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# Sleep characteristics and inflammatory biomarkers among midlife women FREE

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## Abstract

### Study Objectives

Research suggests that sleep disturbances are associated with elevated levels of inflammation. Some evidence indicates that women may be particularly vulnerable; increased levels of inflammatory biomarkers with sleep disturbances are primarily observed among women. Midlife, which encompasses the menopause transition, is typically reported as a time of poor sleep. We tested whether poorer objectively measured sleep characteristics were related to a poorer inflammatory profile in midlife women.

### Methods

Two hundred ninety-five peri- and postmenopausal women aged 40–60 completed 3 days of wrist actigraphy, physiologic hot flash monitoring, questionnaires (e.g. Berlin sleep apnea risk questionnaire], and a blood draw for the assessment of inflammatory markers, including C-reactive protein (CRP), interleukin-6 (IL-6), and von Willebrand factor (VWF) antigen. Associations of objective (actigraphy) sleep with inflammatory markers were tested in regression models. Sleep efficiency was inverse log transformed. Covariates included age, race/ethnicity, education, body mass index, sleep apnea risk, homeostatic model assessment (a measure of insulin resistance), systolic blood pressure, low-density lipoprotein cholesterol, and physical activity.

### Results

In separate models controlling for age, race/ethnicity, and education, lower sleep efficiency was associated with higher IL-6 [$b(SE)$ = .02 (.10), $p$ = .003] and VWF [$b$(SE) = .02 (.08), $p$ = .002]. More minutes awake after sleep onset was associated with higher VWF [$b(SE)$ = .12 (.06), $p$ = .01]. Findings persisted in multivariable models.

### Conclusions

Lower sleep efficiency and more minutes awake after sleep onset were independently associated with higher circulating levels of VWF. Lower sleep efficiency was associated with higher circulating levels of IL-6. These findings suggest that sleep disturbances are associated with greater circulating inflammation in midlife women.

menopause, sleep, actigraphy, inflammation

## Statement of Significance

Growing literature suggests an association between sleep disturbance and markers of systemic inflammation, particularly for women. Inflammation plays an important role in the pathophysiology of cardiovascular disease (CVD). CVD increases with age and is the leading cause of death in postmenopausal women. However, little is known about the relationship between sleep and inflammation during the menopause transition, a time in which women are vulnerable to poor sleep and increased CVD risk. The present study provides data showing a relationship between poor sleep and higher levels of inflammatory biomarkers in midlife women. These findings may have implications for women's health. Future work should consider improving midlife women's inflammatory profile by treating their sleep problems.

# Introduction

Sleep problems are common among women during midlife and the menopause transition [1]. Between 39 per cent and 60 per cent of peri- and postmenopausal women in the United States report sleep disturbances [1–3]. These sleep disturbances can persist well into the postmenopausal years [4], cause considerable distress [5], reduce quality of life, increase health care utilization and costs [5], disability [5], and risk for medical and psychiatric conditions (e.g. diabetes, cardiovascular disease [CVD], depression) [6–9]. Sleep research has increasingly focused on the biological mechanisms underlying these effects, with substantial interest in the role of sleep disturbance and sleep duration on measures of innate immunity [10].

Inflammatory mechanisms contribute to the risk of a wide spectrum of medical and psychiatric disorders. Higher levels in circulating markers of inflammation, such as interleukin-6 (IL-6) and C-reactive protein (CRP), are associated with subsequent CVD events [11, 12], hypertension [13], weight gain [14], type 2 diabetes [15, 16], and depression [17]. Compelling evidence has demonstrated that sleep disturbance (defined as difficulty initiating or maintaining sleep) and shorter sleep duration are associated with elevated inflammatory biomarkers [18–20], which may increase the risk of chronic diseases [21–23]. A recent meta-analysis by Irwin and colleagues [10] examined the association of sleep characteristics with several inflammatory markers in 72 studies ($N > 50000$). It provided evidence for associations between sleep and inflammation, including links between sleep disturbance and higher CRP and IL-6 and shorter sleep duration with higher CRP [10].

