SCINDEKS
Serbian Citation Index
J Med Biochem 2026; 45 DOI: 10.5937/jomb0-63272

UDK 577.1 : 61 **ISSN 1452-8258**

J Med Biochem 45: 1–8, 2026

Original paper
Originalni naučni rad

SERUM CYTOKINES AS POTENTIAL BIOMARKERS FOR DIAGNOSIS AND MONITORING OF SLEEP DISORDERS: A CROSS-SECTIONAL AND LONGITUDINAL STUDY

SERUMSKI CITOKINI KAO POTENCIJALNI BIOMARKERI ZA DIJAGNOSTIKU I PRAĆENJE POREMEĆAJA SPAVANJA: STUDIJA PRESEKA/LONGITUDINALNA STUDIJA

Yongliang Yao[1], Yifan Pan[2], Lei Yan[1], Chaoan Zheng[3]*

[1]Department of Pediatric Surgery, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, 200080, China
[2]Department of Nuclear Medicine, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, 200011, China
[3]Department of Paediatrics, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, 200080, China

Summary

Background: Sleep disorders, particularly Obstructive Sleep Apnea (OSA) and Insomnia Disorder (ID), are associated with systemic inflammation. However, the diagnostic and monitoring utility of specific cytokine profiles remains unclear. To identify distinct serum cytokine signatures in OSA and ID compared to healthy controls (HC) at baseline and to evaluate longitudinal changes in these biomarkers following standard treatment.
Methods: In this pilot study, 75 cases (25 OSA, 25 ID, 25 HC) were enrolled. Serum levels of IL-6, TNF-α, IL-1β, IL-10, and CRP were measured at baseline using multiplex immunoassay. All patients underwent polysomnography and clinical assessment. The OSA and ID cohorts were re-evaluated after 3 months of treatment (CPAP for OSA, CBT-I for ID) with repeat cytokine analysis.
Results: At baseline, the OSA group showed significantly elevated levels of IL-6 ($p<0.001$), TNF-α ($p=0.003$), and CRP ($p<0.001$) compared to HC. The ID group had elevated IL-6 ($p=0.01$) and IL-1β ($p=0.02$) but not CRP. A combined panel of IL-6, TNF-α, and IL-1β differentiated OSA from ID with an AUC of 0.87 (95% CI: 0.78–0.96). Longitudinally, CPAP therapy in adherent patients (>4 hrs/night) led to significant reductions in IL-6 ($p=0.004$)

Kratak sadržaj

Uvod: Poremećaji spavanja, naročito opstruktivna apneja u snu (OSA) i insomnija (ID), su povezani sa sistemskom inflamacijom. Međutim, dijagnostička i prognostička vrednost specifičnih citokinskih profila i dalje nije dovoljno razjašnjena. Identifikovati karakteristične serumskih citokinskih potpisa kod OSA i ID u poređenju sa zdravim kontrolnih pacijentima na početku ispitivanja, kao i proceniti longitudinalne promene ovih biomarkera nakon standardnog lečenja.
Metode: U ovu pilot-studiju je uključeno 75 ispitanika (25 sa OSA, 25 sa ID i 25 zdravih kontrolnih pacijenata). Serumski nivoi IL-6, TNF-α, IL-1β, IL-10 i CRP su određivani na početku ispitivanja primenom multipleks imunotesta. Svi pacijenti su podvrgnuti polisomnografiji i kliničkoj proceni. Grupe sa OSA i ID su ponovo procenjene nakon 3 meseca terapije (CPAP za OSA, KBT-I za ID), uz ponovnu analizu citokina.
Rezultati: Na početku ispitivanja, grupa sa OSA je imala značajno povišene nivoe IL-6 ($p<0,001$), TNF-α ($p=0,003$) i CRP ($p<0,001$) u poređenju sa ZK. Grupa sa ID je pokazala povišene nivoe IL-6 ($p=0,01$) i IL-1β ($p=0,02$), ali ne i CRP. Kombinovani panel IL-6, TNF-α i IL-1β je razlikovao OSA od ID sa AUC vrednošću od 0,87

Address for correspondence:

Chaoan Zheng
Department of Paediatrics, Shanghai General Hospital,
Shanghai Jiao Tong University School of Medicine
Shanghai, 200080, China
e-mail: zcabest@163.com

and CRP (p=0.008), correlating with improvement in apnea-hypopnea index (AHI) (r=0.65, p=0.002). CBT-I in ID led to a reduction in IL-1β (p=0.03), which correlated with improved sleep efficiency (r=-0.52, p=0.02). **Conclusion:** This pilot study identifies disorder-specific inflammatory profiles in OSA and ID. Serum IL-6 and CRP are promising biomarkers of OSA severity and treatment response, whereas IL-1β may be salient to the pathophysiology of insomnia. These findings support the role of cytokines as complementary objective tools for diagnosis and monitoring in sleep medicine.

