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Original Article

The association between sleep characteristics and prothrombotic markers in a population-based sample: Chicago Area Sleep Study

Zehra Tosur [a], David Green [a], Peter John De Chavez [b], Kristen L. Knutson [c], Jeffrey J. Goldberger [b], Phyllis Zee [b], Kiang Liu [b], Kwang-Youn Kim [b], Mercedes R. Carnethon [b,*]

[a] Division of Hematology/Oncology, Department of Medicine, Chicago, IL, USA
[b] Department of Preventive Medicine, Feinberg School of Medicine of Northwestern University, Chicago, IL, USA
[c] Department of Medicine, University of Chicago, Chicago, IL, USA

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ABSTRACT

Background and aim: Short sleep duration and poor quality sleep are associated with coronary heart disease (CHD) mortality; however, the underlying pathophysiologic process remains unclear. Sleep apnea may confound the association because of its relationship with formation of thrombi, the vascular occlusive process in CHD. We tested whether sleep duration and quality were associated with prothrombotic biomarkers in adults with a low probability of apnea.

Methods: We included adults aged 35–64 years recruited from the community and who had an apnea hypopnea index <15 after one night of screening ($n = 506$). Sleep duration and maintenance were determined from 7 days of wrist actigraphy; daytime sleepiness was estimated using the Epworth Sleepiness Scale. Factor VIII (FVIII), von Willebrand factor (vWF), thrombin antithrombin (TAT) complexes, and plasminogen activator inhibitor-1 (PAI-1) were measured in fasting blood.

Results: Sleep duration, maintenance, and daytime sleepiness were not associated with FVIII, vWf, or TAT. Sleep maintenance was modestly inversely associated with higher levels of log-transformed PAI-1 ($\beta = -0.07$, standard error (SE) = 0.03 per 4.8%, $p = 0.04$) following adjustment for demographic characteristics, cardiovascular risk factors, and body mass index (BMI).

Conclusions: Mild impairment in sleep was modestly associated with activation of coagulation; further study is needed to evaluate the role of fibrinolytic factors in sleep-mediated coronary thrombosis.

1. Introduction

Sleep characteristics that represent insufficient or poor quality sleep are associated with the development of coronary heart disease (CHD) and stroke in population studies. A number of pathophysiologic processes that are correlated with sleep and CHD [1] could account for the relationship including inflammation [2], autonomic dysfunction [3,4], endothelial dysfunction [5], and insulin resistance [6]. However, the contribution of the coagulation system is less well studied despite its plausibility as an alternative pathway.

Prior studies have reported an association between obstructive sleep apnea and prothrombotic markers including von Willebrand factor (vWF) and plasminogen activation inhibitor-1 (PAI-1) [7–12]. While additional studies are needed to explore the contribution of obstructive sleep apnea (OSA) to additional prothrombotic markers, there are even fewer studies to explore the pathophysiologic pathways linking shortened or poor-quality sleep with adverse cardiovascular outcomes in adults who are free from apnea. A large proportion of the population reports sleeping fewer than the recommended 7–9 h of sleep and who report poor-quality, non-restful sleep, but who do not have clinical sleep disorders. Prior studies indicate that those individuals are at increased risk for weight gain, developing diabetes and mortality [13–15]. However, few studies have explored potential pathophysiologic processes that could link shortened or poor-quality sleep in the absence of apnea with adverse outcomes. Consequently, the objective of our study is to test the hypothesis that impaired sleep represented by shortened sleep duration, lower sleep maintenance, and daytime sleepiness is associated with elevated prothrombotic factors (vWF, Factor VIII, thrombin antithrombin (TAT) and PAI-1) in adults who have a low probability of OSA.

* Corresponding author. Address: 680 N Lake Shore Drive, Suite 1400, Chicago, IL 60611, USA. Tel.: +1 (312) 503 4479; fax: +1 (312) 908 9588.
E-mail address: carnethon@northwestern.edu (M.R. Carnethon).

