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ORIGINAL RESEARCH

The Relationship Between Global Sleep Score And Inflammatory Markers In Obese Adults From The United States

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Ying Huang[1,*]
Ying Jiang[2,*]
Meilan Zhu[2]

[1]Department of Cardiovascular Medicine, The Second Affiliated Hospital of Nanchang University, Nanchang, Jiangxi 330006, People's Republic of China; [2]Department of Rehabilitation, The Second Affiliated Hospital of Nanchang University, Nanchang, Jiangxi 330006, People's Republic of China

*These authors contributed equally to this work

Background: Poor sleep is a risk factor for cardiovascular diseases (CVDs). The underlying pathogenesis is not clear. Levels of inflammatory markers, such as C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), have been found to be elevated in patients with CVDs.

Aim: The study aimed to investigate the associations between sleep quality and serum inflammatory markers in a cohort of obese adults.

Methods: This was a second analysis of the data from the Midlife in the United States (MIDUS) study, a longitudinal study of a national (US) sample of adults. A total of 1255 participants completed comprehensive biological assessments. The associations between global sleep score and serum levels of inflammatory markers were analyzed.

Results: Univariate analysis showed that a higher global sleep score was correlated with lower age ($r = -0.079$, P= 0.009), higher BMI ($r = 0.100$, P= 0.001) and heavier perceived stress ($r = 0.335$, P<0.001). Multivariate linear regression analysis showed that the global sleep score was positively related to levels of IL-6 (Sβ=0.074, P=0.009), IL-8 (Sβ=0.089, P=0.002), TNF-α (Sβ=0.0.082, P=0.005), E-selectin (Sβ=0.071, P=0.016) and intercellular adhesion molecule-1 (ICAM-1, Sβ=0.117, P<0.001) after adjustments were made for age, gender, race, marital status, education, current smoking status, physician-diagnosed CVDs and respiratory diseases, BMI and perceived stress. However, the global sleep score was not associated with serum IL-10 (Sβ=−0.021, P=0.463) and CRP (Sβ=0.035, P=0.059) levels after adjustments were made for these confounding factors.

Conclusion: Poor sleep is positively associated with serum inflammatory marker levels among obese adults. Sufficient sleep may be particularly important for obese adults to prevent CVDs.

Keywords: global sleep score, inflammation, body mass index, perceived stress, obese adults

Introduction

Concern for sleep problems as risk factors for adverse health has grown since an association between poor sleep and mortality was first described over four decades ago.[1] Studies have generally shown a significantly positive relationship between poor sleep and mortality. In other words, people with poor sleep have a greater mortality risk than those with higher sleep quality. Many publications have begun reporting that poor sleep can predict a growing number of diseases.[2,3] In recent years, however, due to increasingly social and economic factors, shorter sleep time, poor sleep quality and other sleep problems have become increasingly serious.[4–6]

Correspondence: Meilan Zhu
Department of Rehabilitation, The Second Affiliated Hospital of Nanchang University, No. 1 Minde Road, Donghu District, Nanchang, Jiangxi 330006, People's Republic of China
Email 15070896289@139.com

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Poor sleep is related to poor decision making, risk taking and mood disruptions.[7–10] The direct effect of poor sleep is tiredness during low-stimulation activities, including attentiveness while studying, driving, performing repetitive activities and engaging in other activities.[7] Many investigations have shown that sleep in the classroom has become a very common phenomenon in many high schools.[7] A previous study showed that poor-quality sleep and insufficient sleep are pervasive in the general population and are linked with impairments in cognitive control and greater risk taking.[8] Moreover, some other studies suggested that another important effect of sleep deprivation is related to mood. Relationships have been found between poor sleep and depression or mood lability.[9,10]

Although the negative effects of sleep problems on psychosocial and behavioral problems are well understood, less is known about the relationship between sleep and biomarkers of physical health in the general population. It is well known that inflammation has attracted increasing attention and is considered a biomarker of risk for several chronic adult health conditions, such as cardiovascular diseases (CVDs), that may be associated with sleep problems.[11–15] Research has suggested that chronic sleep problems lead to increased inflammation levels, such as C-reactive protein (CRP), among adults.[16–18] Some studies have also shown that disrupted sleep has negative effects on the production and activation of cells involved in immune regulation, causing an alteration of inflammatory factors.[19,20] Therefore, the aim of this study was to assess the relationships between global sleep score and systemic inflammatory factors in a comprehensive and multi-level manner.