Keywords: biomarkers, inflammation, cytokines, obstructive sleep apnea, insomnia, CPAP, cognitive behavioural therapy

(95% CI: 0,78–0,96). Longitudinalno, CPAP terapija kod adherentnih pacijenata (>4 sata/noć) je dovela do značajnog smanjenja IL-6 (p=0,004) i CRP (p=0,008), što je bilo u korelaciji sa poboljšanjem indeksa apneja-hipopneja (AHI) (r=0,65; p=0,002). KBT-I kod ID rezultirala je smanjenjem IL-1β (p=0,03), koje je bilo u korelaciji sa poboljšanjem efikasnosti spavanja (r=-0,52; p=0,02). **Zaključak:** Ova pilot-studija identifikuje specifične inflamatorne profile kod OSA i ID. Serumski IL-6 i CRP predstavljaju obećavajuće biomarkere težine OSA i odgovora na terapiju, dok IL-1β može da ima ključnu ulogu u patofiziologiji insomnije. Ovi nalazi ukazuju na ulogu citokina kao komplementarnih objektivnih alata za dijagnostiku i praćenje pacijenata u medicini sna.

Ključne reči: biomarkeri, inflamacija, citokini, opstruktivna apneja u snu, insomnija, CPAP, kognitivno-bihejvioralna terapija

Introduction

Sleep disorders represent a significant global public health burden, with Obstructive Sleep Apnea (OSA) and Insomnia Disorder (ID) being among the most prevalent (1). Current diagnostic gold standards polysomnography (PSG) for OSA and clinical interviews/questionnaires for ID, are resource-intensive, not always accessible, and in the case of ID, lack objective biological correlates (2). There is a critical need for accessible, objective biomarkers to aid in diagnosis, phenotyping, and monitoring of treatment efficacy (3).

A compelling link exists between disordered sleep and systemic inflammation (4). Intermittent hypoxia and sleep fragmentation in OSA activate nuclear factor-kappa B (NF-κB) pathways, leading to the production of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) (5). In insomnia, sustained hyperarousal of the stress axis and noradrenergic systems is hypothesised to promote a low-grade inflammatory state, though findings have been less consistent (6).

Prior research has primarily been cross-sectional, comparing single cytokines between one disorder and controls (7, 8). Few studies have directly compared inflammatory profiles across different sleep disorders or tracked their longitudinal change in response to targeted therapy (9). We therefore aimed to test the hypothesis that OSA and ID exhibit distinct serum cytokine profiles (IL-6, TNF-α, IL-1β, IL-10, CRP) and that these profiles normalise with disorder-specific treatment. This pilot study addresses these gaps with a dual cross-sectional and longitudinal design. We hypothesise that: 1) OSA and ID possess distinct serum cytokine signatures, and 2) Effective treatment will normalise these inflammatory markers, correlating with clinical improvement.

Materials and Methods

Study design and participants

This single-centre pilot study employed a combined cross-sectional and longitudinal design. Participants were recruited from the Sleep Disorders Centre at University MetroHealth between January 2024 and June 2025. The Institutional Review Board approved the study, and all participants provided written informed consent.

Three groups were enrolled, including:

1. OSA Group (n=25): Newly diagnosed, untreated cases with moderate-to-severe OSA (Apnea-Hypopnea Index, AHI ≥15) (10),
2. ID Group (n=25): Cases meeting DSM-5 criteria for Chronic Insomnia Disorder, confirmed by a sleep specialist, with PSG excluding significant OSA (AHI<5) (11),
3. Healthy Control (HC) Group (n=25): Cases with no subjective sleep complaints, normal PSG (AHI <5, sleep efficiency >85%), and matched for age and BMI. Healthy control participants were recruited from the general population and matched to the patient group using a group-level (frequency) matching strategy, rather than individual one-to-one matching. Matching was performed primarily on age and sex distributions, while BMI was applied as an inclusion-range criterion to ensure that controls fell within a clinically comparable range to the patient cohort at the time of recruitment.