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2. Methods

2.1. Participants

Men and women aged 35–64 years old who lived in the Chicago, IL area or surrounding suburbs and self-reported their race/ethnicity as non-Hispanic white, African American, Hispanic or Asian were randomly identified using commercial telephone listings. During an initial telephone screening, potential participants were asked to self-report their height and weight and complete the Berlin Sleep Questionnaire [16] and a modified Snoring, Tiredness, Observed apnea, high blood Pressure-BMI, Age, Neck Circumference and Gender (STOP-BANG) [17] (modified to use self-reported neck circumference for men). Participants whose body mass index (BMI) was <35 kg/m^2 and had a low likelihood of sleep-disordered breathing based on a Berlin score <3 (women) or <2 (men), and a STOP-BANG <2 affirmative responses for women or <3 affirmative responses for men were invited to join the Chicago Area Sleep Study (CASS). Informed consent was obtained from all participants and all protocols were approved by the Northwestern University Institutional Review Board.

Among the 631 who had valid actigraphy data to determine sleep duration and maintenance, 602 completed the clinical examination. We excluded 19 participants for whom we could not determine their apnea–hypopnea index (AHI) and 50 participants with AHI >15 using the multi-channel Apnealink® Plus (ResMed Germany Inc., Fraunhoferstr, Germany), four participants who did not have prothrombotic markers available, and 20 participants who were using sleep medications or hypnotic antidepressants. After exclusions, there were 506 participants available for analysis.

2.2. Study design

CASS is a cross-sectional study. All participants attended two clinical examinations approximately 1 week apart. Women were scheduled to attend their first examination during the mid-follicular phase of their menstrual cycle. At the first examination, participants gave their consent and the procedures for wearing the Apnealink Plus® apnea screening device and the wrist actigraph were explained. Participants were given the equipment and a set of questionnaires to complete prior to the next examination that was scheduled to take place a minimum of 8 days later and a maximum of 14 days later. On the morning of the clinical examination, participants were instructed to arrive between 7:30 and 11 am after having fasted for a minimum of 12 h, and to bring all prescription medications and over-the-counter supplements that they were currently taking. All clinical measurements (ie, phlebotomy, blood pressure, anthropometry, heart rate, and rhythm) were conducted during a 3-h examination at the second visit.

2.3. Measurements

2.3.1. Sleep characteristics

Participants were eligible if they wore the Apnealink Plus® apnea screening device for at least 4 h on one night. The ApneaLink Plus® is a multichannel apnea screening device that has a nasal cannula to measure airflow, chest belt to detect respiratory effort, and pulse oximeter to measure oxygen saturation. Prior research has demonstrated a high sensitivity (91%) and specificity (95%) between the ApneaLink Plus® and laboratory polysomnography [18]. We restricted our primary analysis to the sample of participants whose AHI was <15. In a sensitivity analysis, we repeated the analyses in the subset of 361 participants with AHI <5.

Participants wore the Actiwatch™ 2 device (Phillips Respironics, Bend, OR, USA) on their wrists for 7 days. Participants kept a daily sleep log to record when they went to sleep and awoke each day and the times that they napped during the preceding 24-h interval. If the participants did not use the marker on the Actiwatch device to indicate time in bed, self-reports based on the Karolinska sleep diary were used to identify the bedtimes and wake times. Sleep duration was determined using software algorithms that quantified the absence of movement obtained during time in bed. Sleep maintenance was calculated as a percent of time between initial sleep onset and sleep end. Average sleep duration and maintenance were calculated for the 7 days. Our primary analysis evaluated sleep duration as a continuous variable; however, in a secondary analysis, we categorized sleep to compare participants who slept for <6 h or >8 h to participants who slept between 6 and 8 h. Daytime sleepiness was measured using the 8-item Epworth Sleepiness Scale [19]; higher scores (range 0–24) indicate greater sleepiness.