Women may be particularly vulnerable to the inflammatory impact of sleep disturbance demonstrating greater increases of IL-6 and CRP with sleep disturbance relative to men [24–27]. These findings have implications for understanding the different sex-specific risk factors associated with chronic diseases [28]. For example, insomnia symptoms are associated with a greater risk of CVD in women than men, even after controlling for relevant confounders [29]. Thus, it is important to gain a better understanding of women's particular susceptibility to the inflammatory effects of poor sleep. Notably, women experience periods of sleep vulnerability, such as during midlife and menopause; when women are more likely to experience hormonal fluctuations and hot flashes [1].

Few studies have examined sleep-related inflammatory markers in women during midlife and the menopause transition. In a subset of participants from the Study of Women's Health Across the Nation (SWAN) longitudinal cohort study, investigators found that sleep disordered breathing is associated with inflammatory biomarkers in midlife women (median age 52 years; 89% pre- or perimenopausal) [20]. Further, in this study, among African American women only, polysomnography (PSG)-assessed shorter sleep duration was associated with higher CRP, and less efficient sleep was associated with higher fibrinogen, an inflammatory and prothrombotic marker [20]. However, whether short and disturbed sleep is independently associated with greater inflammation in midlife women, and the potential role of other menopausal symptoms such as estradiol and sleep hot flashes in this relationship, requires further investigation.

Examining sleep-inflammation relations with a range of inflammatory biomarkers is warranted. Markers that also index endothelial function/damage are of particular interest, given evidence of a relation between sleep characteristics and CVD risk [30, 31]. Endothelial dysfunction plays a central role in CVD pathophysiology [32], as well as in regulating the local inflammatory response [32], and the vascular endothelium is well-established to be sensitive to menopause-related factors [33, 34]. Plasma von Willebrand factor (VWF), traditionally viewed as a hemostatic biomarker that stabilizes procoagulant activity of clotting factor VIII, is also a marker of endothelial dysfunction, mediating platelet adhesion to sub-endothelial structures [35, 36]. VWF also plays a role in inflammation by directly binding to leukocytes [37–39]. VWF has a documented association with future risk for disease, particularly CVD [40–42].

We tested the relation between sleep as assessed by actigraphy and CRP, IL-6, and VWF among a cohort of 304 midlife women. We hypothesized that lower sleep efficiency, more time awake after sleep onset, and shorter sleep duration would be associated with higher levels of CRP, IL-6, and VWF among midlife women after adjusting for key covariates. We considered the moderating role of race as well as the role of menopause-specific

factors (objectively assessed sleep hot flashes, endogenous estradiol concentrations) in sleep-inflammation relations.

# Methods

## Participants

Participants were 304 late perimenopausal (2–12 months amenorrhea) and postmenopausal (≥12 months amenorrhea) [43] nonsmoking women between the ages of 40 and 60 years. Midlife women were recruited from the community via local advertisements, electronic and paper mailings, referrals from local clinics, and online postings for a study investigating the relationship between menopausal symptoms and CVD risk. By study design, 50 per cent of the women reported daily hot flashes or night sweats, and 50 per cent reported no hot flashes or night sweats in the past 3 months. Exclusion criteria included hysterectomy and/or bilateral oophorectomy; history of heart disease, stroke, arrhythmia, ovarian/gynecological cancer, pheochromocytoma, pancreatic tumor, kidney failure, seizures, Parkinson's disease, Raynaud's phenomenon; current pregnancy; endometrial ablation; endarterectomy; currently undergoing dialysis or chemotherapy; and having used medications impacting hot flashes or inflammatory biomarkers in the past 3 months, including: oral/transdermal estrogen or progesterone, selective estrogen receptor modulators, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, gabapentin, insulin, beta blockers, calcium channel blockers, alpha-2 adrenergic agonists, or other antiarrhythmic agents.

Of the 304 women, 21 women who were shift workers were excluded from the present report due to possible confounding effects of circadian rhythm disturbance on the sleep–inflammation relationship. Two hundred ninety-five women were included in primary models using actigraphy sleep data and markers of inflammation.

## Procedures

After telephone and in-person screening procedures, participants completed physical measurements and questionnaires and 3 days of ambulatory monitoring that included hot flash measurement by sternal skin conductance and sleep measurement by actigraphy. Procedures were approved by the University of Pittsburgh Institutional Review Board; and participants provided written, informed consent.