Exclusion criteria for all groups included: active infection, autoimmune/inflammatory disease, severe psychiatric disorder, pregnancy, shift work, and use of immunomodulators or sleep medications (12).

Clinical and polysomnographic assessment

All participants underwent a full-night, in-lab PSG (Natus® SleepWorks). Standard parameters (AHI, arousal index, sleep stages, oxygen desaturation index) were scored by a blinded technician according to AASM guidelines (13). Participants completed the Pittsburgh Sleep Quality Index (PSQI) (14), Epworth Sleepiness Scale (ESS) (15), and Insomnia Severity Index (ISI) (16) as appropriate.

Intervention and follow-up

Patients with obstructive sleep apnea (OSA) were treated with continuous positive airway pressure (CPAP), whereas patients with insomnia disorder (ID) received cognitive behavioural therapy for insomnia (CBT-I).

The OSA group was prescribed and titrated on Continuous Positive Airway Pressure (CPAP). Adherence was objectively monitored via device metrics. While the ID Group received 6 sessions of standardised Cognitive Behavioural Therapy for Insomnia (CBT-I) over 8 weeks, delivered by a certified therapist.

Both patient groups underwent a 3-month follow-up with repeat PSG, clinical questionnaires, and blood sampling.

Adherence to cognitive behavioural therapy for insomnia (CBT-I) was defined a priori as attendance at ≥5 of the 6 scheduled sessions, consistent with standard CBT-I protocols and prior clinical studies.

Adherence to continuous positive airway pressure (CPAP) therapy was defined in accordance with established clinical guidelines as use of CPAP for ≥4 hours per night on at least 70% of nights, calculated as an average over the 3-month follow-up period.

Blood sampling and cytokine analysis

Fasting morning blood samples were drawn between 7:00 and 8:00 AM. Serum was separated, aliquoted, and stored at -80 °C. Levels of IL-6, TNF-α, IL-1β, and IL-10 were quantified using a high-sensitivity multiplex electrochemiluminescence assay (Meso Scale Discovery) (17). High-sensitivity CRP was measured by immunoturbidimetry (18). All assays were performed in duplicate by personnel blinded to group allocation.

Assay reliability was assessed using the manufacturers' reported coefficients of variation. For cytokine measurements (IL-6, TNF-α, IL-1β, and IL-10), the intra-assay coefficients of variation were <8%, and the inter-assay coefficients of variation were <10%. For high-sensitivity C-reactive protein (hs-CRP), the intra-assay CV was <5% and the inter-assay CV was <7%. All samples were analysed in duplicate according to the manufacturers' instructions, and mean values were used for statistical analyses.

Statistical analysis

Data were analysed using SPSS v.28.0. Cross-sectional comparisons used one-way ANOVA with Tukey's post-hoc test for normally distributed variables and Kruskal-Wallis test for non-parametric data. Normality of continuous variables was assessed using the Shapiro-Wilk test. Variables with non-normal distributions were summarised as median [IQR], while normally distributed variables were reported as mean ± SD. The discriminative power of cytokine panels was assessed using Receiver Operating Characteristic (ROC) curve analysis 21. Longitudinal changes within groups were analysed using paired t-tests or Wilcoxon signed-rank tests. Correlations were assessed using Pearson's or Spearman's coefficients. A p-value <0.05 was considered significant.

Results

Baseline demographic and clinical characteristics

Groups were well-matched for age and sex. As expected, the OSA group had a significantly higher BMI than both ID and HC groups ($p<0.001$). The OSA group had significantly higher AHI and oxygen desaturation index (ODI), while the ID group had worse sleep efficiency, PSQI, and ISI scores (*Table I)*.

Cross-sectional baseline serum cytokine and CRP profiles

Baseline serum analysis revealed distinct inflammatory signatures (*Table II*). The OSA group had significantly elevated levels of IL-6, TNF-α, and CRP compared to both the HC and ID groups. The ID group showed elevated IL-6 compared to HC, but CRP levels were not significantly different from HC and were significantly lower than in OSA. For IL-1β, a significant overall group effect was observed ($p=0.015$). Post-hoc analyses revealed that IL-1β concentrations were significantly higher in patients with ID than in HC and OSA patients. In contrast, the difference between the OSA and HC groups did not reach statistical significance ($p=0.082$).