2.3.2. Prothrombotic markers

Phlebotomy was conducted between 7:30 and 11:30 am on the morning of the second examination from participants who were seated in phlebotomy chairs. Blood was drawn from participants into citrate vacutainer tubes and centrifuged at 3000 rpm at 4 °C for 20 min, and stored at −70 °C. vWF was assayed by an immunoturbidimetric method using antibody-coated beads (Liatest vWF Antigen Reagent). Assay calibration was performed with STA-VWF: Ag Calibrator (Cat No: 00520) (Diagnostica Stago, Parsippany, NJ, USA). FVIII coagulant activity was assayed in citrate plasma using a one-stage method. The percent activity in the sample plasma was determined from a standard curve generated with FVIII deficient plasma from George King Biomedical, Overland Park, Kansas. The assay was calibrated using the Unicalibrator from Diagnostica Stago (Parsippany, NJ, USA), standardized against World Health Organization (WHO) standards. TAT complexes were measured using the Enzygnost TAT micro ELISA kit (Siemens Healthcare Diagnostics Inc, Newark, DE, USA). TAT in the sample bind to thrombin antibodies attached to a microplate well, then peroxidase-conjugated antibodies to human antithrombin are added and color developed with a chromogen and hydrogen peroxide. The assay detection range for TAT is 2–60 μg/L, and in our relatively healthy population sample, 303 participants had TAT in this range. PAI-1 antigen was quantitated with the Trinilize PAI-1 antigen kit (Catalog #: T6003) from Tcoag Ireland Ltd, Co. Wicklow, Ireland. Quality control analysis of 10% of duplicate samples was carried out to determine the technical errors. The technical errors for samples that fell within the detectable range for vWf, Factor VIII, TAT, and PAI-1 were 7.7%, 11.6%, 14.7%, and 15.2%, respectively.

2.3.3. Covariates

Age, gender, and race/ethnicity were queried. Participants were asked to self-report any history of myocardial infarction, stroke, coronary bypass, or angioplasty. At the clinical examination, blood pressure was measured using an Omron automated cuff from participants in a seated position after 5 min of rest. Three measurements were collected and the final two were averaged. Hypertension was defined if participants had systolic blood pressure >140, diastolic blood pressure >90, or self-reported using antihypertensive medications. Height and weight were measured in light examination clothes and no shoes. BMI was calculated as weight in kilograms divided by the height in meters squared. Fasting glucose was determined from plasma using spectrophotometry. Whole blood was assayed for determination of hemoglobin A1c using an immunoturbidimetric assay. Diabetes status was determined if fasting glucose >126 mg/dL, or hemoglobin A1c >6.5%, or if participants reported taking diabetes control medications [20]. Smoking status (current, former, never) was queried.

2.4. Statistical analyses

The distribution of sample characteristics and sleep indices was calculated for the total sample. Means and standard deviations (SDs) were presented for continuous variables and proportions were calculated for categorical variables. The mean, SD, median, and interquartile range and quintile cutpoints were calculated for each of the prothrombotic markers. Because the markers of thrombosis were right skewed and not normally distributed, we log-transformed each index prior to conducting linear regression analyses. We fit logistic regression models to test the association of each sleep index (the independent variable) with the odds of having elevated FVIII, vWf, TAT or PAI-1 (dependent variables) as represented by values in the uppermost quintile. Parameter estimates and standard errors (SEs; linear regression models) or odds ratios and 95% confidence intervals (logistic models) were calculated per SD higher sleep index. To investigate the previously reported U-shaped association of sleep with cardiovascular outcomes, we categorized sleep duration into short (<6 h), normal (6–8 h), or long (>8 h) and repeated our analyses. Both the linear and logistic regression models were conducted unadjusted, adjusted for age, race, and gender (Model 1) and adjusted additionally for hypertension, diabetes, self-reported CHD and BMI (Model 2). We carried out a series of secondary analyses. First, we restricted the sample to participants whose AHI was <5 and repeated all analyses. Next, we excluded participants who reported shift work (work start times after 5 pm) and repeated all analyses. All analyses were carried out using Statistical Analysis Software version 9.3 (SAS Institute, Cary, NC, USA). Statistical significance was determined at alpha = 0.05; however, because we evaluated the association between multiple sleep measures and each outcome, we additionally evaluated whether statistical significance was achieved according to a Bonferroni-corrected criterion for statistical significance that took into account the three independent variables. The Bonferroni corrected cutpoint for statistical significance was alpha = 0.05/3 = 0.017.