Materials And Methods

Study Population

This was a reanalysis of the data from the Midlife in the United States (MIDUS) study, a longitudinal study of a national (US) sample of adults aged 34–84 years at baseline. The MIDUS study investigates the association between psychological, behavioral, and social factors and age-related physical and mental health problems. As a sub-component of the MIDUS study, 1255 participants completed the Biomarkers Project, in which participants provided comprehensive biological assessments as a way to integrate behavioral and psychosocial factors with biology.[21] The measures described below were included to best capture our contents of interest.

Full details of the MIDUS study biomarker protocol are available elsewhere.[21,22] Complete data and specific codebooks are also available at http://www.midus.wisc.edu/. In summary, participants in the MIDUS study were originally recruited in 1995–1996 by means of a national sample collected by random-digit dialing procedures. To be as inclusive as possible, all living participants in the first MIDUS survey who could safely go to the clinic were considered eligible for participation in the Biomarkers Project. They were recruited to participate using e-mail and follow-up phone calls. Data were collected between 2004 and 2009 at one of three affiliated General Clinical Research Centers of the MIDUS study (University of Wisconsin-Madison; Georgetown University; University of California-Los Angeles). By using a standardized protocol that was consistent across the three sites, participants completed detailed self-administered questionnaires, medical history interviews, and the collection of blood specimens during a 2-day visit. Each participant was remunerated $200 for participating, and traveling expenses were covered. The Biomarkers Project protocol was approved by the institutional review boards of each General Clinical Research Center, and all participants gave written informed consent.

Serum samples from all participants were collected and tested during a 2-day visit between 2004 and 2009. The following serum inflammatory markers were measured: CRP, interleukin-6 (IL-6), IL-8, IL-10, E-selectin, intracellular adhesion molecule-1 (ICAM-1), and tumor necrosis factor-α (TNF-α). These serum biomarkers were collected during a medical exam at one of three General Clinical Research Centers. Biomarkers were obtained from a fasting blood draw. Full measurement methods have been described in detail elsewhere.[21,22] In this study, body mass index (BMI) $\geq$ 25 was defined as overweight or obesity. For our purposes, all included participants were overweight or obese adults.

Global Sleep Score

The global sleep score was measured with the Pittsburgh Sleep Quality Index (PSQI).[23] The PSQI is widely used and a reliable measure of global sleep quality and sleep disturbances over the past month. The 19 items are divided into seven component scores that reflect the frequency of sleep problems in the following areas: subjective sleep quality, sleep latency, sleep duration,

habitual sleep efficiency, sleep disturbance, use of sleep medication, and daytime dysfunction. A global sleep score ranging from 0 to 21 can be obtained by summing the seven components after weighting them on a scale ranging from 0 to 3 [α=0.74]. For each component as well as the global score, higher scores show worse sleep quality.[23]

Perceived Psychological Stress

The Perceived Stress Scale (PSS) is a 10-item measure that can assess the degree of pressure on participants in their lives.[24] Each item (e.g., "In the past month, how often have you been upset because of something that happened unexpectedly?") used a 5-point scale ranging from 1 (never) to 5 (very often), and items were reverse-coded as needed so that higher scores show greater perceived stress [α=0.84].

Statistical Analysis

The normality of the data was analyzed by the Kolmogorov–Smirnov test combined with Q-Q plots. The data that were not normally distributed were expressed as the median (interquartile range [IQR]), and data with normal distributions were expressed as the mean ± standard deviation (M±SD). First, the correlations between global sleep score and age, BMI and perceived stress were computed with Spearman correlation analysis in this study. Then, all variables with non-normal distributions were standardized with z-scores and analyzed with Pearson's correlation coefficient. The associations between global sleep score and serum inflammatory markers were further assessed by multivariate linear regression analysis. All of the analyses were performed using R3.4.4 and SPSS. $P \leq 0.05$ was considered to be statistically significant.

Results

The Characteristics Of The Study Subjects

Due to the lack of complete serum test data for 148 participants during the follow-up period, data for the remaining 1107 participants were included in the study and further analyzed.

Table 1 presents the N (%), M±SD and median (IQR) for the variables. The sociodemographic characteristics were as follows: 474 participants (42.8%) were males, 1018 participants (92.0%) were white, 702 participants (63.4%) were married, 443 participants (40.0%) had bachelor's degrees or higher, and 163 participants (14.6%) were current smokers. The median age of the entire population in this study was 54 years. A higher global sleep score was correlated with younger age (r = −0.079, P= 0.009, Figure 1), higher BMI (r = 0.100, P= 0.001, Figure 2) and heavier perceived stress (r = 0.335, P<0.001, Figure 3).

