Nature and Science of Sleep

ORIGINAL RESEARCH

Association of Complete Blood Count-Derived Inflammatory Markers with Trouble Sleeping: Evidence from Population Data and Experimental Sleep Deprivation

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Purpose: Trouble sleeping is a common pathophysiological feature underlying sleep disorders and affects both the number and function of immune cells. This study investigated the associations between complete blood count (CBC)-derived inflammatory markers and trouble sleeping, aiming to provide a simple and rapid reference for evaluating sleep-related conditions.

Patients and methods: A total of 39,156 participants from the 2011–2018 NHANES cycles were included. Survey-weighted multivariable logistic regression was performed to examine the associations between CBC-derived inflammatory markers and trouble sleeping. Restricted cubic spline models were applied to assess potential nonlinear relationships, and stratified analyses were conducted for robustness. Additionally, a human study in healthy volunteers evaluated the effects of short-term sleep deprivation (36 h) and subsequent recovery on CBC-derived inflammatory markers and circulating pro-inflammatory cytokines.

Results: Participants with trouble sleeping had shorter sleep duration and elevated levels of several CBC-derived inflammatory markers compared with those without trouble sleeping. Sleep insufficiency was particularly associated with increased monocyte-to-lymphocyte ratio (MLR, $p < 0.001$). Besides, systemic inflammation response index (SIRI) emerged as an independent predictor of trouble sleeping [OR = 1.07 (95% CI: 1.02–1.12), $p = 0.008$], particularly in adults aged 30–60, males, non-Hispanic Whites, individuals with obesity, and those with higher education; this association persisted in never smokers and participants without major comorbidities. In the human experimental study, acute sleep deprivation markedly increased CBC-derived markers, which largely returned to baseline following recovery sleep. Regarding circulating cytokines, only IL-6 remained elevated despite recovery, highlighting its key role in the inflammatory response to sleep loss.

Conclusion: The findings highlight the link between trouble sleeping and CBC-derived inflammatory markers, with SIRI emerging as a potential predictor of trouble sleeping and IL-6 as a key cytokine involved in the inflammatory response to sleep deprivation.

Keywords: blood cell count, inflammation, cytokines, NHANES

Introduction

Trouble sleeping represents a major global public health concern and, when persistent, may progress to clinically significant sleep disorders. In the United States, approximately 37% of adults report an average sleep duration of less than seven hours.[1] Globally, insomnia affects nearly 30% of the population, with about 10% experiencing chronic insomnia.[2] Despite the high prevalence, many sleep disorders remain undiagnosed and untreated, leading to serious and concerning health consequences.[3] Sleep disorders encompass a heterogeneous group of conditions that disrupt normal sleep patterns.[4] According to the International Classification of Sleep Disorders (ICSD-3), they are categorized into six major groups: 1) insomnia disorders; 2) sleep-related breathing disorders (eg, obstructive sleep apnea and central sleep apnea); 3) central disorders of hypersomnolence (eg, narcolepsy and idiopathic hypersomnia); 4) circadian rhythm sleep–wake disorders (eg, shift work disorder and jet lag disorder); 5) parasomnias

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(eg, sleepwalking and REM sleep behavior disorder); and 6) sleep-related movement disorders.[3] Meanwhile, prolonged trouble sleeping is associated with numerous adverse health outcomes, including anxiety, hypertension, diabetes, and cardiovascular disease.[5–7] Their underlying pathophysiology involves complex mechanisms related to immune dysregulation, inflammatory activation, neuroendocrine disturbance, and metabolism.[2,8] These multifactorial mechanisms not only contribute to disease progression but also complicate the diagnosis and management of sleep disorders.

Sleep duration is a crucial indicator of sleep health and is closely associated with trouble sleeping.[9] Sleep deprivation or insufficient sleep represents a common pathophysiological process and major consequence shared across various sleep disorders, including insomnia,[2] circadian rhythm disturbances,[10] and sleep-related breathing disorders.[11] Short-term sleep deprivation (24 hours) markedly alters nearly half of the detectable molecules in human peripheral blood, with 46.4% of detected genes, 59.3% of plasma proteins, and 55.6% of metabolites showing differential expression. These changes particularly affect immune-related signaling pathways, such as neutrophil-mediated immunity.[8] Insufficient sleep has also been associated with elevated levels of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), as well as increased concentrations of C-reactive protein (CRP).[12] Nevertheless, results from a 19-day in-hospital sleep disruption experimental model indicate that sleep disturbance causally alters inflammatory pathways, exhibiting evident sex-specific differences, characterized by decreased monocyte IL-6 production in females and increased IL-6 production in males.[13] Experimental studies in mice have demonstrated that prolonged sleep deprivation induces severe systemic inflammation, resulting in approximately 80% mortality and a cytokine storm–like syndrome.[14] Moreover, many molecular and immune parameters fail to fully return to baseline even after a recovery period following sleep deprivation.[12,15]

The complete blood count (CBC) is a routine test evaluating blood cell composition. Several CBC-derived inflammatory markers integrating neutrophil, lymphocyte, monocyte, and platelet counts have been proposed to provide a more comprehensive assessment of the host's immune–inflammatory status than individual parameters.[16] These indices include monocyte-to-lymphocyte ratio (MLR), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), neutrophil-monocyte-to-lymphocyte ratio (NMLR), pan-immune-inflammation value (PIV), systemic immune-inflammation index (SII), and systemic inflammation response index (SIRI), and have been widely employed as prognostic biomarkers across a range of diseases. For instance, NLR has been identified as an effective marker for predicting the prevalence and burdens of intracranial atherosclerosis as well as carotid plaque burden of type 1 diabetes individuals.[17,18] In addition, MLR has been proposed as an additional cardiovascular risk factor in women with suspected acute coronary syndrome.[19] Studies using data from the National Health and Nutrition Examination Survey (NHANES) database have reported that SII is positively associated with sleep problems, symptoms of obstructive sleep apnea, and daytime sleepiness among U.S. adults.[20] The PIV reflects uncontrolled inflammation during heart failure progression and serves as a strong prognostic indicator in patients with acute heart failure.[21] Moreover, SIRI has also been extensively investigated in the context of chronic kidney diseases and cancers, demonstrating superior prognostic performance compared with other inflammatory biomarkers.[22–24] Importantly, CBC testing is inexpensive and easily accessible, suggesting that these derived inflammatory indices may have broader potential for clinical application and disease risk prediction. Although experimental evidence has demonstrated that sleep deprivation and sleep restriction induces significant alterations in immune cells and inflammatory pathways,[2,13] the association between CBC-derived inflammatory markers, sleep duration, and trouble sleeping remains unelucidated. Moreover, the reversibility of these inflammatory alterations following sleep recovery remains insufficiently characterized. Therefore, further investigation integrating epidemiological data with experimental validation is warranted.

