ORIGINAL ARTICLE

Sleep Characteristics and Carotid Atherosclerosis Among Midlife Women

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Introduction: Midlife, which encompasses the menopause transition in women, can be a time of disrupted sleep and accelerated atherosclerosis accumulation. Short or poor sleep quality has been associated with cardiovascular disease (CVD) risk; few studies have investigated relations among midlife women. We tested whether shorter actigraphy sleep time or poorer subjective sleep quality was associated with carotid atherosclerosis among midlife women.
Aims and Methods: Two hundred fifty-six peri- and postmenopausal women aged 40–60 years completed 3 days of wrist actigraphy, hot flash monitoring, questionnaires (Pittsburgh Sleep Quality Index [PSQI], Berlin), a blood draw, and carotid ultrasound [intima media thickness (IMT), plaque]. Associations of objective (actigraphy) and subjective (PSQI) sleep with IMT/plaque were tested in regression models (covariates: age, race, education, body mass index, blood pressure, lipids, insulin resistance, medications, snoring, depressive symptoms, sleep hot flashes, and estradiol).
Results: Shorter objective sleep time was associated with higher odds of carotid plaque (for each hour shorter sleep, plaque score ≥ 2, odds ratio (OR) [95% confidence interval, CI] = 1.58 [1.11–2.27], $p = .01$; plaque score = 1, OR [95% CI] = 0.95 [0.68–1.32], $p = .75$, vs. no plaque, multivariable). Poorer subjective sleep quality was associated with higher mean IMT [β, *b* (standard error, *SE*) = 0.004 (0.002), $p = .03$], maximal IMT [*b* (*SE*) = 0.009 (0.003), $p = .005$], and plaque [plaque score ≥ 2, OR (95% CI) = 1.23 (1.09–1.40), $p = .001$; score = 1, OR (95% CI) = 1.06 (0.93–1.21), $p = .37$, vs. no plaque] in multivariable models. Findings persisted additionally adjusting for sleep hot flashes and estradiol.
Conclusions: Shorter actigraphy-assessed sleep time and poorer subjective sleep quality were associated with increased carotid atherosclerosis among midlife women. Associations persisted adjusting for CVD risk factors, hot flashes, and estradiol.
Keywords: menopause, sleep, intima media thickness, cardiovascular disease.

Statement of Significance
Disrupted sleep is common for midlife women. Midlife, which includes the menopause transition, is also typically a time of increasing cardiovascular disease (CVD) risk in women. However, little is known about the relations between sleep and CVD risk during midlife and the menopause transition in women. In this investigation of 256 midlife women, shorter actigraphy-assessed sleep time and poorer subjective sleep quality were associated with increased carotid atherosclerosis. Associations persisted adjusting for CVD risk factors, hot flashes, and estradiol. Future work should consider any cardiovascular benefit of treating midlife women's sleep problems as well as the role of sleep problems in the cardiovascular changes observed in women during midlife.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death among women.[1] Midlife is an important time for women's health. It includes the menopause transition, a time of changes in menstrual cycling, reproductive hormones, and vasomotor symptoms that has long been of interest for women's cardiovascular health. Risk for clinical CVD among premenopausal women is low and markedly lower than that of men, yet accelerates postmenopausally to match those of men later in life.[2] Midlife and the menopause transition are also marked by accelerated atherosclerosis accumulation[3] and worsening of key CVD risk factors.[4] The cardiovascular changes that occur during midlife and the menopause transition are typically attributed to changes in reproductive hormones and, foremost, declines in endogenous estradiol. However, midlife is accompanied by many other symptoms and experiences for women that may have implications for women's cardiovascular health.

One such symptom is poor sleep. Poor sleep is reported by at least a third of midlife women and in some studies over 60% of peri- and postmenopausal women.[5–8] In fact, sleep problems are so common among midlife women that they are considered by some to be a core menopausal symptom.[5] Although findings of objective sleep changes, such as total sleep time (TST), specifically associated with menopause stage are mixed,[9,10] it is clear that reported sleep problems increase over the menopause transition beyond chronological aging alone.[11] Menopausal hot flashes are also common[12] and may play an important role in poorer subjective or objective sleep quality in midlife women.[10,13] Other aging-related factors that likely contribute to poor sleep among midlife women are decreases in sleep continuity and increases in sleep disorders such as sleep apnea.[9] Poor sleep during midlife among women can be persistent[14] and cause considerable distress and impairment.[15]

A growing literature links short (or long) self-reported sleep duration[16–18] and to a lesser extent objectively assessed sleep duration[19] with indicators of CVD risk. Furthermore, other work has shown an accelerated accumulation of atherosclerosis with advancing menopause stage.[3] However, despite the co-occurrence of sleep problems and adverse changes in CVD risk profiles during midlife and the menopause transition, the cardiovascular implications of poor sleep specifically among midlife women are not well understood.