Table I Baseline demographic and polysomnographic characteristics.

Characteristic	Healthy Controls (HC) (n=25)	OSA Group (n=25)	ID Group (n=25)	p-value
Demographics				
Age (years), Mean ± SD	15.8±2.2	14.9±1.6	14.7±1.2	0.72
Sex, Male/Female	13/12	15/10	11/14	0.55
BMI (kg/m^2), Mean ± SD	26.5±3.1	30.8±4.5*	27.2±3.8†	<0.001
Polysomnographic Measures				
AHI (events/hr), Mean ± SD	2.1±1.2	32.5±12.4*	2.8±1.5†	<0.001
ODI (events/hr), Median [IQR]	1.5 [0.8–2.3]	28.0 [19.5–41.2]*	2.1 [1.2–3.0]†	<0.001
Sleep Efficiency (%), Mean ± SD	88.5±4.2	82.1±8.3*	74.8±9.1*†	<0.001
Arousal Index (events/hr), Median [IQR]	12.1 [9.5–15.0]	31.5 [24.8–42.0]*	25.8 [20.1–32.4]*	<0.001
Questionnaire Scores				
ESS Score, Mean ± SD	5.2±2.1	14.8±4.5*	8.1±3.2*†	<0.001
PSQI Global Score, Mean ± SD	3.1±1.5	10.2±3.1*	14.8±2.5*†	<0.001
ISI Score, Mean ± SD	4.5±2.8	12.1±5.2*	21.4±4.1*†	<0.001

Abbreviations: AHI, apnea-hypopnea index; ODI, oxygen desaturation index; ESS, Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index; ISI, Insomnia Severity Index; IQR, interquartile range.
*Post-hoc analysis: * p<0.05 vs. HC; † p<0.05 vs. OSA group.*
Values are presented as mean ± standard deviation (SD) for normally distributed variables and as median [interquartile range (IQR)] for variables with non-normal distributions. The Oxygen Desaturation Index (ODI) and Arousal Index demonstrated skewed distributions and were therefore summarised using median [IQR].

Table II Baseline serum inflammatory biomarker levels.

Biomarker	Healthy Controls (HC) (n=25)	OSA Group (n=25)	ID Group (n=25)	p-value (ANOVA)	Post-hoc p-values
IL-6 (pg/mL) Mean ± SD	1.52±0.61	3.85±1.21*	2.42±0.84*†	<0.001	HC vs. OSA: <0.001
					HC vs. ID: 0.010
					OSA vs. ID: <0.001
TNF-α (pg/mL) Mean ± SD	1.82±0.52	2.91±0.94*	2.15±0.71	0.001	HC vs. OSA: 0.003
					HC vs. ID: 0.320
					OSA vs. ID: 0.011
IL-1β (pg/mL) Median [IQR]	0.52 [0.41–0.68]	0.71 [0.55–0.90]	0.85 [0.62–1.10]*†	0.015	HC vs. OSA: 0.082
					HC vs. ID: 0.018
					OSA vs. ID: 0.045
IL-10 (pg/mL) Median [IQR]	0.95 [0.72–1.20]	1.10 [0.80–1.38]	1.05 [0.81–1.25]	0.450	NS
hs-CRP (mg/L) Mean ± SD	1.21±0.70	4.12±2.01*	1.85±0.92†	<0.001	HC vs. OSA: <0.001
					HC vs. ID: 0.105
					OSA vs. ID: <0.001

Abbreviations: IQR, interquartile range; NS, not significant.
*Post-hoc analysis: * p<0.05 vs. HC; † p<0.05 vs. OSA group*

Table III Longitudinal changes in the OSA group after 3 months of CPAP therapy.

Parameter	CPAP-Adherent (n=20)			CPAP non-adherent (n=5)		
	Baseline	3-Month	Within-group p-value	Baseline	3-Month	Within-group p-value
AHI (events/hr)	33.8±11.5	4.2±3.5	**<0.001**	27.2±15.1	25.8±14.3	0.750
ESS Score	15.1±4.2	7.3±3.1	**<0.001**	13.4±5.1	12.8±4.9	0.812
IL-6 (pg/mL)	3.95±1.18	2.42±0.95	**0.004**	3.25±1.30	3.40±1.25	0.465
hs-CRP (mg/L)	4.25±2.10	2.30±1.25	**0.008**	3.52±1.45	3.65±1.50	0.688
TNF-α (pg/mL)	2.98±0.99	2.45±0.85	0.062	2.55±0.71	2.60±0.68	0.891

Table IV Longitudinal changes in the ID group after 3 months of CBT-I.