Given this context, the present study aims to investigate the associations between CBC-derived inflammatory markers, sleep duration, and self-reported trouble sleeping using data from NHANES. In addition, a human experiment involving healthy volunteers was conducted to examine the effects of short-term sleep deprivation and subsequent recovery on CBC-derived inflammatory markers and pro-inflammatory cytokines. Hence, our study sought to characterize the inflammation-related alterations associated with sleep insufficiency from the perspective of the inflammatory markers derived from CBC, and to provide a simple and rapid reference for the detection and evaluation of trouble sleeping and their related comorbidities.

Methods

Study Population and Data Sources

The National Health and Nutrition Examination Survey (NHANES) is a U.S. program assessing population health through demographic, socioeconomic, dietary, clinical, and laboratory data (www.cdc.gov/nchs/nhanes/). All survey protocols and data releases were approved by the National Center for Health Statistics (NCHS) Ethics Review Board, and informed consent was obtained from all participants. Detailed information on the NHANES design and procedures is available on its official website. As illustrated in Figure 1, we analyzed publicly accessible NHANES data from 2011 to 2018, encompassing 39,156 participants. The study population was selected according to the following criteria: Inclusion criteria: availability of complete data on sleep duration and sleep data. Exclusion criteria: (1) pregnancy; (2) age <18 years; (3) missing sleep duration data or reported sleep >9 hours; (4) missing information on blood counts, education, marital status, or BMI. A total of 18,605 participants met these criteria and were included in the final analysis.

To complement the population-based associations observed in the NHANES data and to determine whether inflammatory alterations induced by sleep deprivation can be reversed by subsequent sleep recovery, we next conducted a study in healthy human volunteers. For the subsequent human validation experiment, 38 healthy volunteers (aged 21 ± 2 years) were recruited. Inclusion criteria were: (1) male, right-handedness, and age between 18 and 25 years; (2) body mass index (BMI) between 18.5–24.9; and (3) normal or corrected-to-normal vision, with myopia ≤ 400 diopters and astigmatism ≤ 200 diopters. The vision criteria were applied to ensure uniform visual functioning during sleep deprivation and to minimize potential confounding effects related to visual strain, autonomic nervous activation, or circadian light sensitivity. Exclusion criteria included: (1) a history of sleep disorders prior to study enrollment; (2) cardiovascular disease or dependence on beverages such as coffee or strong tea; (3) the presence of metallic or electronic implants or prostheses; and (4) a history of claustrophobia, traumatic brain injury, or psychiatric disorders. Participants maintained regular sleep (7–9 hours per night) for one week before the experiment. Sleep duration was objectively monitored using a wrist-worn sleep monitoring device to ensure compliance with the predefined requirement of maintaining regular sleep. They then underwent 36 hours of total sleep deprivation (SD group, from 8:00 a.m. to 8:00 p.m. the following day), followed by 12 hours of recovery sleep. During the sleep deprivation period, participants remained in the laboratory under standardized indoor lighting conditions. Blood samples were collected at three time points: before sleep deprivation, after sleep deprivation, and after recovery sleep, for following experiments. This study was conducted in full accordance with the ethical standards of the Helsinki Declaration and its subsequent revisions and was approved by the Medical Ethics Committee of the First Affiliated Hospital of the Fourth Military Medical University (No. KY20252035-F-1). Written informed consent was obtained from all enrolled participants, and all personal information collected was treated with strict confidentiality, used solely for research purposes, and anonymized in all presentations of the data.

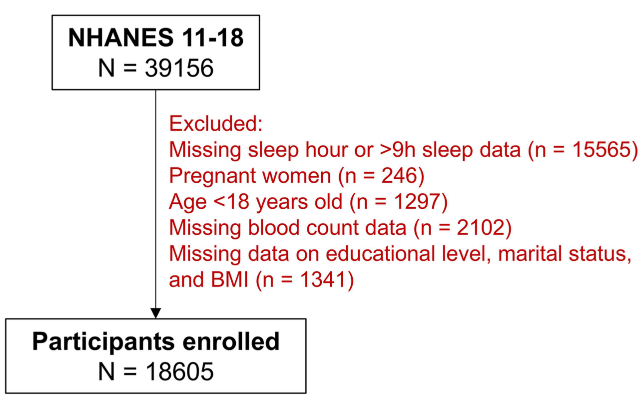

Figure 1 Flowchart of the study population selection from NHANES 2011–2018.

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Trouble Sleeping and Sleep Duration Grouping

Sleep-related variables were derived from standardized items administered during the NHANES household interview. The assessment of trouble sleeping is primarily based on participants' responses to questions regarding sleep habits and problems in the NHANES personal interview questionnaire. Participants were asked whether they had ever told doctor that they had trouble sleeping. Based on their responses, individuals were classified as having or not having trouble sleeping. Habitual sleep duration was assessed using the question, "How many hours of sleep do you usually get on weekdays or workdays?" and was categorized as sleep deprivation (SD, <5 hours), less sleep (LS, 5–7 hours), or recommended sleep (RS, 7–9 hours).

CBC Counts and CBC-Derived Inflammatory Index

We comprehensively evaluated complete blood count (CBC) parameters, including white blood cells (WBC), lymphocytes (Lym), monocytes (Mono), neutrophils (Neu), eosinophils (Eosi), basophils (Baso), and platelets (PLT). Given that platelet counts are reported in absolute values, all CBC-derived inflammatory indices were computed from absolute cell counts (10^3 cells/μL). Seven inflammation-related indicators were derived as follows:[16]

MLR: Mono/Lym;
NLR: Neu/Lym;
PLR: PLT/Lym;
NMLR: (Neu + Mono)/Lym;
PIV: (Neu × Mono × PLT)/Lym;
SII: (PLT × Neu)/Lym;
SIRI: (Neu × Mono)/Lym.

Covariates of NHANES

To strengthen the robustness of the associations between CBC parameters, CBC-derived inflammatory indices, and trouble sleeping, analyses were adjusted for age, sex, race, BMI, marital status, education level, and smoking status. Age was categorized as <30 years, 30–60 years, and >60 years. Race was grouped into Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, and Other (including multiracial). BMI was calculated as weight (kg)/height (m^2) and classified as underweight (<18.5), normal (18.5–24.9), overweight (25.0–29.9), or obese (≥30.0). Education level was divided into <high school, high school diploma or GED, some college (no bachelor's degree), and college graduate or above. Marital status was categorized as married, divorced, living with partner, never married, or separated/widowed. Smoking status was determined based on two questionnaire items: "have you smoked at least 100 cigarettes in your entire life?" and "Do you now smoke cigarettes?" Participants who answered "No" to the first question were classified as never smokers; those who answered "Yes" to the first but "No" to the second one as former smokers; and those who answered "Yes" to both as current smokers. Major comorbidities, including diabetes, stroke, and coronary heart disease, were self-reported based on participants' responses to standardized NHANES interview questionnaires.

Human CBC and ELISA Assay

Human blood samples were sent to a certified laboratory for routine hematological analysis using the XN-9000 Haematology Systemisation series (Sysmex Corporation, Kobe, Japan). Serum samples were collected and stored at −80 °C. Serum levels of human interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and interleukin-1β (IL-1β) were determined using corresponding uncoated enzyme-linked immunosorbent assay (ELISA) kits, following the manufacturer's instructions (IL-6, #88-7066-88; TNF-α, #88-7346-88; IL-1β, # 88–7261-88; Invitrogen, Waltham, MA, USA).