Carotid intima media thickness (IMT) is a subclinical CVD index measured via ultrasound that quantifies the thickness of the intimal and medial layers of the carotid artery.[20] Plaque is also quantified.[20] Both carotid IMT and plaque are predictive of later events, even among relatively low-risk populations,[20,21] and are particularly useful for investigating CVD risk among midlife women among whom clinical events are rare. Some work suggests that short objectively assessed sleep time or

poorer sleep quality may be related to higher IMT among select populations,[22–24] although findings have been mixed in community samples, particularly for women.[25] One study indicated that poorer subjective sleep quality and reports of early morning wakening among midlife women may be related to greater calcified plaque in the aorta.[26] Subjective and objective sleep indices correlate modestly, with some evidence suggesting that objective sleep duration may be particularly important for cardiovascular outcomes.[19] Investigation of relations between objectively and subjectively assessed sleep and the well-validated subclinical CVD marker of carotid IMT in midlife women is now warranted.

We tested the relation between sleep as assessed by actigraphy and questionnaire and subclinical CVD as assessed by carotid ultrasound among a cohort of 304 midlife women. We hypothesized that shorter actigraphic sleep time and poor subjective sleep quality would be associated with higher carotid IMT and plaque among midlife women after adjusting for traditional CVD risk factors. We carefully considered the role of sleep hot flashes (e.g., as a potential mediator or moderator) in sleep–subclinical CVD relations, given our prior work showing associations between hot flashes and IMT.[27] Finally, we considered additional covariates of endogenous estradiol concentrations and novel CVD risk factors (e.g., inflammatory markers, heart rate variability) in sleep–subclinical CVD relations, given evidence of their potential importance to sleep as well as CVD risk.[28,29]

METHODS

Study Sample

The study sample comprised 304 late perimenopausal (2–12 months amenorrhea) and postmenopausal (≥12 months amenorrhea)[30] nonsmoking women aged 40–60 years recruited for a study investigating relations between menopausal symptoms and CVD risk. By design, half of the women reported daily hot flashes or night sweats, and half reported no hot flashes or night sweats in the past 3 months. Women were recruited from the community via local advertisements, electronic and paper mailings, referrals from local clinics, and online message board postings. Exclusion criteria included current (past year) smoking, hysterectomy, and/or bilateral oophorectomy; history of heart disease, stroke, arrhythmia, ovarian/gynecological cancer, pheochromocytoma, pancreatic tumor, kidney failure, seizures, Parkinson's disease, and/or Raynaud's Phenomenon; endarterectomy; endometrial ablation; current pregnancy; or having used the following medications in the past 3 months: 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. Women who were undergoing dialysis or chemotherapy were also excluded.

Of the 304 women, 10 women were excluded due to missing carotid data (equipment failure: $n = 3$; carotid stent: $n = 1$; poor image: $n = 1$) or select blood marker data [Homeostatic Model Assessment (HOMA): $n = 3$, low-density lipoprotein cholesterol (LDL-C): $n = 2$]. Women who were shift workers ($n = 18$) or who were taking sleep medication (hypnotics, melatonin, over the counter sleep aids) during the protocol ($n = 14$) were excluded from the present report due to possible confounding. Women missing actigraphy data ($n = 6$) were excluded from models using actigraphy data. Therefore, 262 women were included in primary models using self-report sleep data and 256 women in actigraphy models.

Design and Procedures

After telephone and in-person screening procedures, participants underwent physical measurements and questionnaire completion; 3 days of ambulatory monitoring, including sleep measurement by actigraphy, hot flashes, and electrocardiography; and a carotid artery ultrasound. Procedures were approved by the University of Pittsburgh Institutional Review Board. Participants provided written informed consent.

Measures

Sleep

Women wore an Actiwatch 2 wrist actigraph unit on the wrist of the nondominant hand (Respironics, Inc., Murrysville, PA)[31] and completed a sleep diary[32] for 3 consecutive days. Actigraphy data were collected in 1-min epochs and analyzed with Philips Actiware v6.0.0 software, with a wake threshold of 40 and number of epochs of sleep/wake for sleep onset/offset of 10. Bedtime (time tried to go to sleep) and rise time (final wake time) were determined via sleep diary reports. TST = (difference between actigraphy-defined sleep onset and actigraphy-defined final wake time)−(actigraphy-defined wake after sleep onset, WASO) was our primary actigraphy-assessed variable of interest given its association with CVD risk.[19,25] WASO (minutes of wakefulness between actigraphy-defined sleep onset time and actigraphy-defined final wake time), sleep efficiency [percentage of time in bed scored as sleep, calculated as (TST/time in bed) × 100], and number of awakenings were also considered. Women completed the Pittsburgh Sleep Quality Index (PSQI), a widely used and well-validated measure of sleep quality that includes a total scale score and subscales (sleep duration, sleep disturbance, sleep latency, sleep efficiency, daytime dysfunction, use of sleep medications, and sleep quality).[33] Women also completed the Berlin Questionnaire, a validated inventory assessing sleep apnea symptoms including snoring.[34]