Parameter	Completers (n=22)		
	Baseline	3-Month	p-value
ISI Score	21.6±4.0	9.1±4.5	<0.001
PSQI Global Score	14.9±2.6	7.2±3.8	<0.001
Sleep Efficiency (%)	74.5±9.3	84.2±7.1	0.001
IL-1β (pg/mL)	0.86 [0.64–1.12]	0.61 [0.48–0.80]	0.030
IL-6 (pg/mL)	2.40±0.82	2.15±0.75	0.210
hs-CRP (mg/L)	1.82±0.90	1.78±0.85	0.850

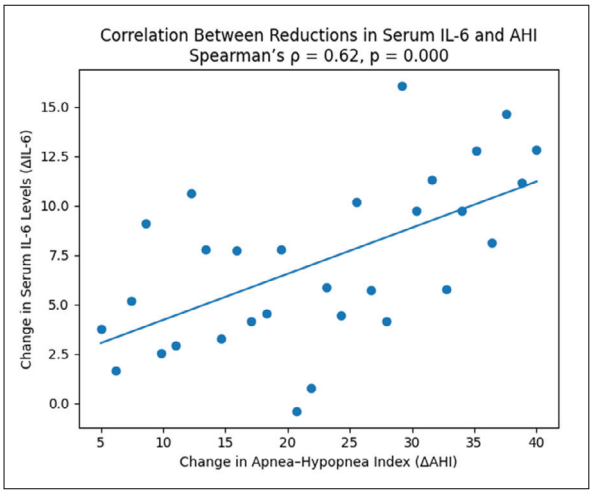

Figure 1 Scatterplot illustrating the association between the magnitude of reduction in serum interleukin-6 (ΔIL-6) and the reduction in apnea-hypopnea index (ΔAHI) among CPAP-adherent patients.

A logistic regression model incorporating IL-6, TNF-α, and IL-1β was constructed to differentiate OSA from ID. The receiver operating characteristic (ROC) curve for the combined inflammatory biomarker panel demonstrated excellent discriminative ability, with an area under the curve (AUC) of 0.87 (95% CI: 0.78–0.96). The optimal cut-point, identified using the Youden index, corresponded to a composite panel score of 0.56, yielding a sensitivity of 84% and a specificity of 80%. At this threshold, the positive predictive value (PPV) was 81%, and the negative predictive value (NPV) was 83%.

Longitudinal changes in biomarkers and clinical parameters post-treatment

Of the 25 OSA patients, 20 (80%) were adherent to CPAP therapy. In these adherent patients, significant improvements in AHI, ESS, and inflammatory markers were observed after 3 months. Non-adherent patients (n=5) showed no significant change in clinical or biomarker measures (*Table III*).

In adherent patients, the magnitude of reduction in serum IL-6 correlated strongly with the reduction in AHI (Spearman's rho=0.65, p=0.002) (*Figure 1*).

ID cohort

Twenty-two (88%) ID patients completed CBT-I. Post-treatment, significant improvements in insomnia severity and sleep continuity were observed, accompanied by a specific reduction in IL-1β (*Table IV*).

The reduction in serum IL-1β levels correlated inversely with the improvement in subjective sleep efficiency (Pearson's r =-0.52, p=0.02) (*Figure 2*).

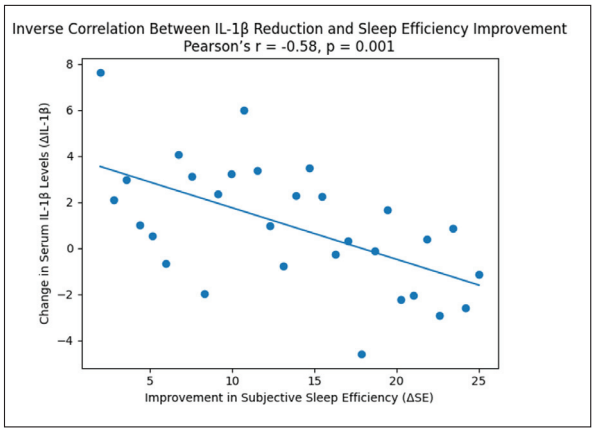

Figure 2 Scatterplot illustrating the inverse association between the magnitude of reduction in serum interleukin-1β (ΔIL-1β) and improvement in subjective sleep efficiency (ΔSE).