Table 1 Participant Characteristics

Variables	N (%) or M(IQR) or M ±SD
Sociodemographic characteristics	
Age (years)	54 (45–63)
Gender (% male)	474 (42.8%)
Race (% white)	1018 (92.0%)
Marital status (married), n (%)	702 (63.4%)
Education (with bachelor's degree or higher), n (%)	443 (40.0%)
Current smoker, n (%)	163(14.6%)
BMI	28.59 (26.13–33.05)
Perceived stress scale	22 (18–26)
Global Sleep Score	6.21±3.67
Subjective Sleep Quality	1.00±0.69
Sleep Latency	0.95±0.94
Sleep Duration	0.84±0.80
Habitual Sleep Efficiency	0.69±1.06
Sleep Disturbances Range	1.32±0.58
Sleeping Medication	0.58±1.08
Daytime Dysfunction	0.83±0.67
Physician diagnosed cardiovascular diseases	
Heart diseasen, (%)	`126 (11.4%)
TIA or stroke, (%)	43 (3.9%)
Diabetes, (%)	132 (11.9%)
High blood pressure, (%)	402 (36.3%)
Physician diagnosed respiratory diseases	
Asthma, n (%)	127 (11.7%)
Emphysema/COPD, n (%)	29 (2.6%)
Serum inflammatory biomarkers	
IL-6 (pg/mL)	0.80 (0.56–1.22)
IL-8 (pg/mL)	12.40 (9.13–15.79)
IL-10 (pg/mL)	0.22 (0.17–0.32)
CRP (ug/mL)	1.43 (0.69–3.66)
TNF-α (pg/mL)	2.05 (1.69–2.51)
E-Selectin (ng/mL)	39.11 (28.09–51.85)
ICAM-1 (ng/mL)	273.92 (221.03–336.05)

Notes: M (IQR) for nonnormally distributed data, M ±SD for normally distributed data and n (%) for categoric variables.

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; IL, Interleukin; CRP, C-reactive protein, TNF-α, tumor necrosis factor-α; ICAM-1, intercellular adhesion molecule-1; M (IQR), median interquartile range; M ±SD, mean±standard deviation.

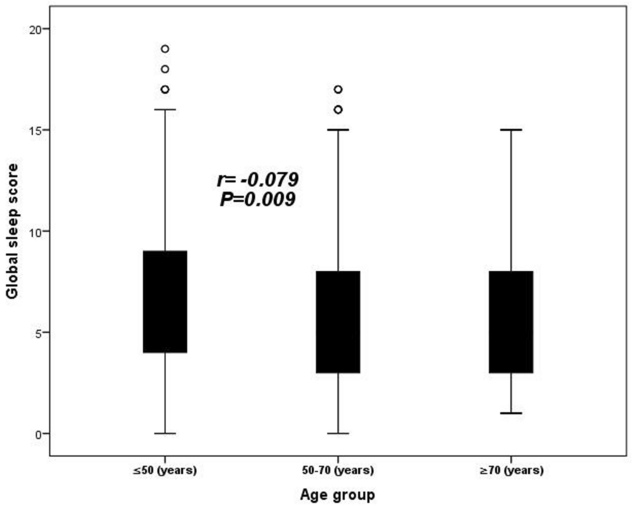

Figure 1 The relationship between global sleep score and age in all subjects.

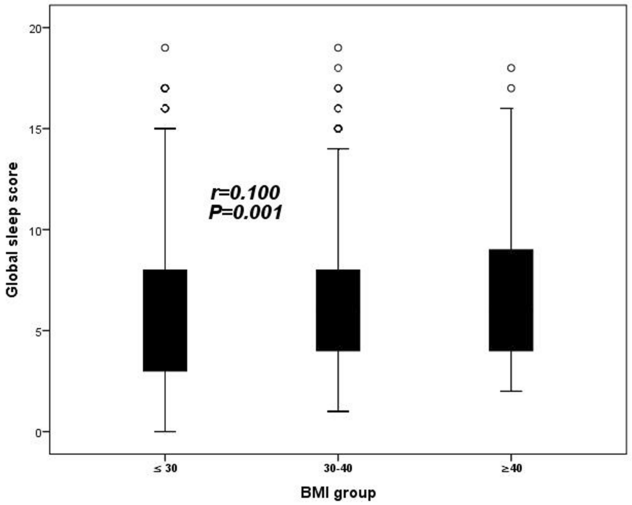

Figure 2 The relationship between global sleep score and BMI in all subjects.