Statistical Analysis

To address the complex, multistage probability sampling design of NHANES, all analyses incorporated appropriate survey weights, strata, and primary sampling units, as recommended by the NHANES analytic guidelines.[25,26] We summarized categorical variables as numbers and weighted proportions and continuous variables as mean with standard error. Group comparisons were performed using the chi-squared test with Rao and Scott's second-order correction for categorical variables and the Wilcoxon rank-sum test for continuous variables. To explore the associations between CBC-derived inflammatory indices and trouble sleeping, survey-weighted multivariable logistic regression models were constructed. Model 1 adjusted for demographic and behavioral factors (age, sex, BMI, marital status, educational level, smoking, diabetes, stroke, and coronary heart disease), whereas Model 2 further adjusted for additional hematological parameters. For instance, SIRI was additionally adjusted for WBC, eosinophils, basophils, and platelets. Results were reported as odds ratios (ORs) with 95% confidence intervals (CIs). Multivariable logistic regression and stratified analyses were performed to examine the associations between CBC-derived inflammatory indices and sleep duration. Restricted cubic spline (RCS) regression with four knots was further applied to explore potential nonlinear relationships. In addition, subgroup analyses stratified by sleep duration were conducted, and stratified analyses by SIRI levels were used to evaluate differences in trouble sleeping risk across subpopulations. SIRI was selected for stratified analysis because it demonstrated the most robust association with trouble sleeping, whereas other CBC-derived inflammatory markers showed minimal or non-significant effects. Normality was assessed using the Shapiro–Wilk test. The Friedman test with Dunn's post hoc comparisons was applied to CBC-derived inflammatory indices, and paired repeated-measures one-way ANOVA with Tukey's multiple comparisons test was used for serum pro-inflammatory cytokines across various SD groups. All analyses were performed using Graphpad Prism 8 and R Statistical Software (Version 4.2.2) with Free Statistics analysis platform (Version 2.2, Beijing, China). The statistical data were reported to three decimal places. Statistical significance was ascertained by a two-sided P value <0.05.

Results

Population Characteristics

According to the inclusion and exclusion criteria, a total of 18,605 participants from NHANES 2011–2018 were included in the present analysis. After sampling weights, these individuals represented approximately 816 million U.S. adults, among whom nearly 30% (equivalent to 236.98 million individuals) reported trouble sleeping (Table 1). Compared with those without trouble sleeping, participants with trouble sleeping exhibited a significantly shorter average sleep duration of

Table 1 Weighted Descriptive Characteristics Across Trouble Sleeping in NHANES 2011–2018

Variable	Total (N=816,177,843)*	Non-Trouble Sleeping (N=579,202,645)*	Trouble Sleeping (N=236,975,198)*	*P*
Sleep duration (h)	7.08 (0.02)	7.16 (0.02)	6.86 (0.03)	**<0.001**
Age	47.81 (0.31)	46.36 (0.36)	51.32 (0.35)	**<0.001**
<30	2956 (17.52%)	2513 (20.47%)	443 (10.34%)	**<0.001**
30≤X<60	9565 (55.79%)	6970 (54.81%)	2595 (58.18%)	
≥60	6084 (26.69%)	4192 (24.72%)	1892 (31.48%)	
Gender				**<0.001**
Male	9151 (48.80%)	7087 (51.46%)	2064 (42.33%)	
Female	9454 (51.20%)	6588 (48.54%)	2866 (57.67%)	
Race				**<0.001**
Mexican American	2522 (8.54%)	2027 (9.91%)	495 (5.21%)	
Other Hispanic	1951 (6.29%)	1483 (7.02%)	468 (4.51%)	
Non-Hispanic white	6941 (65.63%)	4649 (62.48%)	2292 (73.30%)	
Non-Hispanic black	4101 (10.76%)	3018 (11.20%)	1083 (9.68%)	
Other race (including multi-racial)	3090 (8.78%)	2498 (9.38%)	592 (7.30%)	
BMI	29.29 (0.12)	28.80 (0.11)	30.50 (0.18)	**<0.001**
Underweight	280 (1.40%)	220 (1.42%)	60 (1.35%)	**<0.001**
Normal	5062 (27.15%)	3987 (28.92%)	1075 (22.84%)	
Overweight	6011 (32.60%)	4579 (33.68%)	1432 (29.95%)	
Obese	7252 (38.85%)	4889 (35.99%)	2363 (45.86%)	

(*Continued*)

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Table 1 (Continued).

Variable	Total (N=816,177,843)*	Non-Trouble Sleeping (N=579,202,645)*	Trouble Sleeping (N=236,975,198)*	*P*
Marital status				**<0.001**
Married	9622 (55.81%)	7263 (56.73%)	2359 (53.57%)	
Divorced	2032 (10.25%)	1293 (8.84%)	739 (13.68%)	
Living with partner	1515 (8.18%)	1148 (8.40%)	367 (7.64%)	
Never married	3478 (18.12%)	2683 (19.41%)	795 (14.97%)	
Separated/windowed	1958 (7.64%)	1288 (6.62%)	670 (10.14%)	
Educational level				**<0.001**
<High school	3925 (13.37%)	2985 (14.19%)	940 (11.37%)	
High school/GED	4098 (22.03%)	2968 (21.59%)	1130 (23.11%)	
Some college	5787 (32.37%)	4079 (31.41%)	1708 (34.72%)	
>College	4795 (32.23%)	3643 (32.81%)	1152 (30.80%)	
Smoke				**<0.001**
Never	10,693 (56.85%)	8318 (60.77%)	2375 (47.32%)	
Former	4348 (24.69%)	2945 (22.35%)	1403 (30.41%)	
Now	3553 (18.45%)	2404 (16.89%)	1149 (22.26%)	
Diabetes				**<0.001**
No	16,082 (89.86%)	12,128 (91.76%)	3954 (85.25%)	
Yes	2513 (10.14%)	1540 (8.24%)	973 (14.75%)	
Stroke				**<0.001**
No	17,932 (97.37%)	13,280 (97.97%)	4652 (95.90%)	
Yes	657 (2.57%)	387 (2.00%)	270 (3.94%)	
Coronary heart disease				**<0.001**
No	17,834 (96.63%)	13,229 (97.34%)	4605 (94.91%)	
Yes	714 (3.37%)	408 (2.66%)	306 (5.09%)	
CBC count (10^3/μL)				
WBC	7.26 (0.04)	7.19 (0.04)	7.45 (0.06)	**<0.001**
Lym	2.15 (0.02)	2.15 (0.02)	2.15 (0.02)	0.75
Mono	0.57 (0.00)	0.56 (0.00)	0.58 (0.00)	**<0.001**
Neu	4.30 (0.03)	4.23 (0.03)	4.46 (0.04)	**<0.001**
Eosi	0.20 (0.00)	0.20 (0.00)	0.21 (0.00)	**<0.001**
Baso	0.05 (0.00)	0.05 (0.00)	0.05 (0.00)	**<0.001**
PLT	238.26 (1.00)	236.96 (0.92)	241.43 (1.70)	**0.005**
CBC inflammatory index				
MLR	0.29 (0.00)	0.28 (0.00)	0.30 (0.00)	**<0.001**
NLR	2.19 (0.02)	2.15 (0.02)	2.28 (0.03)	**<0.001**
PLR	121.67 (0.72)	120.87 (0.72)	123.62 (1.15)	0.11
NMLR	2.48 (0.02)	2.44 (0.02)	2.58 (0.03)	**<0.001**
SIRI	1.27 (0.01)	1.24 (0.01)	1.36 (0.02)	**<0.001**
SII	522.30 (4.74)	511.01 (4.70)	549.88 (8.08)	**<0.001**
PIV	308.27 (3.53)	298.26 (3.72)	332.75 (5.61)	**<0.001**