Discussion

This pilot study provides novel evidence for disorder-specific inflammatory cytokine profiles in OSA and ID and for their dynamic responses to targeted therapy, building on the existing literature (5, 19, 20).

Our cross-sectional findings confirm a pronounced inflammatory state in OSA, characterised by elevated levels of IL-6, TNF-α, and CRP. This aligns with the well-established pathophysiological model, in which intermittent hypoxia activates NF-κB and inflammasome pathways (5, 21). Notably, ID presented a more selective inflammatory signature (elevated IL-6 and IL-1β), supporting the hypothesis that cognitive-emotional hyperarousal and hypothalamic-pituitary-adrenal (HPA) axis dysregulation in insomnia engage specific pro-inflammatory pathways, potentially via NLRP3 inflammasome activation, distinct from the hypoxia-driven inflammation of OSA (20). The differential elevation of CRP, a downstream marker of IL-6 signalling, in OSA but not ID suggests a more robust and sustained hepatic acute-phase response in OSA, possibly due to greater IL-6 amplitude or additional metabolic triggers such as visceral adiposity (22, 23).

The longitudinal data offer crucial insights into the potential of cytokines as »theranostic« biomarkers. The reduction of IL-6 and CRP with effective CPAP therapy aligns with the reversibility of OSA-related inflammation and correlates with clinical improvement, as suggested in prior studies (9, 24). More originally, our finding that successful CBT-I reduces IL-1β levels provides a novel biological correlate of treatment efficacy in insomnia. This suggests that non-pharmacological amelioration of sleep continuity and hyperarousal can modulate specific central and peripheral inflammatory pathways, potentially mitigating the long-term cardiovascular risk associated with ID (25, 26). The lack of a significant change in IL-6 in the ID group post-CBT-I suggests that different inflammatory mediators may be more or less sensitive to behavioural interventions than to mechanical treatments like CPAP.

From a theranostic perspective, these findings suggest that inflammatory biomarkers could inform individualised treatment strategies. For example, elevated IL-6 levels may help identify OSA patients at higher inflammatory risk who could benefit from targeted interventions to enhance CPAP adherence, while baseline or early changes in IL-1β may indicate responsiveness to CBT-I in patients with insomnia disorder. Although exploratory, such biomarker-guided approaches could support more personalised and proactive management of sleep disorders in future clinical settings.

Although body mass index is a well-established determinant of circulating CRP levels, the observed differences between OSA and insomnia disorder were not fully attenuated after adjustment for BMI, suggesting that disorder-specific pathophysiological mechanisms, beyond adiposity alone, may contribute to CRP elevation in OSA, consistent with the results of BMI-adjusted (ANCOVA) analyses.

Sleep continuity disruption may promote systemic inflammation by coordinating the activation of stress-immune pathways. Repeated arousals and fragmented sleep can activate the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis, increasing cortisol secretion and altering circadian immune regulation. In parallel, disrupted sleep has been mechanistically linked to inflammasome biology, particularly the NLRP3 pathway that governs maturation and release of IL-1β. Preclinical work indicates that activation of the NLRP3 inflammasome can modulate sleep homeostasis and the sleep response to prolonged wakefulness, supporting a bidirectional relationship between sleep loss and inflammasome signalling (27).

Experimental sleep disruption studies provide convergent evidence that IL-1β is sensitive to sleep loss in humans. For example, 40 hours of total sleep deprivation has been shown to increase circulating IL-1β (alongside other inflammatory markers) under controlled circadian conditions, suggesting that acute sleep loss can upregulate IL-1β pathways independent of habitual sleep patterns (28). Furthermore, sleep fragmentation paradigms in animal models have demonstrated increased NLRP3 inflammasome expression and activation/activation with downstream IL-1β signalling in brain tissue, providing a plausible mechanistic link between disrupted sleep continuity and inflammatory activation (29).