3. Results

On average, participants were 48.1 years old (SD = 8.2) and 40% were men. Race/ethnicity was fairly evenly distributed with a slightly higher proportion of black and white participants, 31.4% and 25.9%, respectively than Asian (21.9%) and Hispanic (20.9%). Mean BMI in the cohort was 26.4 kg/m^2 (SD = 4.6), 16.8% had hypertension, and 5.5% had diabetes (Table 1). The 7-day average sleep duration was 7 h (SD = 1.1), sleep maintenance was 89.8% (SD = 4.8%), and the Epworth Sleepiness Scale score was 6.9 (SD = 4.1). The proportion of participants who slept for <6, 6–8, and >8 h/night were 16.2%, 70.3%, and 13.5%, respectively.

The distribution of prothrombotic markers is reported in Table 2. None of the markers is normally distributed; rather, each is right-skewed with a preponderance of low values. The uppermost quintile for Factor VIII, vWF, TAT, and PAI-1 is 134 U/ml, 156 U/ml, 4.0223 μg/L, and 32.1 μg/L, respectively. Tables 3 and 4 describe the association of sleep measures with each of the prothrombotic markers modeled as log-transformed continuous variables (Table 3) or as categorically elevated (Table 4). There was no association between sleep duration and daytime sleepiness with any of the prothrombotic markers. Analyses comparing short sleepers (<6 h) or long sleepers (>8 h/night) to participants in the middle category (6–8 h) were equally null. Sleep maintenance was the only sleep measure to suggest modest associations with log-transformed prothrombotic factors. In unadjusted models, each 4.8% higher sleep maintenance was associated with significantly lower log-transformed vWf ($\beta = -0.011$, SE = 0.02) and PAI-1 ($\beta = -0.117$, SE = 0.04). Following statistical adjustment for demographic characteristics, cardiovascular risk factors, and BMI (Model 2) the only significant relationship that remained was between sleep maintenance and PAI-1 ($\beta = -0.069$, SE = 0.033). Identical patterns were observed for the association of sleep maintenance with categorically elevated vWF and PAI-1 whereby the statistically significant association with elevated vWF attenuated following statistical adjustment but the relationship of sleep maintenance with elevated PAI-1 remained significant. After correcting for multiple testing (alpha = 0.017), the fully adjusted association between sleep maintenance and log-transformed PAI-1 did not achieve statistical significance. Findings were similar when we restricted the analysis to the subset of 361 participants whose AHI was <5 (data not shown).

Table 1
Distribution of demographic, clinical and sleep characteristics (n = 506).

	Mean (SD)	Number (%)
Demographic characteristics		
Age, Years	47.7 (8.2)	
Race, %		
Black		155 (31.4%)
Asian		108 (21.9%)
Hispanic		103 (20.9%)
White		128 (25.9%)
Male gender, n (%) male		203 (40.2%)
Clinical characteristics		
Systolic blood pressure, mmHg	115.3 (14.3)	
Diastolic blood pressure, mmHg	71.6 (10.4)	
Hypertension, n (%)		85 (16.8%)
Fasting glucose, mg/dL	91.9 (17.4)	
Diabetes, n (%)		28 (5.5%)
Total cholesterol, mg/dL	195.4 (37.7)	
HDL cholesterol, mg/dL	59.5 (16.6)	
LDL, mg/dL	113.3 (33.9)	
Triglycerides, mg/dL	114.8 (73.2)	
Body mass index, kg/m^2	26.4 (4.6)	
Prevalent CHD, n (%)		9 (1.8%)
Sleep characteristics		
Sleep duration, hours	7.00 (1.07)	
Sleep duration <6 h		82 (16.2%)
Sleep duration 6 to <8 h		355 (70.3%)
Sleep duration >8 h		68 (13.5%)
Sleep maintenance, n (%)	89.8 (4.8)	
Epworth sleepiness score, units	6.92 (4.11)	

4. Discussion

In a population-based sample of adults with a low probability of apnea, we observed an inverse association between sleep maintenance, an estimate of sleep quality, and PAI-1 that was independent of demographic characteristics and other cardiovascular disease risk factors. Neither sleep duration nor daytime sleepiness was associated with PAI-1 or any other prothrombotic markers. Our findings differ from those observed comparing participants with apnea to those without [21–23], which describe multiple thrombotic processes that are influenced by sleep.