Relationships Between Sleep And Inflammation Markers By Univariate Analysis

As shown in Table 2, higher global sleep scores were associated with higher serum levels of all inflammation markers in this study except IL-10 (all P<0.05). Worse subjective sleep quality was related to higher levels of TNF-α, E-selectin and ICAM-1 (all P<0.05). Longer sleep latency showed a positive association with IL-6, CRP and ICAM-1 levels (all P<0.05), and shorter sleep duration was associated with higher levels of CRP, E-selectin and ICAM-1 (all P<0.05). Worse habitual sleep efficiency was positively related to levels of IL-6, IL-8, CRP, E-selectin and ICAM-1 (all P<0.05). Those with a greater range of sleep disturbances had higher IL-8, TNF-α, CRP and ICAM-1 levels (all P<0.05). The frequency of sleeping medication use was positively associated with IL-6, IL8 and ICAM-1 (all P<0.05), and the frequency of daytime dysfunction did not show a positive relationship with inflammation markers (all P>0.05). These results showed that worse sleep quality was associated with higher serum inflammation levels by Pearson correlation analysis. However, the 7 factors were not associated with serum IL-10 levels.

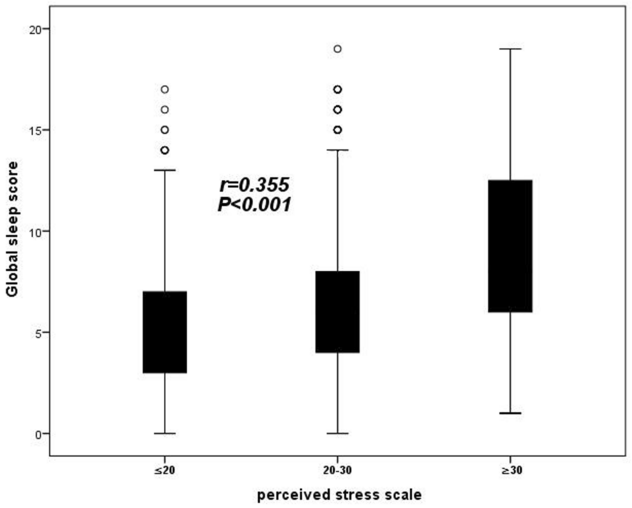

Figure 3 The relationship between global sleep score and perceived stress in all subjects.

Associations Between Global Sleep Score and Inflammatory Markers After Adjusting For Confounding Factors

To further prove the correlation between sleep quality and serum inflammatory biomarkers, multiple linear regression analysis was performed. As shown in Table 3, the global sleep score was positively related to IL-6 (Sβ=0.095, P=0.001), IL-8 (Sβ=0.097, P=0.001), CRP (Sβ=0.106, P<0.001), TNF-α (Sβ=0.102, P=0.001), E-selectin (Sβ=0.114, P<0.001) and ICAM-1 (Sβ=0.140, P<0.001) after adjusting for age, gender, race, marital status, education, current smoking status and physician-diagnosed CVDs and respiratory diseases (Model 1). After other confounding factors were added, including BMI and perceived stress in addition to CRP, the global sleep score still had a strong relationship with these inflammatory biomarkers (all P<0.05, Model 3). However, consistent with univariate analysis, the global sleep score was not associated with serum levels of IL-10 after adjustments were made