Notes: *The data are presented as numbers that have been weighted for a national estimate. Values with $p < 0.05$ are shown in bold.
Abbreviations: BMI, body mass index; Lym, Lymphocytes; Mono, Monocytes; Neu, Neutrophils; Eosi, Eosinophils; Baso, Basophils; PLT, Platelets; MLR, Monocyte-to-lymphocyte ratio; NLR, Neutrophil-to-lymphocyte ratio; PLR, Platelet-to-lymphocyte ratio; NMLR, Neutrophil-tomonocyte-plus-lymphocyte ratio; PIV, Pan-immune-inflammation value; SII, Systemic immune inflammatory index; SIRI, Systemic inflammation response index.

approximately 6.86 hours, which was below the 7.16 hours in the non-trouble sleeping group. Consistent with this finding, the unweighted distribution of sleep duration also demonstrated significantly shorter sleep duration in the trouble sleeping group (6.71 vs. 7.09 hours, $p < 0.001$) despite slight numerical differences attributable to weighting procedures (Figure 2). Baseline characteristics further indicated that individuals with trouble sleeping were generally older, had higher BMI, and

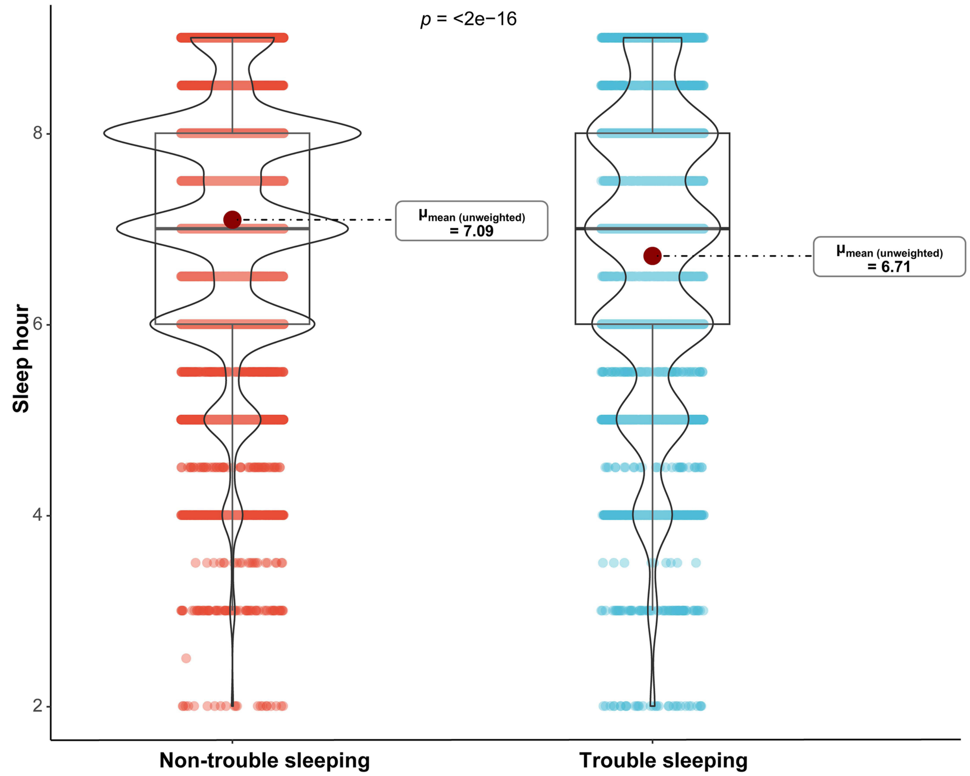

Figure 2 Violin and box plot illustrating the unweighted distribution of sleep hours between participants with and without trouble sleeping. Statistical analysis was performed using Wilcoxon test.

were more likely to be non-Hispanic White, divorced or separated/widowed, lack college-level education, and be current smokers. Importantly, the trouble sleeping group also exhibited a higher prevalence of major comorbidities, including diabetes, stroke, and coronary heart disease ($p < 0.001$). Regarding CBC parameters, trouble sleeping were associated with significantly elevated levels of WBC, Mono, Neu, and PLT counts ($p < 0.01$). In contrast, lymphocyte counts showed no substantial changes. Moreover, several CBC-derived inflammatory indices, including the MLR, NLR, NMLR, SIRI, SII, and PIV values, were also markedly increased in participants with trouble sleeping ($p < 0.001$).

Sleep Duration is Correlated with MLR

Table 2 demonstrated a consistent negative association between sleep duration and the presence of trouble sleeping across all models [unadjusted model: OR = 0.83 (95% CI: 0.80–0.86); minimally adjusted model 1 and fully adjusted model 2: OR = 0.82 (95% CI: 0.79–0.85); all $p < 0.001$], suggesting a close relationship between trouble sleeping and insufficient sleep duration. To further explore the effects of shorter sleep duration on CBC parameters and CBC-derived inflammatory indices, participants were categorized into three groups based on sleep duration: sleep deprivation (SD), less sleep (LS), and recommended sleep (RS) (Table S1). Baseline characteristics indicated that age, sex, race, BMI, marital status, educational attainment, and smoking status were all associated with sleep duration. Besides, shorter sleep duration was associated with

Table 2 Multivariable Logistic Regression of the Association of Sleep Duration and Trouble Sleeping

	Unadjusted		Model 1		Model 2	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Sleep duration	0.83 (0.80, 0.86)	**<0.001**	0.82 (0.79, 0.85)	**<0.001**	0.82 (0.79, 0.85)	**<0.001**

Notes: Values with $p < 0.05$ are shown in bold. Model 1: Adjusted for Age, gender, BMI, marital status, educational level, smoke, diabetes, stroke, and coronary heart disease. Model 2: Adjusted for Age, gender, BMI, marital status, educational level, smoke, diabetes, stroke, coronary heart disease, and all CBC counts.