In the only other population-based observational study to investigate the relationship between sleep duration and thrombosis, there was an association between sleep duration and vWf that varied by gender. The Whitehall II Study examined the relationship between sleep duration and vWF in 6400 London civil service employees and reported that VWF levels were significantly higher in men who slept either less or more than 7 h per night as compared with those who slept for 7 h per night [9]. Among women, higher vWF was observed only with sleep duration $\geqslant$8 h. Our findings may have differed because we attempted to exclude participants who had apnea, which may have contributed to the shortened sleep duration. Additionally, in contrast to the self-reported

Table 2
Distribution of prothrombotic markers in the sample.

	Range (min, max)	Median (Interquartile range)	Mean (SD)
Factor VIII (U/ml)	19, 305	101 (45)	106.5 (41.5)
Von Willebrand factor (U/ml)	33, 420	112.5 (60)	120.9 (51.1)
Thrombin antithrombin complex (μg/L)[a]	2, 21.7	3.35 (1.44)	3.76 (2.42)
Plasminogen activation inhibitor-1 (μg/L)	1.94, 182.00	16.79 (17.65)	23.0 (22.0)

[a] $N = 303$.

Table 3
Association of sleep characteristics with log-transformed prothrombotic factors.

	Log FVIII		Log vWf		Log TAT		Log PAI-1	
	β (SE)	P	β (SE)	P	β (SE)	P	β (SE)	P
Unadjusted								
Sleep duration (per 1.1 h)	−0.021 (0.018)	0.23	−0.029 (0.018)	0.10	−0.019 (0.021)	0.37	0.039 (0.036)	0.27
Sleep maintenance (per 4.8%)	−0.002 (0.004)	0.56	−0.011 (0.021)	<0.01	−0.011 (0.021)	0.62	−0.117 (0.035)	<0.01
Daytime sleepiness (per 4.1)	0.001 (0.017)	0.96	0.010 (0.006)	0.51	0.010 (0.006)	0.08	−0.010 (0.035)	0.78
Model 1								
Sleep duration (per 1.1 h)	−0.025 (0.018)	0.15	−0.029 (0.018)	0.10	−0.013 (0.023)	0.56	0.040 (0.036)	0.26
Sleep maintenance (per 4.8%)	0.008 (0.018)	0.65	−0.030 (0.018)	0.09	0.004 (0.022)	0.87	−0.092 (0.036)	0.01
Daytime sleepiness (per 4.1)	−0.001 (0.017)	0.95	0.007 (0.017)	0.69	0.038 (0.023)	0.11	−0.022 (0.035)	0.52
Model 2								
Sleep duration (per 1.1 h)	−0.023 (0.018)	0.20	−0.028 (0.018)	0.12	−0.011 (0.023)	0.64	0.052 (0.032)	0.10
Sleep maintenance (per 4.8%)	−0.002 (0.018)	0.91	−0.032 (0.018)	0.08	0.008 (0.023)	0.72	−0.069 (0.033)	0.04
Daytime sleepiness (per 4.1)	−0.010 (0.017)	0.56	0.001 (0.018)	0.97	0.039 (0.023)	0.10	−0.040 (0.031)	0.20

Model 1: Adjusted for age, race, gender and start time for the blood draw.
Model 2: Model 1 + smoking status, hypertension, diabetes, coronary heart disease and BMI.