Subclinical CVD

Trained and certified sonographers at the University of Pittsburgh's Ultrasound Research Laboratory obtained bilateral carotid images via B-mode ultrasound using a Sonoline Antares (Siemens, Malvern, PA) high-resolution duplex scanner equipped with a VF10-5 transducer according to a standardized protocol.[35] Digitized images were obtained at end-diastole from 8 locations (4 locations each from the left and right carotid arteries): the near and far walls of the distal common carotid artery, the far walls of the carotid bulb, and the internal carotid artery. Images were read using semiautomated reading software.[36] Values were obtained by electronically tracing the lumen–intima interface and the media–adventitia interface across a 1-cm segment for each of these 8 segments. Average

and maximal values were recorded for each of the 8 locations; the mean of the average and maximal readings across the 8 locations comprised mean and maximal IMT, respectively. Reproducibility of IMT measures was excellent (intraclass correlation coefficient between sonographers ≥ 0.87, between readers = 0.92).

Carotid plaque was defined as a distinct focal area protruding into the vessel lumen ≥50% thicker than the adjacent IMT.[37] Sonographers assessed plaque in 5 carotid artery segments in the left and right side: proximal common, distal common (1 cm proximal to the carotid bulb), carotid bulb (the point in which the near and far walls of the common carotid are no longer parallel, extending to the flow divider), and internal and external carotid (beginning at the flow divider). For each segment, the degree of plaque was graded using the following criteria: grade 0 = no observable plaque; grade 1 = one small plaque (<30% of the vessel diameter); grade 2 = one medium plaque (30–50% of the vessel diameter) or multiple small plaques; grade 3 = one large plaque (> 50% of the vessel diameter) or multiple plaques with at least 1 medium plaque. The grades were summed across segments to create a plaque index, a measure of extent of plaque,[38] categorized as 0, 1, or ≥2 for analysis. Reliability of plaque index scoring between sonographers was κ = 0.78, demonstrating high reliability.

Hot Flashes

Hot flashes during wake and sleep were measured via both physiologic monitor (worn over 24 h) and electronic hot flash diary/event marker (carried over 3 days). The hot flash monitor was the VU-AMS (VU University Amsterdam, the Netherlands),[39,40] a portable ambulatory monitor that quantifies hot flashes via sternal skin conductance, a validated measure of hot flashes.[41,42] 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 continuously for 24 h, a monitoring duration that optimizes data quantity, data quality (electrode adherence degrades after 24 h), and participant burden (women must refrain from showering while wearing the monitor).[42] After 24 h, women removed the monitor and stored it in a provided case. For the remaining 2 days, participants reported their hot flashes via electronic diary and actigraph. After monitoring, hot flash data were downloaded, reviewed, and scored via UFI software (DPSv3.7; Morro Bay, CA) according to standard, validated methods[41–43] that have demonstrated reliability including the present laboratory (κ = 0.86).[44] Hot flashes were classified as occurring during sleep or wake according to sleep diary sleep onset and offset times. Hot flash rates were calculated as number of hot flashes/monitoring time and standardized to a 7-h and 17-h sleep and wake times for ease of interpretation.

Covariates

Height and weight were measured via a fixed stadiometer and a calibrated balance beam scale and body mass index calculated (in kilograms per square meter). Seated blood pressure (mean of the second and third of 3 measurements) was measured via a Dinamap device after 10-min rest. Demographics and medical history were assessed by standard instruments. Menopause status was obtained from reported menstrual bleeding patterns.[30] Depressive symptoms were assessed by the Center for Epidemiologic Studies Depression scale.[45] State/trait anxiety was measured via the Spielberger State Trait Anxiety Inventory.[46] Habitual physical activity was measured via the International Physical Activity Questionnaire.[47] All medications currently being used were documented at the outset of the study during the medical history interview and on sleep diary during ambulatory monitoring, and classified according to their indication (for blood pressure-lowering, lipid-lowering, diabetes, depression, anxiety). Phlebotomy was performed after a 12-h overnight fast. Glucose, triglycerides, and high-density lipoprotein cholesterol (HDL-C) were measured enzymatically (Vital Diagnostics, Lincoln, RI, USA). Total cholesterol was determined enzymatically and LDL-C calculated.[48] Insulin was measured via radioimmunoassay. HOMA, reflecting insulin resistance, was calculated.[49]