## Measures

### Sleep

Women wore an Actiwatch 2 (Respironics, Inc., Murrysville, PA) [44] on their nondominant wrist and completed a daily sleep diary [45] for three consecutive days. Actigraphy data were collected 90 per cent of the time during weekdays and 10 per cent across weekday and weekend. Actigraphy data were collected in 1 min epochs and analyzed with Philips Actiware v6.0.0 software. Bedtime (time into bed), lights out (time sleep was attempted), wake time (final wake time), and rise time (time out of bed) were determined via sleep diary reports. Sleep efficiency (%) was calculated by Philips Actiware software using the formula: total sleep time/time in bed × 100. Sleep efficiency was our primary actigraphy-assessed variable of interest given its clinical importance in measuring sleep continuity. Wake after sleep onset (WASO) defined as the number of minutes of wakefulness between actigraphy-defined sleep onset time and actigraphy-defined final wake time; and total sleep time (TST) defined as the difference between actigraphy-defined sleep onset and actigraphy-defined final wake time minus actigraphy-defined WASO were also considered.

### Inflammatory biomarkers

Phlebotomy was performed after a 12 hr overnight fast. All women were free of acute illness (e.g. colds) when blood was drawn. CRP was measured using a high sensitivity (hs-CRP) reagent set (Beckman Coulter, Brea, CA; norm values 0.6–.3.1 mg/L [46]), IL-6 with an R&D Systems (Minneapolis, MN) high sensitivity ELISA (norm values 0.7–3.5 pg/mL [46]), and VWF antigen using an immunoturbidimetric method (STA Liatest VWF:Ag, norm values 50%–160%; Diagnostica Stago, Asnieres sur Seine, France).

## Covariates and additional measures

Demographics (age, education, race/ethnicity) and medical history were assessed by standard instruments. All medications used by participants during the study were documented at the outset of the study during the medical history interview and on sleep diary during ambulatory monitoring.

Medications were subsequently classified according to their indication: blood pressure-lowering, lipid-lowering, diabetes, depression, anxiety. Menopause status was obtained from reported menstrual bleeding patterns and categorized according to STRAW+10 criteria [43]. Habitual alcohol use was measured as yes/no to alcohol consumption and if yes, how many 12 ounce glasses of beer, 4–6 ounce glasses of wine and/or shots of liquor do participants drink in a month, week, or day. Habitual physical activity (metabolic equivalent of task [MET] min/week) was measured via the International Physical Activity Questionnaire [47]. Sleep apnea symptoms including snoring were measured via the Berlin Questionnaire [48]. Depression was measured via the Center for Epidemiological Studies Depression Scale (CES-D) [49]. Height and weight were measured via a fixed stadiometer and a calibrated balance beam scale and body mass index (BMI) calculated ($kg/m^2$). Seated blood pressure (mean of second and third of three measurements) was measured via a Dinamap device after a 10 min rest. Low-density lipoprotein cholesterol (LDL-C) was measured and calculated [50]. Insulin was measured via radioimmunoassay and homeostatic model assessment (HOMA) was used to calculate insulin resistance [51]. Estradiol was assessed via liquid chromatography-tandem mass spectrometry, the gold standard method to measure estradiol at the low levels typical of the postmenopause (lower limit of quantitation = 2.5 pg/mL; lower limit of detection = 1.0 pg/mL) [52].

Hot flashes during wake and sleep were measured both by physiologic monitor (over 24 hr) and electronic hot flash diary/event marker (over 3 days). The hot flash monitor was the VU-AMS (VU University Amsterdam, the Netherlands) [53, 54], a portable ambulatory monitor that quantifies hot flashes via sternal skin conductance, a validated measure of hot flashes [55, 56]. At the time of a subjectively experienced hot flash, women completed an electronic diary (Palm Z22) entry and pressed event mark buttons on the VU-AMS monitor and actigraph, providing date and time-stamped hot flash reports. Participants wore the VU-AMS monitor for 24 hr, after which time they removed it and stored it in a provided case. For the remaining 2 days, participants reported their hot flashes via electronic diary and actigraphy event marker. After monitoring, hot flash data were downloaded, reviewed, and scored via UFI software (DPSv3.7; Morro Bay, CA) according to standard, validated methods [55–57] that have demonstrated reliability including in the present laboratory ($\kappa = .86$) [58]. Hot flashes were classified as occurring during wake or sleep according to sleep diary sleep onset and offset times. To account for unequal monitoring duration across participants, physiologically measured hot flashes were calculated as a rate, whereby the number of physiologically recorded hot flashes is divided by the participant-reported sleep period (i.e. participant-reported bedtime to the final wake time) and standardized to the median of 6 hr for ease of interpretation.