Table 4
Association of sleep characteristics with elevated prothrombotic factors.[a]

	Factor VIII		vWF		TAT		PAI-1	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Unadjusted								
Sleep duration (per 1.1)	0.97	(0.78, 1.21)	0.82	(0.67, 1.02)	0.96	(0.73, 1.26)	1.16	(0.92, 1.46)
Sleep maintenance (per 4.8%)	0.94	(0.76, 1.16)	0.80	(0.66, 0.99)	0.88	(0.68, 1.14)	0.76	(0.62, 0.93)
Daytime sleepiness (per 4.1)	0.94	(0.75, 1.18)	1.06	(0.85, 1.32)	1.32	(1.00, 1.74)	0.93	(0.74, 1.16)
Model 1								
Sleep duration (per 1.07)	0.97	(0.77, 1.22)	0.81	(0.65, 1.02)	1.02	(0.76, 1.37)	1.15	(0.91, 1.47)
Sleep maintenance (per 4.8%)	1.09	(0.86, 1.39)	0.98	(0.78, 1.23)	0.97	(0.74, 1.28)	0.78	(0.63, 0.97)
Daytime sleepiness (per 4.1)	0.92	(0.73, 1.16)	1.03	(0.81, 1.29)	1.32	(0.99, 1.76)	0.91	(0.72, 1.15)
Model 2								
Sleep duration (per 1.1)	0.97	(0.76, 1.23)	0.82	(0.65, 1.03)	1.02	(0.76, 1.38)	1.21	(0.94, 1.57)
Sleep maintenance (per 4.8%)	1.02	(0.80, 1.31)	0.94	(0.73, 1.20)	0.99	(0.74, 1.31)	0.81	(0.63, 1.03)
Daytime sleepiness (per 4.1)	0.86	(0.68, 1.10)	0.99	(0.78, 1.25)	1.32	(0.98, 1.76)	0.87	(0.68, 1.12)

Model 1: Adjusted for age, race, gender and start time for the blood draw.
Model 2: Model 1 + smoking status, hypertension, diabetes, coronary heart disease and BMI.
[a] Prothrombotic markers in the uppermost quintile. Factor VIII >134 U/ml; von Willebrand factor (vWf) >156 U/ml; thrombin antithrombin (TAT) complex >4.23 μg/L; and plasminogen activation inhibitor-1 (PAI-1) >32.1 μg/L.

sleep duration that was used in Whitehall, we relied on objectively determined sleep duration and efficiency which would have led to greater precision estimating the exposure.

Hemostasis and the formation of thrombosis (ie, blood clots) are commonly initiated by injury to the endothelium which can arise in response to CHD risk factors such as hypertension, diabetes, and cigarette smoking. Following endothelial damage, vWF is released and mediates the binding of platelets to the vessel wall. Clotting factor VIII (FVIII) is activated and participates in the formation of thrombin. Antithrombin binds thrombin and the measurement of TAT complexes provides an indirect assessment of intravascular thrombin generation. The final stage of hemostasis occurs when fibrin is formed and undergoes lysis by plasmin. Plasmin generation is inhibited by PAI-1. Our participants whose values fell in the uppermost quintile of Factor VIII, vWF, TAT, and PAI-1 had values that would be considered "abnormal" as compared with published reference ranges in the population [24–27]. There is some evidence that the prothrombotic process is relevant to the development of CHD in the setting of OSA. Elevated vWF [21] and TAT [22,23] are observed in patients with OSA, and intervention studies demonstrate that treating OSA with continuous positive airway pressure can lower FVIII levels [28].

The only significant finding we observed was between sleep maintenance and PAI-1. Recent studies describe circadian variability in PAI-1 whereby levels peak in the early morning [5,29], possibly contributing to excess morning peak in cardiovascular events. In several studies, PAI-1 was higher in patients with moderate-to-severe OSA (AHI >10 or 15) as compared with levels in

adults free from OSA [7,10,12,30,31]. In a study of perimenopausal women from the Study of Women's Health across the Nation (SWAN), PAI-1 was significantly associated with AHI but not sleep duration [8]. Similarly, there was no association between self-reported sleep duration and PAI-1 in a sample of 183 adolescents [32]. In the Cleveland Family Study, there was a threshold effect between AHI and PAI-1 whereby levels of PAI-1 were 12% higher per 5-unit higher AHI until an AHI of 15. However, there was no association between PAI-1 and AHI when AHI was >15 [33].