Additional Measures

High-frequency heart rate variability was calculated via standard methods[50] from electrocardiograph sampled via the VU-AMS via 3 Ag/Ag Cl electrodes in a standard 3-lead configuration. High-frequency heart rate variability indexes vagal influence on the heart, and vagal influences predominate at rest.[51] Heart rate variability was measured over both sleep and wake for 24 h. The electrocardiogram was sampled at 1000 Hz, and each R-wave marker was assessed for artifacts by an artifact detection algorithm (VU-AMS.5fs software) and verified by trained coders. Estimates of heart rate variability were conducted using VU-AMS software, estimated in 4-min intervals. Intervals with ≥10% ectopic beats were eliminated. The interbeat interval event series was resampled at 4 Hz excluding artifactual beats, interpolated, and detrended (convoluted with a smoothness prior matrix) to yield a stationary signal on which a discrete Fourier analysis was performed. High-frequency band cutoffs were 0.15–0.40 Hz.

C-reactive protein was measured using a high-sensitivity reagent set (Beckman Coulter, Brea, CA, USA), interleukin-6 with an R&D Systems (Minneapolis, MN, USA) high sensitivity enzyme-linked immunosorbant assay, and Fibrinogen activity via a modified Clauss method and Siemens (Newark, DE, USA) Multifibren U reagent. Factor VII clotting activity was assessed via standard clotting methods using Siemens Innovin thromboplastin reagent with Factor VII-deficient plasma (HRF, Raleigh, NC, USA), von Willebrand factor antigen using Diagnostica Stago's (Asnieres sur Seine, France) STA-Liatest reagent, and quantitative D-dimer using Diagnostica Stago's (Asnières, France) Asserachrom assay. 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]

Data Analysis

WASO, HOMA, triglycerides, estradiol, C-reactive protein, interleukin-6, and high-frequency heart rate variability values were natural log-transformed and sleep efficiency was inverse

log transformed for analysis. Associations between sleep variables and carotid outcomes were evaluated using linear and multinomial logistic regression. Sleep variables were considered as continuous variables in primary models and as categorical variables in secondary models (TST quartiled broadly according to the distribution; WASO and efficiency dichotomized at 30 min and 85%, respectively[53]; and PSQI dichotomized according to cutpoints[33] except where noted). Covariates for base models were selected based upon their association with the outcome at $p < .10$, with snoring forced into models as a marker of potential apnea. Covariates for expanded multivariable models were selected based upon their prior documented associations with subclinical CVD. Additional secondary models included covariates sleep hot flashes, inflammatory/hemostatic markers, high-frequency heart rate variability (24-h, sleep), anxiolytics, antidepressants, anxiety, habitual physical activity, habitual alcohol use, and estradiol levels considered separately in expanded multivariable models. 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 SAS v9.2 (SAS Institute, Cary, NC, USA). Models were 2-sided at $\alpha = 0.05$.

RESULTS

Participants were on average 54 years old, overweight, and normotensive. The majority of the sample was white and postmenopausal. The mean actigraphy-assessed TST was 371 min and median WASO was 42 min, and the mean PSQI score was 5.4 (Table 1). TST was inversely correlated with PSQI ($r = -0.20$, $p = .002$) and marginally positively correlated with WASO ($r = 0.12$, $p = .05$). The PSQI was not associated with WASO ($r = 0.08$, $p = .19$).

Shorter actigraphy-assessed TST was associated with higher odds of plaque in minimally adjusted models, and models remained significant with adjustment for multiple CVD risk factors, demographic factors, and depressive symptoms (Table 2, Figure 1). When considered as a continuous variable, shorter TST was not significantly related to IMT [mean IMT: $b(SE) = 0.007$ (0.006), $p = .21$; maximal IMT: $b(SE) = 0.013$ (0.009), $p = .14$; fully adjusted models]. However, when TST was categorized, there was some evidence of nonlinearity in relations between TST and IMT for mean IMT [≤300 min: $b(SE) = 0.03(0.02)$, $p = .20$; 301–360 min: $b(SE) = 0.03(0.01)$, $p = .02$; ≥420 min: $b(SE) = 0.02(0.02)$, $p = .30$, relative to 361–420 min, fully adjusted models; Figure 2], as well as for maximal IMT [≤300 min: $b(SE) = 0.05(0.03)$, $p = .12$; 301–360 min: $b(SE) = 0.05(0.02)$, $p = .01$; ≥420 min: $b(SE) = 0.03(0.02)$, $p = .28$, relative to 361–420 min, fully adjusted models]. WASO was not related to IMT [mean IMT: $b(SE) = -0.006$ (0.01), $p = .61$; fully adjusted models] or to plaque [plaque score ≥2: OR (95% CI) = 1.06 (0.52–2.15), $p = .68$; plaque score = 1: OR (95%CI) = 1.35 (0.69–2.64), $p = .38$, relative to no plaque, fully adjusted models].