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a higher prevalence of diabetes ($p = 0.014$) and stroke ($p < 0.001$), whereas no significant association was observed between sleep duration and coronary heart disease. Regarding CBC parameters, participants with shorter sleep duration were more likely to have higher counts of WBC, Lym, and Neu. Among the CBC-derived inflammatory indices, only the MLR and PLR showed associations with sleep duration ($p < 0.01$). The associations between the sleep duration and CBC counts and CBC-derived inflammatory markers were modeled and visualized using restricted cubic splines (Figures 3 and S1). After adjusting for all variables, only MLR displayed a significant association with sleep duration (p for overall < 0.001, p for non-linearity = 0.049, Figure 3). Sleep insufficiency is linked to a general increase in MLR. However, Sleep duration did not show any significant correlations with other CBC parameters (Figure S1).

SIRI is Positively Associated with the Risk of Trouble Sleeping

We further examined the associations between CBC counts, CBC-derived inflammatory markers, and trouble sleeping. Restricted cubic spline modeling revealed both SIRI and PIV had a significant overall correlation with trouble sleeping, with patterns that were largely linear (both p for overall < 0.05, Figure 4). Subsequent multivariable regression analyses confirmed the relevance of these two indices to the risk of trouble sleeping (Tables 3 and S2); however, the effect size of PIV was minimal, as reflected by an OR approaching 1 despite a statistically significant p value. In contrast, after adjustment for all potential confounders, SIRI demonstrated a robust positive association with the risk of trouble sleeping. Specifically, each one-unit increase in SIRI was associated with an approximately 7% higher risk of trouble sleeping [OR = 1.07 (95% CI: 1.02–1.12), $p = 0.008$; Table 3]. These findings suggest that SIRI may serve as an independent risk factor for trouble sleeping.

Subgroup Analysis by SIRI

We further evaluated the role of CBC-derived inflammatory markers in the occurrence of trouble sleeping across different sleep duration categories. Stratified analyses were performed to assess the effects of each inflammatory index within the three sleep duration groups (Figure 5A). The results showed that within the less sleep and recommended sleep duration groups, SIRI remained significantly and positively associated with trouble sleeping ($p = 0.04$). To further minimize residual confounding, additional stratified analyses were conducted according to age, gender, race, BMI, marital status, educational level, smoking status, diabetes, stroke, and coronary heart disease (Figure 5B). After adjustment for all other covariates, SIRI demonstrated a significantly positive association with trouble sleeping among individuals aged 30–60 years, males, non-Hispanic Whites, those with obesity, and with education beyond the college level. Notably, this positive association persisted among never smokers and individuals without major comorbidities, including diabetes, stroke, and coronary heart disease (all ORs > 1 and $p < 0.05$), suggesting that the relationship was not solely attributable to smoking status or underlying chronic disease burden.

Alterations of CBC-Derived Inflammatory Markers and Serum Proinflammatory Cytokines After Sleep Deprivation and Recovery

To investigate whether sleep deprivation–induced inflammatory alterations could be restored by subsequent sleep recovery, we conducted a human study involving healthy volunteers. The results showed that all CBC-derived inflammatory markers including NLR, MLR, NMLR, PIV, SII, and SIRI increased significantly after 36 hours of sleep deprivation, but returned to nearly baseline levels following 12 hours of recovery sleep (Figure 6A). Serum cytokine measurements revealed that only IL-6 levels were markedly elevated after 36 hours of sleep deprivation, and its level continued to rise even after 12 hours of recovery (Figure 6B). In contrast, the levels of pro-inflammatory cytokines TNF-α and IL-1β showed no significant changes under either condition.

Discussion

The present study integrates population-based epidemiological evidence with controlled experimental data. In the NHANES cohort, trouble sleeping was consistently associated with elevated CBC-derived inflammatory markers. Given the significant inverse association between sleep duration and trouble sleeping, our results further demonstrate

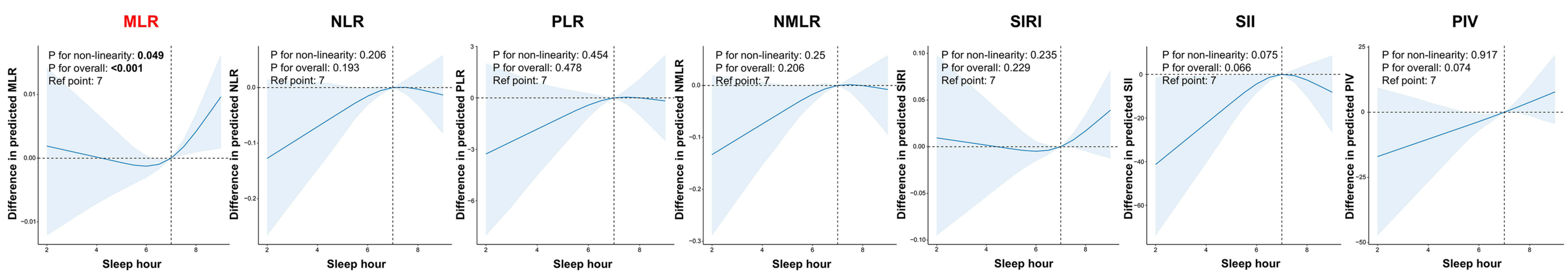

Figure 3 Restricted cubic spline curves showing the relationships between sleep duration and CBC-derived inflammatory markers. OR (solid blue lines) and 95% confidence levels (shaded blue areas) were adjusted for Age, gender, BMI, marital status, educational level, smoke, diabetes, stroke, coronary heart disease, and other CBC counts.

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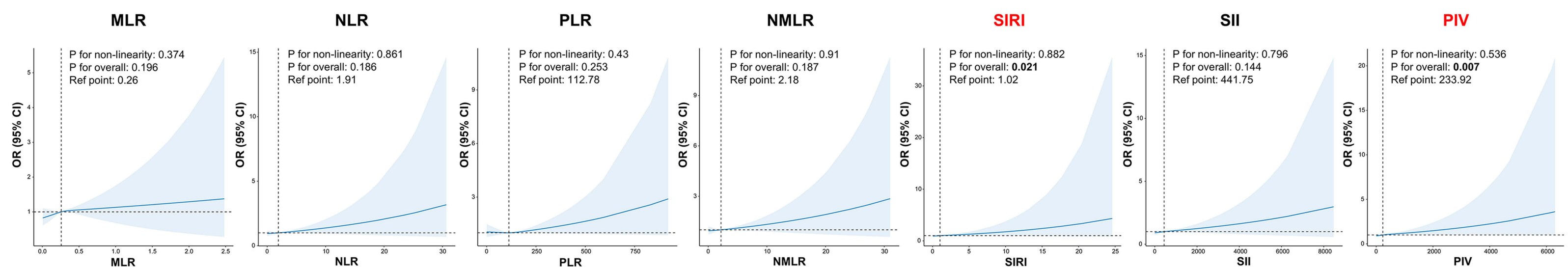

Figure 4 Restricted cubic spline curves showing the relationships between CBC-derived inflammatory markers and the risk of trouble sleeping. OR (solid blue lines) and 95% confidence levels (shaded blue areas) were adjusted for Age, gender, BMI, marital status, educational level, smoke, diabetes, stroke, coronary heart disease, and other CBC counts.