Table 2 Bivariate Correlations Using Standardized Variables

Variables	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. Global Sleep Score														
2. Subjective Sleep Quality	0.70 #													
3. Sleep Latency	0.70 #	0.42#												
4. Sleep Duration	0.64 #	0.42#	0.28#											
5. Habitual Sleep Efficiency	0.71 #	0.41#	0.39#	0.53#										
6. Sleep Disturbances	0.55 #	0.39#	0.36#	0.21#	0.22#									
Range														
7. Sleeping Medication	0.56 #	0.23#	0.31#	0.12#	0.19#	0.21#								
8. Daytime Dysfunction	0.53 #	0.38#	0.24#	0.27#	0.21#	0.32#	0.17#							
9. IL-6	0.10&	0.06	0.08&	0.02	0.09&	0.04	0.08&	0.04						
10. IL-8	0.09&	0.04	0.06	0.05	0.07*	0.07*	0.07*	0.05	0.06					
11. IL-10	−0.02	−0.06	0.00	−0.02	−0.02	−0.01	−0.01	0.01	0.03	0.02				
12. TNF-α	0.07*	0.06*	0.04	0.04	0.04	0.06*	0.05	0.04	0.05	0.18#	0.08&			
13. CRP	0.12 #	0.05	0.09&	0.08&	0.12#	0.06*	0.05	0.06	0.08&	0.02	0.20#	0.17#		
14. E-Selectin	0.11 #	0.08&	0.05	0.11#	0.09&	0.03	0.04	0.09	0.08	0.12#	0.03	0.08&	0.15&	
15. ICAM-1	0.13#	0.09&	0.07*	0.07&	0.10#	0.10#	0.08&	0.05	0.02	0.07*	0.08&	0.29&	0.15&	0.07*

Notes: *P<0.05, &P<0.01, #P<0.001. Pearson correlation analysis was used.
Abbreviations: IL, Interleukin; CRP, C-reactive protein, TNF-α, tumor necrosis factor-α; ICAM-1, intercellular adhesion molecule-1.

for these confounding factors in multivariate analysis (all P>0.05, Model 3).

Discussion

This study with obese adults aimed to investigate the associations between sleep quality and key biomarkers of inflammation that predict chronic health problems, such as CVDs, in adulthood. In addition to daytime dysfunction, the other 6 indicators from the PSQI were strongly associated with inflammatory factors by univariate analysis. Higher global sleep scores were significantly linked to higher levels of inflammatory factors after adjustments were made for other confounding factors in multivariate analysis.

Sleep-related research has been ongoing for more than 40 years. Poor sleep is a risk factor for CVDs.[25–30] A large number of studies have shown that poor sleep and sleep-related diseases play an important role in the morbidity and mortality of adults, but these studies cannot prove this association.[31–33] Few studies have tried to establish a model of long-term partial sleep deprivation that can best reflect the daily decline in sleep quality. These studies did not include a comprehensive sleep score, had insufficient inflammatory indicators, had insufficient correction for confounding factors, had flawed research designs and had unrepresentative research populations.[11–15,34,35] Thus, to achieve this goal, well-designed prospective studies with assessments of all aspects of sleep, inflammation, many confounding factors of sleep and associated risks are necessary. Our research has met these conditions. The results of our study contribute to the literature in three different ways. On the one hand, the data of this study were from the MIDUS study, a longitudinal investigation of a national (US) sample of adults. Multiple aspects of sleep quality were assessed, thus expanding upon existing research on the association between adult sleep and inflammation.[13–15] On the other hand, our results via multivariate analysis first proved that sleep quality, as evaluated with the global sleep score, was significantly and independently associated with levels of inflammatory factors, including IL-6, IL-8, TNF-α, E-selectin and ICAM-1. These serum inflammatory markers have been proven to play an important role in the occurrence and development of CVDs among middle-aged and elderly adults.[36–39] Additionally, this study was the first to explore the relationships between sleep quality and inflammatory factors in an obese population with a high risk of many diseases, such as type 2 diabetes mellitus and CVDs.[38,40] Interestingly, none of the PSQI sleep variables were associated with IL-10 in the univariate and multivariate analyses in this study. A possible explanation is that IL-10 is an anti-inflammatory factor, and the decline in sleep quality is more likely to be related to a pro-inflammatory effect instead of anti-inflammation.[41] Our results are consistent with previous experimental evidence that poor sleep leads immune cells to produce higher levels of pro-inflammatory

Table 3 Multivariate Linear Regression Analysis Of Association Between Global Sleep Scores And Inflammatory Markers