In addition to actigraphically measured sleep, poorer overall subjective sleep quality as assessed by the PSQI was associated

Table 1—Sample characteristics.

N	256
Age, M (*SD*)	53.9 (4.1)
Race/ethnicity, *N* (%)	
White	183 (71.5)
Black	59 (23.0)
Other	14 (5.5)
Education, *N* (%)	
High school/some college/vocational	108 (42.2)
College	75 (29.3)
>College	73 (28.5)
Menopause stage, *N* (%)	
Perimenopausal	41 (16.0)
Postmenopausal	215 (84.0)
BMI, M (*SD*)	29.0 (6.5)
SBP, M (*SD*)	119.7 (14.3)
DBP, M (*SD*)	70.0 (9.2)
LDL, M (*SD*)	129.7 (33.8)
HDL, M (*SD*)	62.5 (14.7)
Triglycerides, Median (IQR)	95.0 (72.0, 128.0)
HOMA, Median (IQR)	2.7 (1.7, 3.2)
Women reporting hot flashes, *N* (%)	126 (49.2)
Number of physiologic overnight hot flashes, *M* (*SD*)‡	2 (2)
Medications, *N* (%)	
Antihypertensive	41 (16.0)
Antidiabetic	9 (3.5)
Lipid-lowering	33 (12.9)
Antidepressants	5 (2.0)
Anxiolytics	3 (1.2)
CESD, Median (IQR)	5.0 (2.0, 11.0)
Total sleep time (actigraphy), M (*SD*) min†	370.8 (61.7)
WASO (actigraphy), Median (IQR)†	42.33 (28.83, 56.50)
Sleep efficiency (actigraphy), Median (IQR) %†	85.26 (80.26, 88.81)
Number of awakenings (actigraphy), Median (IQR)†	18.00 (14.17, 23.33)
PSQI, Mean (*SD*)	5.4 (2.9)
Snoring, *N* (%) yes	117 (45.7)
Mean IMT, M (*SD*)	0.68 (0.10)
Maximal IMT, M (*SD*)	0.85 (0.15)
Adventitial diameter, M (*SD*)	6.97 (0.61)
Plaque, *N* (%)	
0	137 (53.5)
1	58 (22.7)
2+	61 (23.8)

†Average per night from 3 monitoring nights.
‡Sleep hot flash rate standardized to a 7-h night for interpretation.

Table 2—Association between actigraphy-assessed total sleep time and carotid plaque.

	Plaque score	
	OR (CI), 1	OR (CI), ≥ 2
Shorter total sleep time		
Model 1	0.92 (0.66–1.27)	1.48 (1.07–2.05)*
Model 2	0.95 (0.68–1.32)	1.58 (1.11–2.27)*

Model 1: Age, race, education, BMI, SBP, snoring.
Model 2: Age, race, education, BMI, SBP, DBP, HDL, LDL trig, HOMA, medication use (blood pressure-lowering, lipid-lowering, diabetes), snoring, CESD.
Total sleep time considered as a continuous variable; OR for every 60 min decrease in total sleep time.
*$p < .05$.

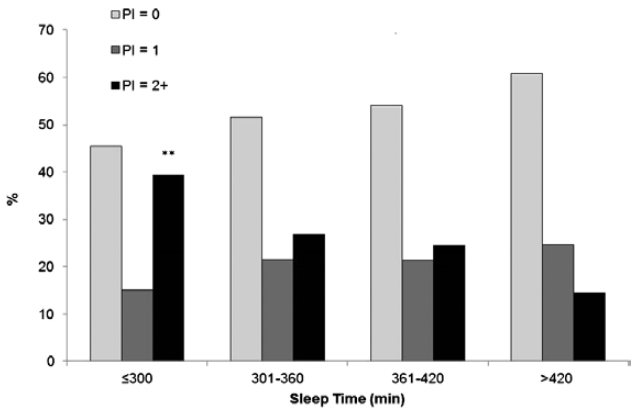

Figure 1—Percentage of women with degrees of carotid plaque by total sleep time. **$p < .01$, relative to >420 min, multivariable. Note: *Y* axis indicates percentage of women in each plaque index (PI) category, stratified by total sleep time.