HPA-axis signalling may further amplify these effects by »priming« innate immune responses. Chronic stress and glucocorticoid signalling have been implicated in regulating inflammasome-related pathways (including GR–NF-κB–NLRP3 signalling in microglia in preclinical models), providing a biologically coherent route by which sustained stress physiology associated with poor sleep could potentiate IL-1β production and downstream inflammatory cascades (30).

Limitations

Several limitations of this study should be acknowledged. In addition to the relatively modest sample size and the limited 3-month follow-up period, the potential influence of unmeasured confounding factors cannot be excluded. Lifestyle-related variables such as dietary habits, physical activity levels, and sleep-related behaviours were not systematically assessed and may independently affect systemic inflammatory markers. Furthermore, subclinical metabolic differences, including early insulin resistance or low-grade metabolic dysfunction not captured by routine clinical measures, could have contributed to interindividual variability in cytokine levels. Although we adjusted for key covariates such as age, sex, and BMI, residual confounding may persist. Future studies with larger cohorts, longer follow-up, and more comprehensive assessment of lifestyle and metabolic factors are warranted to clarify these relationships further.

Conclusion

This study identifies serum IL-6 and CRP as strong candidate biomarkers for OSA severity and treatment response, while IL-1β may be a specific biomarker reflecting insomnia-related hyperarousal and responsive to behavioural therapy. These findings pave the way for larger, longitudinal studies to validate the diagnostic and prognostic utility of multiplex cytokine panels in personalised sleep medicine.

Acknowledgements. The authors thank the research nurses of the Sleep Disorders Centre and the technical staff of the Immunology Laboratory. This work was supported by the University of MetroHealth Sciences Pilot Grant Program (UMHS-2022-SLP-05).

Data availability statement

The de-identified datasets generated during this study are available from the corresponding author upon reasonable request.

Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

References

1. Léger D, Bayon V, Ohayon MM, Philip P, Ement P, Metlaine A, et al. Insomnia and accidents: cross-sectional study on sleep-related home, work and car accidents in 5293 subjects with insomnia from 10 countries. Journal of Sleep Research 2013; 23(2): 143–52.
2. Kapur VK, Auckley DH, Chowdhuri S, Kuhlmann DC, Mehra R, Ramar K, et al. Clinical Practice Guideline for Diagnostic Testing for Adult Obstructive Sleep Apnea: An American Academy of Sleep Medicine Clinical Practice Guideline. Journal of Clinical Sleep Medicine 2017; 13(03): 479–504.
3. Irwin MR. Sleep and inflammation: partners in sickness and in health. Nature Reviews Immunology 2019; 19(11): 702–15.
4. Mullington JM, Simpson NS, Meier-Ewert HK, Haack M. Sleep loss and inflammation. Best Practice & Research Clinical Endocrinology & Metabolism 2010; 24(5): 775–84.
5. Ryan S, Taylor CT, McNicholas WT. Selective Activation of Inflammatory Pathways by Intermittent Hypoxia in Obstructive Sleep Apnea Syndrome. Circulation 2005; 112(17): 2660–7.
6. Irwin MR, Olmstead R, Carroll JE. Sleep Disturbance, Sleep Duration, and Inflammation: A Systematic Review and Meta-Analysis of Cohort Studies and Experimental Sleep Deprivation. Biological Psychiatry 2016; 80(1): 40–52.
7. Liukkonen T, Räsänen P, Ruokonen A, Laitinen J, Jokelainen J, Leinonen M, et al. C-reactive protein Levels and Sleep Disturbances: Observations Based on The Northern Finland 1966 Birth Cohort Study. Psychosomatic Medicine 2007; 69(8): 756–61.
8. Vgontzas AN, Zoumakis E, Lin HM, Bixler EO, Trakada G, Chrousos GP. Marked Decrease in Sleepiness in Patients with Sleep Apnea by Etanercept, a Tumor Necrosis Factor-α Antagonist. The Journal of Clinical Endocrinology & Metabolism 2004; 89(9): 4409–13.
9. Hoyos CM, Drager LF, Patel SR. OSA and cardiometabolic risk: What's the bottom line? Respirology 2017; 22(3): 420–9.