Variables	R^2	Sβ	95% CI	*P* Value
Model 1				
IL-6	0.025	0.095	0.037–0.153	0.001
IL-8	0.026	0.097	0.039–0.156	0.001
IL-10	0.017	−0.019	−0.078–0.039	0.517
CRP	0.028	0.106	0.048–0.165	<0.001
TNF-α	0.026	0.102	0.042–0.162	0.001
E-Selectin	0.029	0.114	0.056–0.173	<0.001
ICAM-1	0.036	0.140	0.082–0.199	<0.001
Model 2				
IL-6	0.036	0.088	0.030–0.146	0.008
IL-8	0.035	0.103	0.044–0.161	0.001
IL-10	0.025	0.017	−0.572–0.042	0.573
CRP	0.031	0.083	0.021–0.145	0.009
TNF-α	0.033	0.090	0.030–0.150	0.003
E-Selectin	0.034	0.098	0.038–0.158	0.001
ICAM-1	0.042	0.086	0.028–0.144	0.004
Model 3				
IL-6	0.125	0.074	0.019–0.129	0.009
IL-8	0.127	0.089	0.033–0.144	0.002
IL-10	0.120	−0.021	−0.076–0.035	0.463
CRP	0.121	0.035	−0.025–0.094	0.059
TNF-α	0.126	0.082	0.025–0.139	0.005
E-Selectin	0.124	0.071	0.014–0.128	0.016
ICAM-1	0.133	0.117	0.061–0.172	<0.001

Notes: Model 1: adjusted for age, gender, race, marital status, education, current smoker and physician diagnosed CVD and respiratory diseases. Model 2: adjusted for age, gender, race, marital status, education, current smoker, physician diagnosed CVD and respiratory diseases and BMI. Model 3: adjusted for age, gender, race, marital status, education, current smoker, physician diagnosed cardiovascular diseases and respiratory diseases, BMI and perceived stress. Multivariate linear regression analysis was used.

Abbreviations: IL, Interleukin; CRP, C-reactive protein, TNF-α, tumor necrosis factor-α; ICAM-1, intercellular adhesion molecule-1; CVD, cardiovascular diseases; BMI, body mass index.

factors when stimulated in vitro. For instance, a study showed that sleep restriction with one night of 3.5 h of sleep was related to a significant increase in monocyte-derived production of TNF-α and IL-1β.[42] Similarly, poor sleep has been linked with the upregulation of TNF-a and IL-6 mRNA expression[43] and promoted the activation of nuclear factor (NF)-kB, which is a transcription factor that plays an important role in promoting the expression of pro-inflammatory genes.[20] Our findings generalize prior laboratory findings to show that the decline in sleep quality is associated with inflammatory competence, suggesting a possible mechanism relating poor sleep to susceptibility to inflammatory diseases, such as CVDs.[44] CVDs remain the main cause of death in many developed and developing countries. Research from the past decades has shown that inflammation plays a key role in the progression of CVDs.[41] The atherosclerotic plaque in the vasculature is known as a complex inflammatory reaction of the vascular wall with inflammatory stimulation from the circulating blood. Therefore, pro-inflammatory cytokines may provide a pathway linking poor sleep to an increased risk of inflammatory diseases, such as CVDs. In summar, previous studies and our findings may explain this association with the consistent results of the activation of immune cells and the elevation of serum inflammatory levels in populations with poor sleep.

In addition, some of our findings diverge from those of previous studies, which showed that elevated CRP levels tended to be more consistently associated with worse sleep quality.[45–48] These inconsistent findings can be at least partly explained by the different study designs used and study populations selected, the hypotheses being investigated, the inherent challenges of obtaining epidemiologic measurements of intricate and the different methods of analyzing data. In our findings, the global sleep score was associated with CRP levels after adjustments were made for age, gender, race, marital status, education, current smoking status, BMI, and physician-diagnosed CVDs and respiratory diseases, but after perceived stress was then added into Model 2, the global sleep score was no longer related to CRP levels. The difference is that in previous studies, adjustments were not made for perceived stress.[45–48] Perceived stress may reduce the correlation between poor sleep and CRP levels.[49] Continued research would need to elucidate the reason. In summary, our results showed a significant negative correlation between sleep quality and serum levels of proinflammatory factors in the obese population.

Limitations

Finally, there are some limitations in our findings. To participate in this study, all participants needed to be healthy enough to go to a MIDUS study research center, thus leading to the potential for bias. Additionally, the PSQI is used for assessing participants' self-reported subjective sleep quality. A more objective tool is necessary to assess the association between sleep quality and inflammatory biomarkers.

Conclusions

Poor sleep is positively associated with serum pro-inflammatory marker levels among obese adults. Pro-inflammatory cytokines may provide a pathway linking poor sleep to an

increased risk of inflammatory diseases. Sufficient sleep may be particularly important for obese adults to prevent chronic health problems, such as CVDs.

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Disclosure

The authors report no conflicts of interest in this work.

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