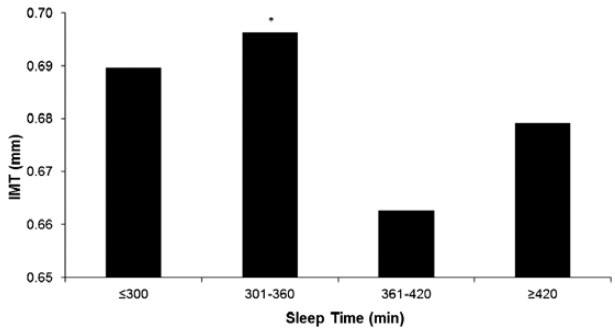

Figure 2—Mean IMT by total sleep time. *$p < .05$, relative to 361–420 min. Adjusted means, adjusted for age, race, education, BMI, SBP, DBP, HDL, LDL trig, HOMA, medication use (blood pressure-lowering, lipid-lowering, diabetes), snoring, and CESD.

with higher IMT and higher odds of plaque in minimally adjusted models (Table 3, Figure 3). Models remained significant with adjustment for additional CVD risk factors, demographic factors, and depressive symptoms. Consideration of PSQI scores dichotomized at > vs. ≤5 in relation to outcomes in multivariable models indicated that relative to women with PSQI scores ≤ 5, women with high PSQI scores (>5) had significantly higher plaque [plaque index 1: OR(95% CI) = 1.73(1.04–2.88), p = .03; plaque index 2: OR(95%CI) = 1.86(1.06–3.28), p = .03, relative to zero plaque] but not IMT [$b(SE)$ = 0.01(0.01), p = .32]. Examination of PSQI subscales indicated that associations were primarily observed for sleep quality, sleep duration, sleep disturbance, and daytime dysfunction (Table 4).

We considered the role of physiologically assessed sleep hot flashes. Inclusion of sleep hot flashes as a covariate did not alter findings. However, we observed an interaction between actigraphy-assessed TST and sleep hot flashes in relation to maximum IMT (p = .04); stratified analyses suggested a possible synergistic effect of shorter measured sleep time on maximum IMT among women with sleep hot flashes [with 2 or more sleep hot flashes/night: $b(SE)$ = 0.0004(0.0002), p = .09; <2 sleep hot flashes/night: $b(SE)$ = 0.00003(0.0002), p = .89]. In additional models, we excluded women with high Berlin scores (N = 96) and findings persisted (see Table S1 in supplemental material). We considered additional measures of sleep continuity, including sleep efficiency and number of awakenings as well as WASO considered as a categorical variable; none of these indices were significantly related to subclinical CVD (data not shown). We considered several additional covariates, further adjusting for estradiol concentrations, inflammatory and hemostatic markers, 24-h and sleep high-frequency heart rate variability, anxiolytics, antidepressants, anxiety, obesity, habitual physical activity, or habitual alcohol use in multivariable models; findings were unchanged (data not shown). We tested interactions between sleep variables and race/ethnicity; no interactions were significant.

DISCUSSION

Shorter actigraphy-assessed TST and poorer subjective sleep quality were associated with higher subclinical CVD among a large sample of midlife women transitioning through the menopause. These associations remained significant after adjustment for traditional and novel CVD risk factors. The present findings underscore that sleep characteristics during midlife and the menopause transition have implications for women's cardiovascular health.

Understanding relations between sleep and atherosclerosis in midlife women is critical. The menopause transition is a period of vulnerability for women's cardiovascular health.[3,4] Furthermore, poor sleep quality and reported sleep problems are prevalent during midlife in women.[54] Data on changes in sleep time with advancing menopause stage are more mixed.[7,9,10] In the present study, the median actigraphy-measured TST was approximately 6 h and WASO was 42 min, indicating objectively assessed short and disrupted sleep. The median PSQI indicated that approximately half of the sample had scores consistent with poor sleep quality. Notably, the Study of Women's Health Across the Nation (SWAN) Sleep Study showed similar sleep characteristics among midlife women.[8,54] Other prospective cohort studies indicate that a third or more of women report sleep problems during the menopause transition.[13,55]

Table 3—Association between PSQI and carotid IMT and plaque.

	Mean IMT	Max IMT	Plaque Score	
	B (*SE*)	B (*SE*)	OR (CI), 1	OR (CI), ≥2
PSQI				
Model 1	0.004 (0.002)*	0.008 (0.003)**	1.04 (0.93–1.17)	1.21 (1.08–1.34)***
Model 2	0.004 (0.002)*	0.009 (0.003)**	1.06 (0.93–1.21)	1.23 (1.09–1.40)***

Model 1: Age, race, education, BMI, SBP, snoring.
Model 2: Age, race, education, BMI, SBP, DBP, HDL, LDL trig, HOMA, medication use (blood pressure-lowering, lipid-lowering, diabetes), snoring, CESD.
PSQI considered as continuous variable, β and OR correspond to every 1-unit increase in PSQI score.
*$p < .05$, **$p < .01$, ***$p < .001$.

Table 4—Association between PSQI components and carotid IMT and plaque.