## Statistical analysis

WASO, HOMA, LDL cholesterol, estradiol, CRP, and IL-6 values were natural log transformed and sleep efficiency was inverse log transformed as these transformations normalized the skewed distribution of the raw data to meet model assumptions of normality. Notably, with transformation, greater sleep efficiency values indicated poorer sleep continuity. Differences between participants by included/excluded status or by hot flash group were tested using linear regression, Wilcoxon rank sum, and chi-square tests. Associations between sleep variables and study outcomes were evaluated using linear and multinomial regression. Covariates for base models (i.e. age, education, race/ethnicity) were selected based upon their association with the outcome at $p < .10$, with age forced into models. Covariates for expanded multivariable models were selected based upon their prior documented associations with inflammatory markers and association with the outcomes here at $p < .10$. Additional secondary models included covariates Berlin score, BMI, HOMA, systolic blood pressure, low-density lipoprotein, and leisure physical activity. Menstrual status, 24 hr and sleep hot flashes (physiologic and self-report), estradiol levels, sleep medications, anxiolytics, antidepressants, inflammatory medications, and habitual alcohol use were considered but did not meet $p < .10$ criteria. Interactions between sleep variables and race/ethnicity or sleep hot flashes were tested by cross product terms in multivariable models. $R^2$ values were derived from linear regression models. Residual analysis and diagnostic plots were conducted to verify model assumptions. Analyses were performed with IBM SPSS Statistics v24 (IBM Corporation). Models were two-sided at $\alpha = .05$.

# Results

## Participant characteristics

Participants were on average 54 years old (age range 40–60 years) and overweight. The majority of the participants were white and postmenopausal. The median actigraphy-assessed sleep efficiency was 85 per cent, median WASO was 41 min, and mean TST was 371 min (Table 1).

**Table 1.**

Sample characteristics

| ***N*** | **295** |
|---|---|
| Age, *M* (*SD*) | 53.9 (4.1) |
| Race/ethnicity, *N* (%) | |
| White | 212 (71.9) |
| Black | 66 (22.4) |
| Other | 17 (5.8) |
| Education, *N* (%) | |
| High school/some college/vocational | 123 (41.7) |
| College graduate or higher | 172 (58.3) |
| Menopause stage, *N* (%) | |
| Perimenopausal | 50 (16.9) |
| Postmenopausal | 245 (83.1) |
| BMI, *M* (*SD*) | 29.0 (6.7) |
| SBP, *M* (*SD*) mmHg | 120.1 (14.7) |
| LDL, *M* (*SD*) mg/dL | 130.2 (33.2) |
| HOMA, median (IQR) | 2.3 (1.7, 3.2) |
| Number of physiologic overnight hot flashes, *M* (*SD*)* | 1.8 (2.1) |
| Number of overnight hot flashes, *M* (*SD*) | 0.5 (1) |
| Medications, *N* (%) | |
| Inflammatory† | 48 (16.3) |
| Anxiolytics | 12 (4.1) |
| Hypnotics/sleep‡ | 12 (4.1) |
| Actigraphy sleep | |
| Sleep efficiency, median (IQR) % | 85.4 (80.3, 89) |
| WASO, median (IQR) min | 41.3 (28.3, 55) |
| TST, mean (*SD*) min | 370.8 (62.3) |
| Inflammatory markers, median (IQR) | |
| CRP, mg/L | 1.4 (0.7, 3.6) |
| IL-6, pg/mL | 1.5 (1.0, 2.2) |
| VWF, % | 130 (100, 170) |

BMI = body mass index; SBP= systolic blood pressure; LDL-C= low-density lipoprotein cholesterol; HOMA = homeostatic model assessment; WASO= wake after sleep onset; TST = total sleep time; CRP = C-reactive protein; IL-6 = interleukin-6; VWF = Von Willebrand factor antigen.

