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Original Article

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

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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.

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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.