	Mean IMT	Max IMT	Plaque Score	
	B (*SE*)	B (*SE*)	OR (CI), 1	OR (CI), > = 2
Sleep quality	0.02 (0.009)†	0.03 (0.01)*	1.38 (0.83–2.27)	1.92 (1.14–3.23)*
Sleep duration	0.02 (0.007)*	0.03 (0.01)**	1.18 (0.77–1.81)	1.81 (1.18–2.79)**
Sleep disturbance	0.009 (0.01)	0.03 (0.02)	0.96 (0.50–1.84)	2.13 (1.11–4.06)*
Sleep latency	0.003 (0.007)	0.004 (0.01)	0.78 (0.50–1.20)	1.39 (0.93–2.08)
Sleep efficiency	0.003 (0.007)	0.003 (0.007)	1.21 (0.80–1.82)	1.39 (0.93–2.08)
Daytime dysfunction	0.02 (0.01)*	0.03 (0.02)*	1.80 (0.99–3.28)†	2.23 (1.20–4.15)*
Sleep medications	0.009 (0.009)	0.01 (0.01)	1.00 (0.60–1.67)	1.20 (0.75–1.93)

Covariates: age, race, education, BMI, SBP, DBP, HDL, LDL trig, HOMA, meds (BP, lipids, diabetes), snoring, CESD.
PSQI considered as continuous variable, β and OR correspond to every 1-unit increase in PSQI component score.
†$p < .10$; *$p < .05$, **$p < .01$.

Poorer sleep was associated with elevated atherosclerosis in the present study. Shorter actigraphic TST was associated with higher plaque and somewhat nonlinear associations with IMT, and poorer subjective sleep quality was associated with both higher IMT and plaque. Findings were independent of standard and novel CVD risk factors or symptoms of apnea. Prior work has provided evidence that shorter objectively measured sleep time may be related to higher IMT in specific populations such as the elderly,[22] police officers,[23] or diabetics.[24] In the Coronary Artery Risk Development in Young Adults (CARDIA) study, shorter sleep time was associated with coronary artery calcification[19] and among men only, higher IMT.[25] Broadly similar to the nonlinearities observed here, a large study of German adults found both long and short self-reported sleep duration associated with higher IMT.[56] However, these studies did not consider the menopause transition. The one study that has considered sleep among menopausal women and markers of atherosclerosis, the SWAN, provided indication that poorer subjective sleep quality and reports of early morning wakening may be related to greater aortic calcification.[26] Notably, sleep in that study was measured via self-report only, and the carotid ultrasound measures of subclinical CVD used in the present study are better suited to studying midlife women. Unlike measures of coronary calcification that have a high rate of zero readings among midlife women, IMT provides a continuous measure of wall thickness as well as measures of plaque that are demonstrated to be predictive of later events even among low-risk samples.[20,21]

Several additional findings deserve mention. We carefully considered the role of overnight hot flashes, assessed via physiologic monitor, important given difficulties in accurately reporting hot flashes occurring during sleep.[57] Hot flashes have been associated with CVD risk,[27] and women often report that hot flashes wake them up[58] (although poor sleep is common even in the absence of hot flashes[55]). Sleep hot flashes did not account for the observed associations. Alternatively, there was some initial suggestion that sleep hot flashes and poor sleep may have a synergistic relation with respect to atherosclerosis. Moreover, findings relating sleep characteristics to subclinical CVD were somewhat stronger for carotid plaque than for IMT. Notably, plaque is a more direct measure of atherosclerotic lesion development, whereas IMT may also reflect vascular adaptation to sustained hemodynamic changes (e.g., elevated blood pressure).[20] Future work should further investigate associations between sleep and plaque characteristics and stability. We examined both actigraphic and subjective sleep here, which capture slightly different aspects of sleep. The PSQI assesses sleep quality over a longer time period (a month) than our actigraphy protocol, and it is an aggregate measure, capturing

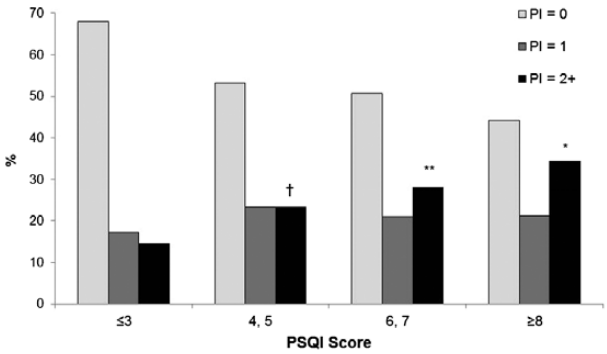

Figure 3—Percentage of women with levels of carotid plaque by PSQI score. †$p < .10$, *$p < .05$, **$p < .01$, relative to ≤3, multivariable. Note: *Y* axis indicates percentage of women in each plaque index (PI) category, stratified by PSQI score.

several dimensions of sleep including reported TST, providing an important representation of a woman's overall sleep characteristics. Although the PSQI is a self-report instrument and may be influenced by psychological characteristics associated with reporting poor sleep, none of the psychological characteristics here accounted for the observed findings.