We observed a modest inverse association of sleep maintenance with PAI-1 that persisted following statistical adjustment for demographic and clinical characteristics as well as health behaviors. The relatively modest association between sleep maintenance and PAI-1 could be attributable to chance given the number of statistical tests that we performed. Once we used a Bonferroni-corrected p value to determine statistical significance ($p < 0.017$), the relationship was no longer significant in a fully adjusted model and so our observation of significance could be attributable to chance based on multiple testing. In stepwise modeling, we observed that the addition of smoking status had the greatest influence on attenuating the relationship of sleep maintenance and PAI-1. As a result, the clinical significance of the strength of association is unclear. In a prospective study, the ARIC investigators reported that persons developing CHD had 31% higher levels of PAI-1, after multivariable adjustment [34]. Although our findings of no association between sleep duration and PAI-1 are consistent with prior studies, it was unexpected that sleep maintenance was associated with PAI. It is possible that individual variation in sleep need makes sleep duration a less accurate representation of the physiologic stress imposed by inadequate sleep. Rather, a higher sleep maintenance, which represents more time during the sleep interval spent sleeping, may be the most beneficial metric of healthy sleep.

4.1. Strengths and limitations

With two exceptions, the Study of Women across the Nation (SWAN) [8] and the Whitehall II study [9], prior studies to test the relationship of sleep with prothrombotic markers have been carried out in small clinical studies. The benefit of having randomly selected men and women from the population rather than studying patients or volunteers, is that our findings are generalizable to adults who have a range of health that may be unrelated to the health behaviors and diseases we wish to study. Unlike both SWAN and Whitehall II, the CASS stratified our enrollment so that we could study approximately equal numbers of men and women of white, black, Hispanic, and Asian race/ethnicity. Additionally, the objective of the CASS study was to identify the subclinical cardiovascular and metabolic disease process in adults who are free from apnea. Unlike prior studies that rely on a self-reported diagnosis of apnea, we screened potential participants to determine apnea risk, and then among those with a low likelihood of apnea we conducted overnight apnea screening. Consequently, our study is the first to be able to describe the associations between sleep characteristics in adults with a low likelihood of disorders with subclinical disease process. Another strength of our study is that we used wrist actigraphy to estimate sleep duration and maintenance objectively, which reduces the measurement error associated with self-report [35].

Our findings must be interpreted in light of some limitations. Participants in our study were generally healthy and middle-aged. Consequently, the prothrombotic markers were relatively low – except in the uppermost quintile. If adults with multiple cardiovascular and metabolic comorbidities had been included, shorter sleep duration may have interacted with other factors to promote thrombosis. However, the prevalence of both hypertension and diabetes in our sample, 16.8% and 5.5%, respectively, is comparable with other population-based estimates of adults aged 35–64. There were relatively few (16%) participants who had measured sleep duration that averaged <6 h/night over 7 days. It is possible that the prothrombotic process is only triggered by shorter sleep averages. Alternatively, it is equally plausible that adults can acclimate to shorter sleep over time and that only acute changes in sleep duration would trigger an inflammatory or prothrombotic process. Because we only captured 1 week of sleep from our participants, we do not know whether this week of sleep is representative of their regular sleep patterns. We additionally did not measure each individual's circadian rhythm and so while we assume the typical morning peak of some prothrombotic markers, this may not be relevant to individuals whose circadian rhythms do not follow a typical 24-h pattern. Finally, it may be possible that the prothrombotic factors that we selected for study – FVIII, vWF, TAT, and PAI-1 – might not represent the thrombotic constituents most affected by short sleep. However, we chose these factors because several published reports suggested that they might be affected by OSA [8,9,11,36].

In conclusion, while prothrombotic markers are elevated in the presence of OSA, short sleep in the absence of apnea was not associated with alterations in selected prothrombotic factors. PAI-1, a thrombotic marker with a significant circadian variability, was the only factor associated with sleep maintenance, a measure of sleep quality. Additional associations such as interactions between the sociodemographic, clinical, and behavioral covariates and prothrombotic markers may emerge in larger cross-sectional studies and longitudinal studies.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2014.04.005.

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