*Sleep hot flash rate standardized to 6 hr night.

†Inflammatory medications include adalimumab, hydrocychloroquine, ibuprofen, naproxen, sulindac, meloxicam, celecoxib, and

diclofenac.

‡Hypnotic/sleep medications include zolpidem, melatonin, night-time pain relievers, & antihistamines.

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# Sleep and inflammatory markers

## Sleep efficiency

Lower actigraphy-assessed sleep efficiency was associated with higher circulating levels of IL-6 and VWF in minimally adjusted models, and models remained significant with adjustment for covariates (Table 2, Figures 1 and 2). Sleep efficiency was not related to CRP.

### Table 2.

Association between actigraphy-assessed sleep characteristics and inflammatory markers

| Model 1 | IL-6 | VWF | CRP | Model 2 | IL-6 | VWF | CRP |
|---|---|---|---|---|---|---|---|
| | *B* (*SE*) | *B* (*SE*) | *B* (*SE*) | | *B* (*SE*) | *B* (*SE*) | *B* (*SE*) |
| Sleep efficiency (%) | .20 (.10)** | .20 (.08) ** | .09 (.17) | Sleep efficiency (%) | .12 (.09)* | .18 (.08)* | .01 (.13) |
| WASO (min) | .10 (.09) | .15 (.06)** | .02 (.14) | WASO (min) | .09 (.07) | .14 (.06)* | .01 (.11) |
| TST (min) | −.08 (.01) | −.04 (.01) | −.02 (.01) | TST (min) | −.06 (.01) | −.04 (.01) | −.02 (.01) |

B = beta; SE = standard error; IL-6 = interleukin-6; VWG = von Willebrand factor antigen; CRP = C-reactive protein; WASO = minutes awake after sleep onset; TST = total sleep time. Model 1: Adjusted for age, race, and education. Model 2: Adjusted for age, race, education, body mass index, systolic blood pressure, low-density lipoprotein cholesterol, homeostatic model assessment, Berlin score, and leisure time physical activity.

*$p < .05$, **$p < .01$.

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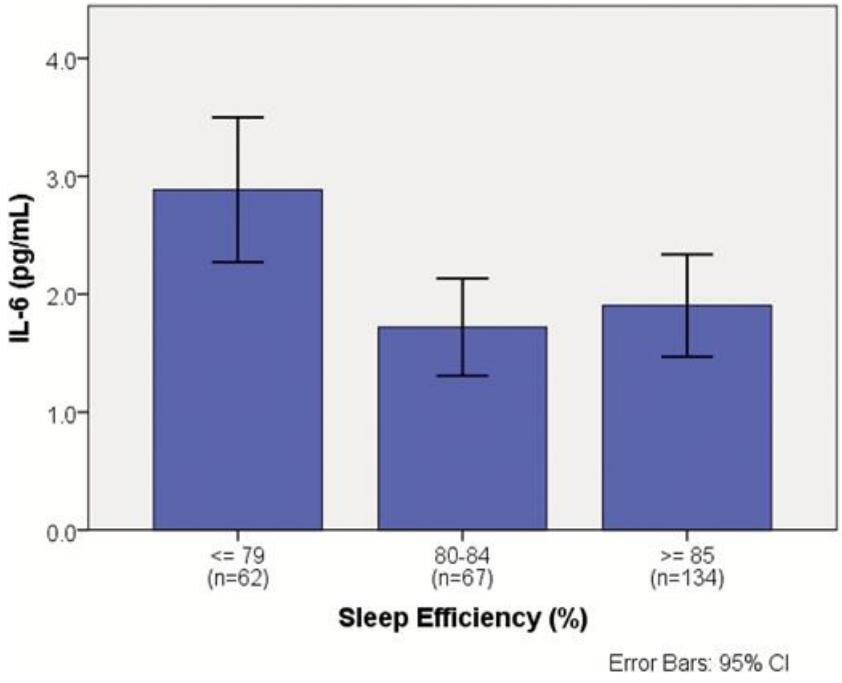
### Figure 1.