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Table 3 The Association Between CBC-Derived Inflammatory Markers and Trouble Sleeping

CBC Inflammatory Index	Unadjusted		Model 1		Model 2	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
MLR	2.09 (1.46, 2.97)	**<0.001**	1.47 (1.02, 2.13)	**0.041**	1.36 (0.93, 1.99)	0.113
NLR	1.10 (1.06, 1.14)	**<0.001**	1.03 (0.99, 1.08)	0.102	1.04 (1.00, 1.08)	0.077
PLR	1.00 (1.00, 1.00)	**0.01**	1.00 (1.00, 1.00)	0.124	1.00 (1.00, 1.00)	0.166
NMLR	1.09 (1.05, 1.13)	**<0.001**	1.03 (1.00, 1.07)	0.082	1.04 (1.00, 1.08)	0.076
SIRI	1.16 (1.10, 1.21)	**<0.001**	1.07 (1.02, 1.12)	**0.009**	1.07 (1.02, 1.12)	**0.008**
SII	1.00 (1.00, 1.00)	**<0.001**	1.00 (1.00, 1.00)	**0.043**	1.00 (1.00, 1.00)	0.055
PIV	1.00 (1.00, 1.00)	**<0.001**	1.00 (1.00, 1.00)	**0.004**	1.00 (1.00, 1.00)	**0.004**

Notes: Values with $p < 0.05$ are shown in bold. Model 1: Adjusted for Age, gender, BMI, marital status, educational level, smoke, diabetes, stroke, and coronary heart disease. Model 2: Adjusted for Age, gender, BMI, marital status, educational level, smoke, diabetes, stroke, coronary heart disease, and other CBC counts (eg, SIRI was adjusted for Age, gender, BMI, marital status, educational level, smoke, WBC, Eosi, Baso, and PLT).

a close link between trouble sleeping and systemic inflammation. These findings support previous studies indicating immune activation following sleep restriction.[2,8,14] Moreover, our controlled sleep deprivation study in healthy volunteers further supports this association by showing acute CBC-derived inflammatory alterations under standardized conditions. Although the experimental cohort consisted of healthy young adults and may not fully reflect the broader population in NHANES, the convergence of findings across these distinct study designs strengthens the biological plausibility of the observed associations. Insufficient sleep, whether voluntary or involuntary, plays a central role in driving sleep disorders.[3] Its effects accumulate over time, leading to progressively worsening and sometimes irreversible physiological consequences.[2,14] The cumulative effects of sleep insufficiency are primarily driven by sustained activation and amplification of inflammatory pathways. Evidence suggests that sleep deprivation enhances the efflux of prostaglandin D_2 from the brain across the blood–brain barrier, thereby promoting the accumulation of circulating pro-inflammatory cytokines, such as IL-6 and IL-17, and neutrophils, leading to a cytokine-storm-like syndrome.[14] Insufficient sleep also impairs the function of multiple immune cells, including T cells, B cells, NK cells, neutrophils, and monocytes, ultimately disrupting immune homeostasis and provokes a pronounced systemic inflammatory response.[2,8,14,27] This inflammatory response not only represents an immediate consequence of sleep loss but also serves as a crucial biological link between trouble sleeping and multiple chronic physical conditions.

Using a cross-sectional design, we found that among several CBC-derived inflammatory markers, sleep duration showed a significant non-linear association with the MLR, displaying a U-shaped pattern. Since the RCS model included sleep durations up to 9 hours only; the apparent increase in MLR at longer sleep durations reflects extrapolation beyond the observed data. Hence, the statistically significant association ($p < 0.05$) mainly reflects the close relationship between shorter sleep duration and higher MLR levels. As a noninvasive inflammatory biomarker, MLR has been reported to outperform other markers such as NLR, SIRI, PLR, and SII in predicting prostate cancer,[28] and it has also demonstrated prognostic value in bladder and breast cancers.[29,30] Moreover, MLR appears to be a superior inflammatory indicator for predicting cardiovascular diseases, including congestive heart failure, coronary heart disease, angina, and stroke, and serves as a strong independent predictor of cardiovascular mortality.[31–33] Given epidemiological evidence linking short sleep duration to increased cardiovascular risk,[34–36] MLR may reflect an inflammatory profile that accompanies insufficient sleep. However, the cross-sectional design of the present study does not allow determination of whether MLR mediates the relationship between sleep duration and cardiovascular outcomes. In our cohort, shorter sleep duration was associated with a higher prevalence of diabetes and stroke, although no significant association was observed with coronary heart disease. These findings further support the link between insufficient sleep and adverse cardiometabolic profiles, but causal inference remains limited.

Furthermore, MLR did not emerge as an independent risk factor for trouble sleeping. In contrast, our findings indicate that SIRI serves as a more robust predictor, showing a significant positive association with the occurrence of trouble sleeping. This may be partly explained by its calculation formula: unlike MLR, SIRI incorporates neutrophils in addition

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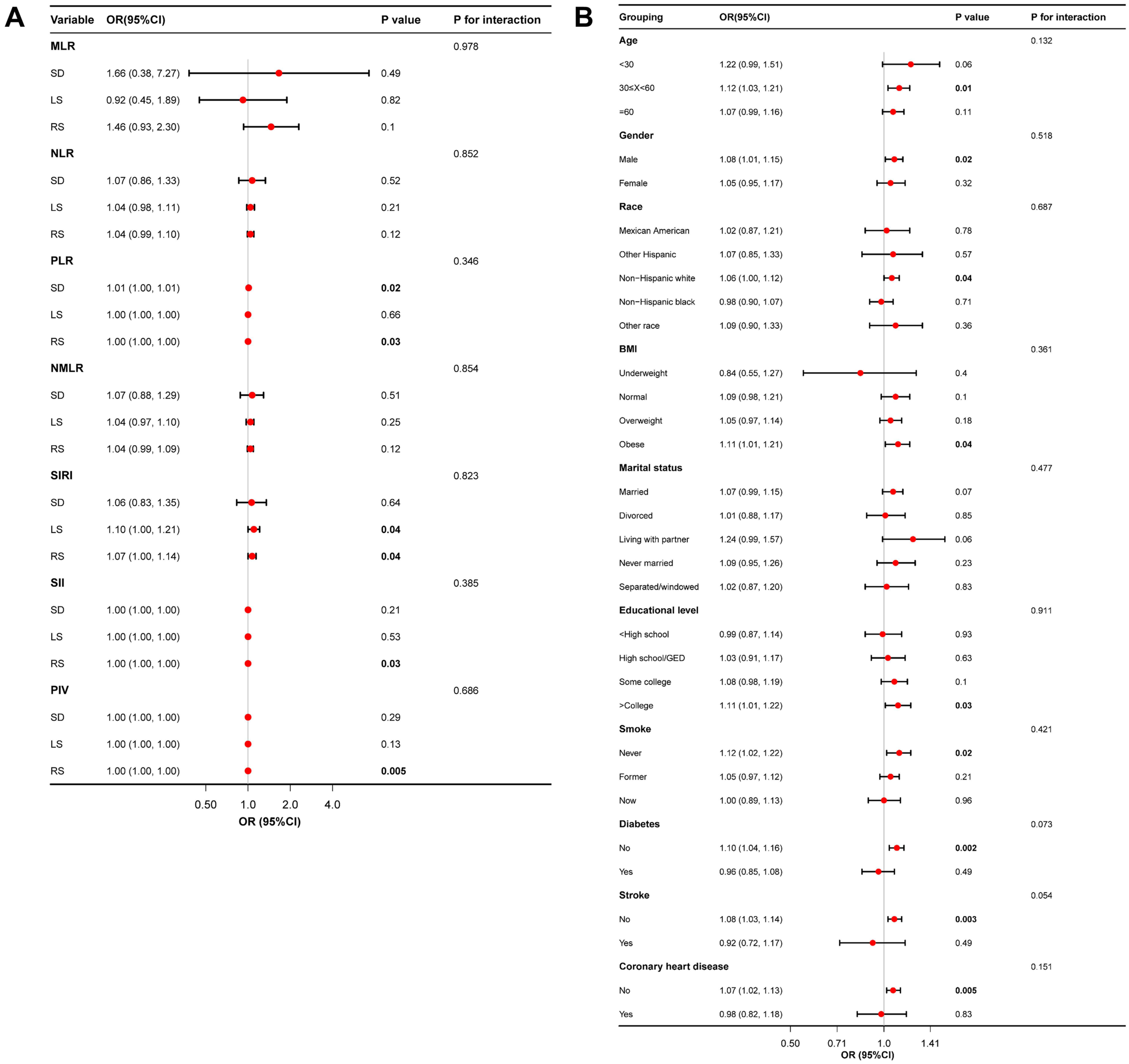