The potential mechanisms that may link poorer sleep to atherosclerosis are many. We considered as covariates established and emerging CVD risk factors, such as blood pressure, obesity, physical activity, or alcohol use; measures of mood or anxiety; symptoms of apnea; 24-h heart rate variability; markers of inflammation or clotting; sleep hot flashes; and estradiol. We conducted sensitivity analyses excluding women with a clinical suspicion of sleep apnea; relationships persisted. Future work should consider additional possible mechanisms, such as the hypothalamic pituitary adrenal axis in sleep–atherosclerosis relations during the menopause transition.

Future work should address the limitations in the present study. Sleep was quantified via questionnaire and actigraphy assessed over 3 days. Although the use of actigraphy represents an advance over a reliance on self-report inventories, this protocol is shorter than other widely used protocols[59] and may not provide a full representation of a woman's sleep. Notably, a 3-day actigraphy protocol was successfully used in CARDIA and data from that protocol were linked to important health outcomes.[25] Furthermore, polysomnographic sleep indices were not available here. Future work should implement these measures to further understand the nature of sleep–IMT relations, with particular attention to sleep microarchitecture such as electrocephalography beta power and delta power due to their link to other markers of cardiometabolic risk.[60,61] Moreover, apnea symptoms were measured via a validated self-report inventory, reported snoring was carefully considered as a covariate, and women with high levels of reported apnea symptoms were excluded from secondary models, all with no change to study conclusions. However, apnea and other relevant sleep indices (e.g., periodic limb movements) should be physiologically quantified in future work. We did not inquire about history of poor sleep and therefore cannot make statements about the duration of poor sleep in relation to study outcomes. Self-reported bedtimes and wake-up times were reported via diary rather than via event marker, which may have added error to these reports. We cannot extrapolate these findings to women with longer sleep times (e.g., >9 h) due to their underrepresentation in this sample. Due to the observational and cross-sectional nature of this study, we cannot make any assertions about the directionality or causality of these relations, including any causal role of the menopausal factors in any poor sleep observed here. Finally, the sample consisted primarily of African American and non-Hispanic White women, and future work should extend this study to additional racial/ethnic groups.

This study had several strengths. It included a large, well-characterized sample of midlife women. Subclinical CVD was rigorously quantified via widely used and well-validated measures. Many potential mechanisms were measured and considered, including both traditional and novel CVD risk factors. Menopause-related factors, including estradiol and hot flashes, were assessed via state of the art methods rarely used in studies of sleep and health and were carefully considered here. Women transitioning through the menopause were studied, a relatively understudied group among whom sleep problems are prevalent and cardiovascular health can be changing markedly.

In summary, poorer sleep quality and shorter actigraphy-assessed sleep duration were associated with higher subclinical CVD among midlife women transitioning through the menopause. These associations were not explained by standard or novel risk factors, estradiol concentrations, or other menopausal symptoms such as sleep hot flashes. Midlife and the menopause transition is a critical window with respect to women's cardiovascular health, representing the years preceding the onset of clinical CVD events, and often a time characterized by atherosclerosis accumulation and worsening in critical CVD risk factors.[3,4] Sleep problems are also common during this time. These data challenge the assumption that midlife sleep problems are solely a troublesome menopausal symptom to be tolerated, with little implications for women's physical health. Future work should consider any cardiovascular benefit of treating midlife women's sleep problems as well as the role of sleep in the cardiovascular changes observed during the menopause transition.

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SUPPLEMENTARY MATERIAL

Supplementary Material is available at *SLEEP* online.

FINANCIAL SUPPORT

This work was supported by the National Institutes of Health, National Heart Lung and Blood Institute (R01HL105647 and K24123565 to Thurston). This work was also supported by the University of Pittsburgh Clinical and Translational Science Institute (NIH Grant UL1TR000005).

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication June, 2016
Submitted in final revised form October, 2016
Accepted for publication October, 2016
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ACKNOWLEDGMENTS

This work was performed at the University of Pittsburgh.

CONFLICTS OF INTEREST

RT and EB-M have received grant support from the NHLBI. DB is a consultant for Cerêve, Inc, Emmi Solutions, and Philips Respironics. DB has received grant support from the NIH and has intellectual property rights to the Pittsburgh Sleep Quality Index (PSQI). NS received a research grant from Bayer Inc and owns stock options in Menogenix. No other authors have conflicts of interest to disclose.

This work does not fall under the definition of a clinical trial and does not have a clinical trial name, URL, or registration number.