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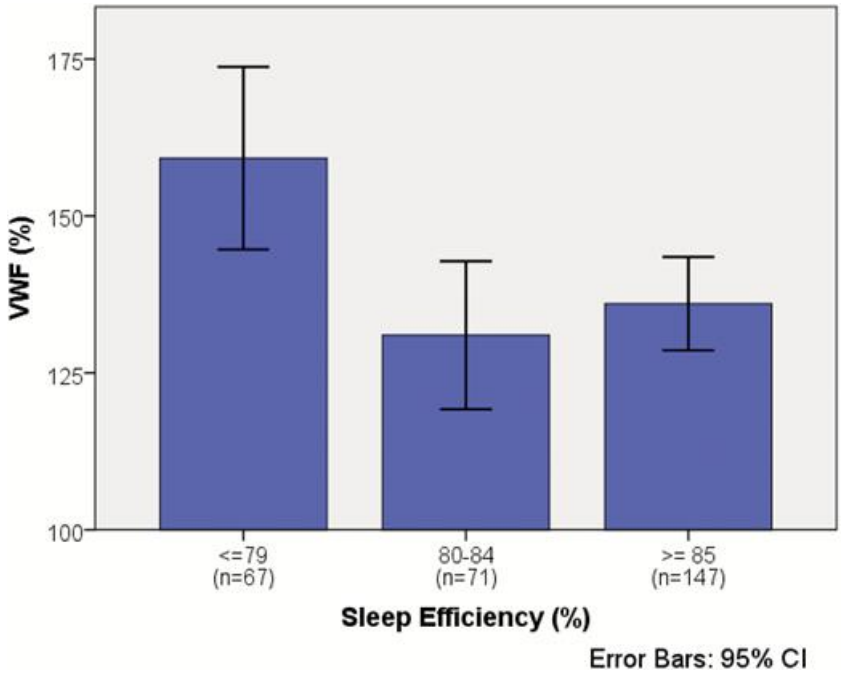
Mean interlekin-6 (pg/mL) values by sleep efficiency stratified by clinical cut-points (≤79%, 80–84%, and ≥85%). $\beta$ = .13, $p$ = .026.

**Figure 2.**

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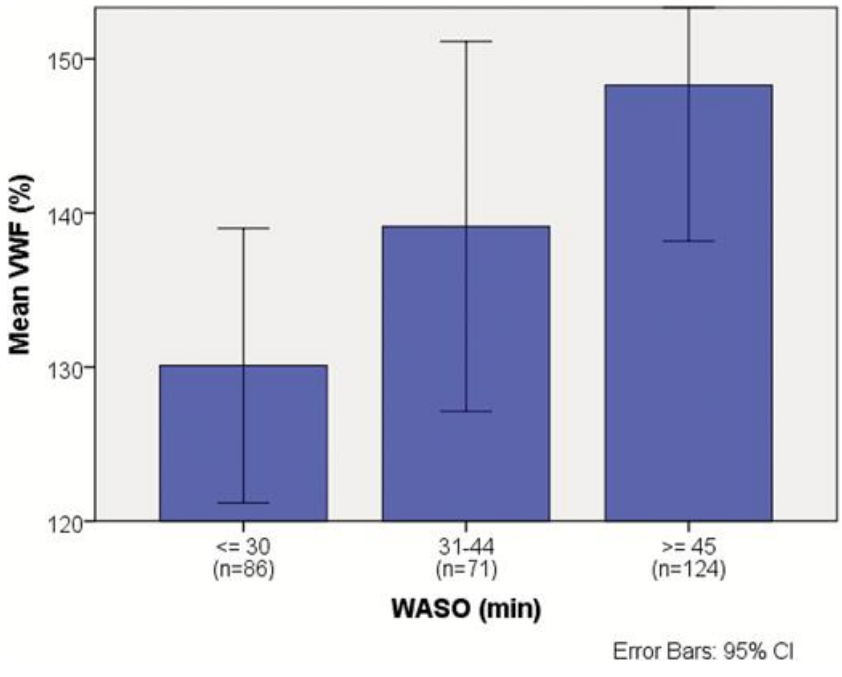
Mean VWF antigen (%) values by sleep efficiency stratified by clinical cut-points (≤79%, 80–84%, and ≥85%). $\beta$ = .19, $p$ = .003.

## Wake after sleep onset

Greater actigraphy-assessed WASO was associated with higher circulating levels of VWF in minimally adjusted models, and models remained significant with adjustment for multiple inflammatory risk and demographic factors (Table 2, Figure 3). WASO was marginally related to IL-6.

