-0.03, -0.001]	4.42	1, 129	0.03	0.033
	Sleep Quality	-0.02 [-0.04, -0.001]	1.04	1, 129	0.04	0.041
IL-6	Executive Functioning	-0.13 [-0.19, -0.06]	13.9	1, 127	< 0.02	0.099
	Sleep Quality	-0.01 [-0.02, < 0.001]	3.77	1, 127	0.05	0.029

General Linear Model (Univariate): hs-CRP = Sleep quality + Covariates
Covariates: age, sex, positive symptoms, negative symptoms, depressive symptoms, daily antipsychotic dose, executive functioning, overall cognition.
FDR = False Discovery Rate
hs-CRP = high sensitivity C-Reactive Protein, IL = interleukin.

differ, a lower proportion of women reported good sleep quality than men (23% vs. 38%, $\chi^2=4.9$, $df=1$, $p=0.03$.) Women had significantly elevated levels of hs-CRP and IL-6, higher mean BMI, and worse global cognitive functioning compared to men.

General linear models of sleep quality, gender, with and without sleep quality x gender interactions were performed for hs-CRP and IL-6 (data not shown). There was no significant effect of sleep quality x gender interactions for the inflammatory markers.

CONCLUSIONS

In this study, we examined relationships of sleep disturbances with four pro- and anti-inflammatory biomarker levels in persons with schizophrenia and NCs. Consistent with our hypotheses, we found that relative to NC participants, persons with schizophrenia had worse sleep quality; were less likely to report optimal sleep duration; and had worse levels of pro-inflammatory markers; worse executive functioning and global cognitive functioning. We did not observe differences in inflammatory marker levels between the sleep duration groups. We did find that among persons with schizophrenia, elevated levels of pro-inflammatory markers were associated with worse sleep quality, consistent with our hypothesis. Women with schizophrenia were less likely to have good sleep quality and elevated pro-inflammatory markers compared to men with schizophrenia. Among persons with schizophrenia, sex, age, global cognition and sleep quality were significantly associated with

hs-CRP levels; while executive functioning and sleep quality were significantly associated with IL-6 levels.

Overall, 62% of participants with schizophrenia reported sleep disturbances that were categorized as poor sleep quality, consistent with the prevalence of sleep disturbances reported by others.^{47,59} The schizophrenia group had longer mean sleep duration compared to the NC group, similar to findings by Afonso et al. who reported participants with schizophrenia have longer sleep duration but lower sleep efficiency and worse sleep quality.⁶⁰

These findings that link sleep and inflammation in persons with schizophrenia confirm those of Fang and colleagues who reported a number of associations between objective sleep measures and measures of generalized inflammation (white blood cell count, neutrophil count, neutrophil-lymphocyte ratio, and platelet-lymphocyte ratio).⁶¹ Fang et al. reported that worse sleep disturbances (e.g., lower sleep efficiency, shorter total sleep time, longer sleep latency, increased wake after sleep onset) was associated with increased levels of inflammatory measures in a group of schizophrenia inpatients on chronic psychiatric wards. In the current study, we examined four pro-inflammatory cytokines that were selected due to previous evidence of their link to sleep in the general population^{40,62-64} and to cognitive functioning in persons with schizophrenia.^{65,66} We also showed that sleep-inflammation relationships remain significant when relevant confounds are included in the models. We report on a stable group of outpatients with schizophrenia, who may have sleeping and lifestyle habits that are distinct from those of chronically institutionalized patients.

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Studies in the general population have shown that extremely short total sleep time (≤ 4 hours/night) as well as acute and chronic sleep loss are associated with higher levels of inflammatory markers (including IL-6 and TNF- α).⁶²⁻⁶⁴ In the present study, we did not examine participants with extremely short duration, as the numbers of participants were too small to conduct analyses. Our comparisons of participants with optimal compared to those with short (< 7 hours) and long sleep duration found no differences in inflammatory markers. Chronicity of the sleep disturbances were not ascertained during this evaluation, however, future studies should endeavor to consider acute and chronic changes in sleep.