10. Sateia MJ. International classification of sleep disorders. Chest 2014; 146(5): 1387–94.

11. Edinger JD, Arnedt JT, Bertisch SM, Carney CE, Harrington JJ, Lichstein KL, et al. Behavioral and psychological treatments for chronic insomnia disorder in adults: an American Academy of Sleep Medicine systematic review, meta-analysis, and GRADE assessment. Journal of Clinical Sleep Medicine 2021; 17(2): 263–98.

12. Buysse DJ, Ancoli-Israel S, Edinger JD, Lichstein KL, Morin CM. Recommendations for a Standard Research Assessment of Insomnia. Sleep 2006; 29(9): 1155–73.

13. Iber C. The AASM manual for the scoring of sleep and associated events: rules, terminology, and technical specification. (No Title) 2007.

14. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research. Psychiatry Research. 1989; 28(2): 193–213.

15. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. sleep 1991; 14(6): 540–5.

16. Bastien C. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Medicine 2001; 2(4): 297–307.

17. Elshal M, McCoy J. Multiplex bead array assays: Performance evaluation and comparison of sensitivity to ELISA. Methods 2006; 38(4): 317–23.

18. Rifai N, Tracy RP, Ridker PM. Clinical Efficacy of an Automated High-Sensitivity C-Reactive Protein Assay. Clinical Chemistry 1999; 45(12): 2136–41.

19. Arnardottir ES, Mackiewicz M, Gislason T, Teff KL, Pack AI. Molecular Signatures of Obstructive Sleep Apnea in Adults: A Review and Perspective. Sleep 2009; 32(4): 447–70.

20. Irwin MR, Opp MR. Sleep Health: Reciprocal Regulation of Sleep and Innate Immunity. Neuropsychopharmacology 2016; 42(1): 129–55.

21. Lavie L. Oxidative stress in obstructive sleep apnea and intermittent hypoxia – Revisited – The bad ugly and good: Implications to the heart and brain. Sleep Medicine Reviews 2015; 20: 27–45.

22. Festa A, D'Agostino Jr R, Williams K, Karter AJ, Mayer-Davis EJ, Tracy RP, et al. The relation of body fat mass and distribution to markers of chronic inflammation. International Journal of Obesity 2001; 25(10): 1407–15.

23. Vgontzas AN. Sleep Apnea and Daytime Sleepiness and Fatigue: Relation to Visceral Obesity, Insulin Resistance, and Hypercytokinemia. Journal of Clinical Endocrinology & Metabolism 2000; 85(3): 1151–8.

24. Nadeem R, Molnar J, Madbouly EM, Nida M, Aggarwal S, Sajid H, et al. Serum Inflammatory Markers in Obstructive Sleep Apnea: A Meta-Analysis. Journal of Clinical Sleep Medicine 2013; 09(10): 1003–12.

25. Fernandez-Mendoza J, Shea S, Vgontzas AN, Calhoun SL, Liao D, Bixler EO. Insomnia and incident depression: role of objective sleep duration and natural history. Journal of Sleep Research 2015; 24(4): 390–8.

26. Prather AA, Vogelzangs N, Penninx BWJH. Sleep duration, insomnia, and markers of systemic inflammation: Results from the Netherlands Study of Depression and Anxiety (NESDA). Journal of Psychiatric Research 2015; 60: 95–102.

27. Zielinski MR, Gerashchenko D, Karpova SA, Konanki V, McCarley RW, Sutterwala FS, et al. The NLRP3 inflammasome modulates sleep and NREM sleep delta power induced by spontaneous wakefulness, sleep deprivation and lipopolysaccharide. Brain Behav Immun 2017; 62: 137–50.

28. Frey DJ, Fleshner M, Wright KP. The effects of 40 hours of total sleep deprivation on inflammatory markers in healthy young adults. Brain, Behavior, and Immunity 2007; 21(8): 1050–7.

29. Yoon DW, Shin S, Choi J, Shin C, Lee C, Lee J, et al. Sleep Fragmentation Induces Activation of NOD-Like Receptor Protein-3 Inflammasome in Rat Hippocampus. Sleep Med Res 2017; 8(1): 26–32.

30. Feng X, Zhao Y, Yang T, Song M, Wang C, Yao Y, et al. Glucocorticoid-driven NLRP3 inflammasome activation in hippocampal microglia mediates chronic stress-induced depressive-like behaviors. Frontiers in molecular neuroscience 2019; 12: 210.

Recieved: December 14, 2025
Accepted: January 16, 2026