**Figure 3.**

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Mean VWF antigen (%) values by wake after sleep onset stratified by clinical cut-points (≤30 min, 31–44 min, and ≥45 min). $\beta$ = .15, $p$ = .012.

### Total sleep time

Actigraphy-assessed TST was not significantly associated with any of the biomarkers considered here (Table 2).

## Complementary analyses

We first tested interactions between sleep variables and race/ethnicity, nighttime hot flashes, and estradiol; no interactions were significant. We also considered several additional covariates, further adjusting for estradiol concentrations, menopause status, 24 hr and sleep hot flashes (physiologically assessed and self-report), medications (anxiolytics, antidepressants, anti-inflammatory medications), habitual alcohol use (dichotomized to below once per month vs more than once monthly), and depressive symptoms in multivariable models; findings were unchanged (data not shown). Although all participants were assessed only when reporting no acute infection, inflammatory markers were examined for extreme values that might indicate infection. Models were run excluding participants with elevated IL-6 > 15 pg/mL ($N = 1$), CRP > 10 mg/dL ($N = 20$), report of osteoarthritis ($N = 6$), or rheumatoid arthritis ($N = 35$); and conclusions were unchanged (data not shown).

# Discussion

The present study examined the association between sleep continuity and sleep duration with inflammatory biomarkers among a large sample of midlife women transitioning through the menopause. In the present study, the median TST was approximately 6 hr and WASO was 42 min, indicating short and disrupted sleep. We found that lower sleep efficiency was associated with higher levels of IL-6 and VWF, and greater WASO associated with higher VWF. These associations remained significant after adjustment for demographic factors, BMI, multiple CVD risk factors, sleep apnea risk, and physical activity. The present findings show that indicators of poorer sleep continuity during the menopause transition are independently associated with inflammatory biomarkers. These findings indicate that sleep continuity may have implications for the development of chronic diseases in which inflammation plays a major role, such as CVD.

Prior studies have provided evidence that sleep characteristics are related to inflammatory biomarkers [18, 19] with potential implications for disease outcomes [21, 22]. A recent meta-analysis confirmed the association between poorer sleep quality, insomnia complaints, and sleep duration on IL-6 and CRP [10]. Women may be particularly vulnerable to the inflammatory impact of sleep disturbance, as they demonstrate higher IL-6 and CRP with poorer sleep quality than men [24, 25]. It may be particularly important to study women during periods of reproductive and hormonal fluctuation, such as during the menopausal transition, when women are more likely to experience sleep disturbance. Notably, menopause may also be a time of accelerating CVD risk [59], a phenomenon in which poor sleep and inflammation may play a role [60].

Few studies have examined the relationship of sleep and inflammatory markers in midlife women. The SWAN sleep study considered sleep among midlife women and inflammatory/hemostatic markers, and found associations between sleep characteristics and CRP or fibrinogen among African American women only [20]. Our findings extend this work, including a wider range of inflammatory markers including VWF and IL-6, the latter being particularly robustly related to sleep characteristics in other work [10]. Our work is also distinguished by a rigorous consideration of the role of sleep hot flashes or endogenous estradiol levels, potential menopause-specific explanatory factors of elevated inflammation. We did not observe any evidence for race/ethnic-specific findings. However, the majority of SWAN participants (89%) were pre- or perimenopausal (2–12 months amenorrhea) while the majority of participants in the present study (83%) were postmenopausal (≥12 months amenorrhea). Taken together, these studies support an association between sleep characteristics and inflammation during the menopause transition and postmenopause.

In contrast to findings for indices of sleep disturbance, we found no significant association of TST with any inflammatory marker assessed. Our null findings related to sleep duration are consistent with a large cohort study showing no significant association between sleep duration and CRP [61] and with the meta-analysis by Irwin and colleagues that found no significant association between continuous measures of objective or subjective sleep duration and IL-6 and minimal association with CRP. Irwin and colleagues also found that when extreme sleep duration (i.e. short sleep defined as <7 hr per night and long sleep defined as >8 hr per night) was evaluated, long sleep duration but not short sleep duration was associated with increases in CRP and IL-6. Seventy-eight percent ($N = 229$) of our sample slept <7 hr and 3 per cent ($n = 9$) slept >8 hr. With this small subgroup of long sleepers in our sample, we were unable to reliably examine the relation between long sleep and inflammation. However, these results do underscore the prevalence of short sleep in this sample of midlife women.