The sex differences observed in this study highlight the importance of sex in the relationships of sleep and inflammation in people with serious mental illnesses. Women with schizophrenia are at higher risk for worse sleep quality and increased inflammatory marker levels. Sex was significantly associated with hs-CRP levels, but not IL-6 levels. The specific biological mechanisms underlying these sex differences are not clear. However, one plausible mechanism involves the role of estrogen. Estrogen has both anti-inflammatory and pro-cognitive effects, and inflammation has been proposed as the mechanism linking estrogen and cognitive functioning.⁶⁷ Some but not all studies of estrogen therapies in persons with schizophrenia, most in postmenopausal women, have reported improvements in cognitive functioning.^{68,69}

Other research groups have reported specific IL-10-related genetic variants to be more common in persons with schizophrenia and linked with lower IL-10 levels and worse attention.⁷⁰ However, in the general population, higher IL-10 levels have been associated with worse executive functioning and processing speed⁷¹ and better sleep quality.⁷² This study did not find any significant associations between IL-10 levels and sleep or cognitive functioning measures in persons with schizophrenia and NCs. Rather than the isolated IL-10 levels, examination of the ratio of pro- and anti-inflammatory levels may capture the overall balance of inflammation. The findings from this study (IL-6:IL-10 and TNF- α :IL-10 ratios) were consistent with the results using IL-6 and TNF- α levels, respectively.

There are several limitations to this study. The cross-sectional design limits causal inferences, but

can inform future longitudinal examinations. Similarly, the sleep, cognitive and inflammatory data presented in this study were assessed at one time-point, rather than specifically assessing the prior evening's sleep and the following morning's inflammatory markers. We used subjective sleep measures, which, although they may be subject to recall biases, have been reported in psychiatric populations to correlate significantly with objective sleep measures⁷³ and physical/mental health outcomes⁵⁹ as well as having clinical utility in diagnosing and treating sleep disorders.^{14,74} Although we did not use a validated sleep questionnaire such as the Pittsburgh Sleep Quality Index, the measures did include key features of sleep that overlap with clinical definitions of insomnia. With the growing availability and accessibility of actigraphy, future studies must include such non-invasive and user-friendly technologies as they become more user-friendly for populations with serious mental illnesses and can provide objective information about sleep. Objective sleep measures may further clarify relationships between sleep and inflammation.

Also, OSA prevalence was assessed via self-reported diagnosis; rates did not differ significantly between schizophrenia and NC groups and yielded subgroups too small to perform comparative statistical analyses. As these values were below the prevalence rates reported in other studies, there is concern for artificially low rates of OSA prevalence due to issues like underreporting, under-diagnosis and underutilization of primary care and other medical services among persons with schizophrenia.^{23,24} Given the high risk for OSA in persons with schizophrenia and the OSA-inflammation link, future studies must assess for OSA objectively. There is a risk of Type I errors given the multiple comparisons carried out, for which we used FDR corrections. Larger samples and longitudinal examinations should be employed to more powerfully probe sleep-inflammation-cognition links.

Strengths of this study include a relatively large sample size of over 140 persons with schizophrenia and over 130 NCs, comprehensive and well-validated mental and physical health assessments, and inclusion of clinically relevant biomarkers. This is one of the first studies to examine links between sleep, inflammation, and cognitive deficits in a clinically well characterized cohort of persons with and

without schizophrenia, using broad and validated inflammatory markers. These results are generalizable to stably treated outpatients with chronic schizophrenia.

These findings suggest that sleep quality and inflammatory markers are linked in persons with schizophrenia, a high-risk group for sleep disturbances and increased levels of inflammatory markers as well as worse cognitive deficits. Elucidation of the mechanisms driving the sex differences may help to develop novel and personalized approaches for persons with schizophrenia. Further probing of the sleep-inflammation link may yield clues to help develop novel therapies for sleep and inflammation as well as the outcomes affected by both sleep and inflammation, including cognitive impairment and psychopathology.

AUTHOR DISCLOSURES

Contributors

Dr. Lee conducted the literature searches and data analyses and wrote the first draft of the manuscript. Drs. Ancoli-Israel and Eyler were involved

with the analyses and interpretation of the data. Dr. Tu was involved in data analyses and interpretation. Dr. Palmer contributed to design of the parent study, interpretation of study results, and manuscript revision. Dr. Irwin was involved in the design of the study protocol, especially regarding the inflammatory markers, as well as the interpretation of the study results. Dr. Jeste designed the study and was involved in the data analyses and interpretation. All authors contributed to and have approved the final manuscript.

Conflict of Interest

Dr. Ancoli-Israel is a consultant for Pfizer, Eisai, Purdue and Merck. All other authors declare that they have no conflicts of interest.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.jagp.2018.09.017](https://doi.org/10.1016/j.jagp.2018.09.017).

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