Figure 5 Subgroup analysis between SIRI and trouble sleeping. (**A**) Stratified analysis of the effects of each CBC-derived inflammatory markers on trouble sleeping within the three sleep duration groups. (**B**) Subgroup analysis of the association between SIRI and trouble sleeping by stratifying participants according to age, gender, race, BMI, marital status, educational level, smoking status, diabetes, stroke, and coronary heart disease. Analyses were adjusted for Age, gender, BMI, marital status, educational level, smoke, diabetes, stroke, coronary heart disease, and other CBC counts.

to the monocyte-to-lymphocyte ratio. Evidence suggests that both neutrophils and monocytes increase following insomnia, amplifying pro-inflammatory activity.[2] This highlights the coordinated involvement of multiple immune cell types in trouble sleeping, rather than the effect of a single cell population. SIRI was initially introduced as a prognostic indicator in patients with malignant tumors, but its utility has also been extended to some inflammation-driven diseases.[37] Studies have shown that SIRI serves as an independent predictor of ischemic stroke and cardiovascular mortality,[38,39] and exhibits notable diagnostic and prognostic value in conditions such as pancreatitis and renal injury.[40] These findings emphasize the important predictive and decision-support role of SIRI in diseases characterized by inflammation-associated pathological processes. Our results demonstrate that elevated SIRI levels are significantly associated with the occurrence of trouble sleeping, suggesting a substantial inflammatory response triggered by sleep disruption. Meanwhile, this inflammatory burden appears to be more pronounced in specific subpopulations. SIRI was significantly

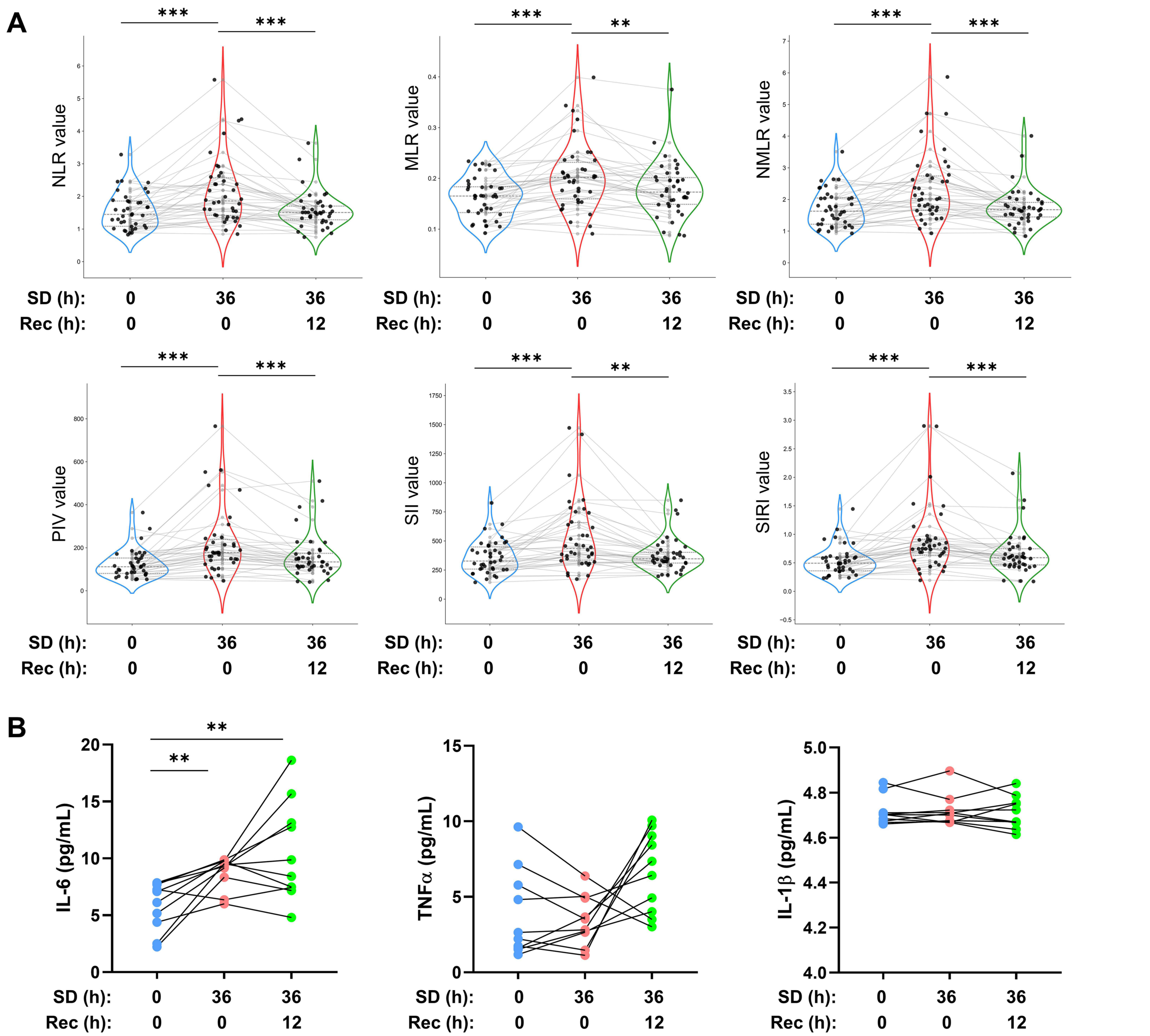

Figure 6 CBC-derived inflammatory markers and serum proinflammatory cytokines in healthy volunteers after sleep deprivation and recovery. (**A**) CBC-derived inflammatory markers in the three groups: before 36 hours of sleep deprivation, after 36 hours of sleep deprivation, and 36 hours of sleep deprivation following 12 hours of recovery sleep. (**B**) Serum levels of proinflammatory cytokines of IL-6, TNF-α and IL-1β. Each dot represents one subject, and lines connecting the dots indicate repeated measurements from the same individual. $^{**}p < 0.01$, $^{***}p < 0.001$.