In addition to adjusting for established inflammatory and key CVD risk factors, we also considered several additional covariates, including estradiol concentrations and depressive symptoms, with no changes in conclusions. We also carefully considered the role of hot flashes, which were assessed via physiologic monitor, important given the difficulties in accurately estimating hot flashes occurring during sleep [62, 63]. Objectively assessed hot flashes did not account for observed associations.

Although residual confounding by unmeasured third factors remains a possibility, the significant associations of poor sleep with inflammatory biomarkers independent of these covariates, may imply direct pathophysiological mechanisms linking lower sleep efficiency and greater WASO with increased levels of IL-6 and VWF. Future work should consider exploring the possibility of such biological mechanisms, including the role of the autonomic nervous system. Given that normal nocturnal sleep is associated with a drop in sympathetic outflow [64], activation of the sympathetic effector pathway is one biologically plausible mechanism to explain the associations between sleep disturbance and increases in markers of inflammation. As an example, plasma VWF levels increase in response to sympathetic activation [65]. Given the association between cortisol and inflammation [66, 67] and the negative impact of sleep on cortisol [19, 68], the hypothalamic-pituitary-adrenal (HPA) axis should also be examined.

Differences in pathways and responses of inflammatory biomarkers to sympathetic activation could help to explain why we found significant associations of sleep measures with VWF and IL-6, but not CRP. As a key proinflammatory cytokine, IL-6 is both an upstream and downstream marker of activated inflammation, regulating CRP production downstream by the liver [69]. It is possible that downstream effects of poor sleep are less pronounced than upstream effects on inflammation. The role of poor sleep and inflammation should be considered when examining the accelerating CVD risk observed during the menopause transition. Such studies might reveal that inflammatory biomarkers directly impact cardiovascular health and/or, mediate/moderate the relationship between established cardiovascular risk factors and CVD incidence.

This study had several limitations. First, sleep was assessed at one time point and we did not assess for the past history of sleep problems, limiting our ability to address questions regarding the temporal nature of relations between sleep and inflammation. Future longitudinal studies could test the possibility the relation of persistent sleep problems with inflammation. Second, in this cross-sectional observational study, we cannot make any inferences about the causality or directionality between poor sleep and inflammation. Third, sleep was assessed for 3 days by actigraphy, which was inconsistently collected across weekdays and weekends. Although 90 per cent of the sleep data collection occurred on weekdays, 10 per cent was across weekday and weekend; which may have caused variability in sleep schedule. It is notable that a 3-day actigraphy protocol has been successfully implemented and linked to important health outcomes [70]. Nonetheless, future work should consider longer monitoring periods for actigraphy or PSG. Finally, although osteoarthritis, rheumatoid arthritis, and inflammatory medications were inquired about and excluded in secondary models, with no changes in results, other autoimmune and inflammatory conditions (e.g. lupus, inflammatory bowel disease) were not assessed and may impact levels of inflammatory biomarkers.

Several study strengths should also be mentioned. First, we studied women transitioning through menopause, a relatively under-studied group with prevalent sleep complaints. Second, our study was large and well-characterized, allowing us to take important covariates into account, such as menopausal symptoms, including sleep hot flashes, endogenous estradiol concentrations, and depressive mood. Third, we assessed inflammatory biomarkers with an established predictive value for adverse health outcomes.

In conclusion, greater actigraphy-assessed sleep disturbance and lower sleep efficiency were associated with higher circulating levels of inflammatory markers among midlife women, independently of key covariates. Midlife and the menopause transition marks a time in which bothersome symptoms such as sleep disturbances become more frequent, and risk for a range of negative health outcomes increases [71–73]. Our findings demonstrate that these sleep problems are associated with elevations in key inflammatory biomarkers, which may have implications for women's health. Our study findings highlight the importance to further examine the health implications of poor sleep-related elevations in inflammation. They also underscore the importance of considering whether treating sleep problems may improve women's inflammatory profile and overall health.

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# Notes

*Conflict of interest statement*. None declared.

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