positively associated with trouble sleeping in individuals aged 30–60 years, males, non-Hispanic Whites, individuals with obesity, and those with higher education. Given that obesity is strongly associated with both trouble sleeping and shorter sleep duration, it may act as an important modifier of the relationship between sleep disturbance and SIRI. In obesity, adipocytes and infiltrating leukocytes produce adipokines and pro-inflammatory cytokines. Notably, IL-6 is not only generated as a pro-inflammatory cytokine but is also secreted by adipose tissue,[41] which may partially explain the persistently elevated IL-6 levels observed after sleep deprivation and recovery in our subsequent experimental cohort. In addition, this association remained significant among never smokers and individuals without major comorbidities, including diabetes, stroke, and coronary heart disease. These findings have two key implications. First, they highlight the clinical need for targeted screening and early intervention in high-risk groups; for instance, individuals with obesity

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or younger adults exhibiting trouble sleeping may benefit from closer monitoring of SIRI. Second, although trouble sleeping often co-occurs with chronic diseases, the association between elevated SIRI and sleep disturbances persists even in healthy individuals without a history of smoking or major chronic conditions, suggesting that systemic inflammation itself may contribute directly to sleep disturbances, independent of common comorbidities.

Several studies have suggested that sleep deprivation induces irreversible inflammatory memory. Sleep deprivation (24 hours) can alter nearly half of blood molecules, including transcripts, proteins, and metabolites, and 1–2 days of recovery are insufficient to fully reverse these changes,[8] resulting in prolonged dysregulation of inflammation-related pathways, such as neutrophil extracellular trap formation and complement activation.[8,27] In contrast, our findings in young adult males (<30 years) indicated that CBC-derived inflammatory markers increased markedly following sleep deprivation and basically returned toward to baseline after sleep recovery, including SIRI. This pattern may partly reflect the nature of these markers, which are calculated from relative immune cell counts rather than cellular function. Quantitative normalization of immune cells may occur relatively rapidly following acute sleep deprivation, whereas functional or molecular alterations could persist after the recovery of cell counts. Besides, because our participants were healthy young men with robust immune and stress-recovery capacity, their immune cell numbers may recover more quickly in response to acute, short-term sleep deprivation. Interestingly, analysis of serum pro-inflammatory cytokines revealed that only IL-6 levels were significantly elevated following sleep deprivation, and remained persistently high even after recovery sleep. Sang et al (2023) reported that IL-6 are the most prominently altered cytokines after sleep loss, acting as an "initial driver" of a cytokine storm.[14] In a 19-day in-hospital sleep disruption model, prolonged sleep disturbance causally altered inflammatory pathways in a sex-specific manner, with decreased monocyte IL-6 production and plasma IL-6 levels in females, but increased production and levels in males.[13] These findings align with our observation of significantly elevated serum IL-6 in male volunteers following sleep deprivation. IL-6 secretion can activate the NF-κB signaling pathway, which promotes further transcription and release of IL-6 and other pro-inflammatory cytokines, forming a vicious cycle.[2] This inflammatory cycle may sustain elevated IL-6 levels for a period even after sleep recovery. Another contributing factor may be the sleep-dependent circadian secretion pattern of IL-6, which resembles that of growth hormone.[42] Sleep deprivation disrupts this rhythm, and a brief 12-hour recovery period may be insufficient to restore normal IL-6 oscillations. Accordingly, in our study, although CBC-derived inflammatory markers largely returned to baseline after 12 hours of recovery sleep, serum IL-6 remained significantly elevated. This apparent discrepancy underscores the hierarchical and complex nature of immune responses to sleep deprivation, highlighting that quantitative immune cell recovery may occur faster than the resolution of cytokine dysregulation.

Our study has several limitations. First, sleep duration and trouble sleeping in NHANES were assessed using self-reported questionnaire items rather than objective measurements such as actigraphy or polysomnography, and no validated sleep instruments were applied. This may introduce recall and misclassification bias. Second, although we adjusted for multiple demographic and clinical covariates, such as age, sex, race, BMI, marital status, educational levels, smoking status, and major comorbidities, residual or unmeasured confounding factors such as dietary patterns and psychological stress, may still influence the results. Third, the sample size for the sleep-deprivation experiment was relatively small, and participants were limited to healthy Chinese young adults. In contrast, the NHANES dataset represents a multi-ethnic U.S. population. Differences in ethnicity, genetic background, and environmental exposures may therefore limit direct comparability of the findings. Larger experimental studies involving more diverse populations are warranted to validate and extend these findings and to enhance their generalizability.

Conclusion

In conclusion, our findings indicate that trouble sleeping is closely associated with reduced sleep duration and heightened systemic inflammation. Sleep insufficiency is linked to a general increase in MLR, and SIRI emerges as an independent predictor of trouble sleeping. In a human experimental study, acute sleep deprivation triggered marked elevations in CBC-derived inflammatory markers, most of which largely normalized after recovery sleep, whereas IL-6 remained persistently elevated. Overall, these results identify SIRI as a potential biomarker for trouble sleeping and highlight IL-6 as a key cytokine mediating the inflammatory response to sleep deprivation.

Data Sharing Statement

The data that support the findings of this study are available from the NHANES website (https://www.cdc.gov/nchs/nhanes/). Other raw data supporting the validation study are available from the corresponding author upon reasonable request.

Ethical Statement

All survey protocols and data releases were approved by the National Center for Health Statistics (NCHS) Ethics Review Board. The human experiment was conducted in full accordance with the ethical standards of the Helsinki Declaration and its subsequent revisions and was approved by the Medical Ethics Committee of the First Affiliated Hospital of the Fourth Military Medical University (No. KY20252035-F-1). All study participants signed an informed consent form.

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Author Contributions

Chujun Duan; Methodology, Visualization, Investigation, Writing – original draft, Formal analysis, Funding acquisition. Yuan Zhang; Methodology, Visualization, Writing - Review & Editing. Peng Fang; Writing – original draft, Formal analysis, Resources, Funding acquisition. Ranran Wang, Yilin Wu, Yuling Wang, and Hanyin Fan; Formal Analysis, Writing – original draft. Yangmengjie Jing; Writing – original draft, Investigation. Linqi Feng and Jinyue Yang; Formal analysis. Ran Zhuang; Conceptualization, Supervision, Project administration, Funding acquisition, Writing - Review & Editing. All authors took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing financial interest in the work described. The authors report no other conflicts of interest.

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