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Association of Sleep Duration and Quality With Subclinical Atherosclerosis

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ABSTRACT

BACKGROUND Sleep duration and quality have been associated with increased cardiovascular risk. However, large studies linking objectively measured sleep and subclinical atherosclerosis assessed in multiple vascular sites are lacking.

OBJECTIVES The purpose of this study was to evaluate the association of actigraphy-measured sleep parameters with subclinical atherosclerosis in an asymptomatic middle-aged population, and investigate interactions among sleep, conventional risk factors, psychosocial factors, dietary habits, and inflammation.

METHODS Seven-day actigraphic recording was performed in 3,974 participants (age 45.8 ± 4.3 years; 62.6% men) from the PESA (Progression of Early Subclinical Atherosclerosis) study. Four groups were defined: very short sleep duration <6 h, short sleep duration 6 to 7 h, reference sleep duration 7 to 8 h, and long sleep duration >8 h. Sleep fragmentation index was defined as the sum of the movement index and fragmentation index. Carotid and femoral 3-dimensional vascular ultrasound and cardiac computed tomography were performed to quantify noncoronary atherosclerosis and coronary calcification.

RESULTS When adjusted for conventional risk factors, very short sleep duration was independently associated with a higher atherosclerotic burden with 3-dimensional vascular ultrasound compared to the reference group (odds ratio: 1.27; 95% confidence interval: 1.06 to 1.52; p = 0.008). Participants within the highest quintile of sleep fragmentation presented a higher prevalence of multiple affected noncoronary territories (odds ratio: 1.34; 95% confidence interval: 1.09 to 1.64; p = 0.006). No differences were observed regarding coronary artery calcification score in the different sleep groups.

CONCLUSIONS Lower sleeping times and fragmented sleep are independently associated with an increased risk of subclinical multiterritory atherosclerosis. These results highlight the importance of healthy sleep habits for the prevention of cardiovascular disease. (J Am Coll Cardiol 2019;73:134-44) © 2019 Published by Elsevier on behalf of the American College of Cardiology Foundation.

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Sleep is an essential physiological process that protects our physical and mental health. Sleep deficiency is highly prevalent in Western societies, and epidemiological studies suggest that not only short but also long sleep duration (LSD) is related to an increased cardiovascular risk (1,2).

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Several studies and meta-analyses have reported associations between short sleep duration (SSD) and hypertension (3,4), with some showing a relationship with incident hypertension in subjects <65 years of age (4,5). No such association has been found with LSD (5). Recent meta-analyses have shown a 30% increased risk of diabetes mellitus among subjects sleeping <5 to 6 h/day, as well as in those who sleep >8 h/day (6). In addition, SSD has been reported to influence food intake and obesity (7).

Although sleep quality and duration have been associated with the risk of coronary heart disease, stroke (1), and subclinical atherosclerosis (8), most studies rely on self-reported questionnaires of sleep evaluation (8,9). The value of previous actigraphy-based studies evaluating atherosclerotic burden is limited because these were mostly small studies (10–12), and they focused on patients with sleep disorders, such as obstructive sleep apnea (OSA) (13,14). Previous studies relying on objectively-assessed sleep have shown that shorter sleep duration is associated with greater carotid intima-media thickness in men (15), and longer sleep duration is associated with a lower coronary calcification incidence, which is related to subclinical atherosclerosis (16). However, studies using newer and more reliable imaging techniques for measuring atherosclerosis are lacking. Moreover, the association of multiterritory atherosclerosis and sleep has not been yet assessed.

The aim of this study was to evaluate the association between actigraphy-measured sleep parameters and subclinical atherosclerosis, investigating possible interactions between sleep parameters, risk factors, dietary habits, and inflammatory markers.

METHODS

STUDY POPULATION. PESA-CNIC (Progression of Early Subclinical Atherosclerosis-Centro Nacional de Investigaciones Cardiovasculares)-Santander is an observational prospective cohort study that recruited 4,184 male and female employees of Santander Bank in Madrid from 40 to 54 years of age (17). All participants were free of known cardiovascular disease (CVD). The baseline visit included a fasting blood test, urine sample, and a 12-lead electrocardiogram. Patients with a history of OSA at baseline (n = 77) and those without actigraphic recording (n = 133) were excluded from the study. The final sample available for this analysis consisted of 3,974 participants. Of those, 3,804 were examined at baseline by 3-dimensional (3D) vascular ultrasound (VUS) (170 were excluded due to incomplete 3D VUS studies and incomplete clinical data necessary for the adjusted models) and 3,899 with noncontrast cardiac computed tomography (CT) (75 were excluded because of incomplete clinical data necessary for the adjusted models).

ASSESSMENT OF CVD RISK FACTORS, METABOLIC SYNDROME, AND DIETARY INTAKE. The participants' medical history, traditional CVD risk factors, lifestyle features (18), and physical examination including anthropometric characteristics were recorded. Obesity was defined as a body mass index (BMI) ≥30 kg/m^2. Metabolic syndrome was defined according to the National Cholesterol Education Program Adult Treatment Panel III criteria (19), which require 3 or more of the following characteristics: 1) abdominal obesity, defined as a waist circumference in men ≥102 cm and women ≥88 cm; 2) serum triglycerides ≥150 mg/dl or drug treatment for elevated triglycerides; 3) serum high-density lipoprotein (HDL) cholesterol <40 mg/dl in men and <50 mg/dl in women or drug treatment for low HDL cholesterol; 4) blood pressure ≥130/85 mm Hg or drug treatment for elevated blood pressure; and 5) fasting plasma glucose (FPG) ≥100 mg/dl or drug treatment for high blood glucose. The Framingham 10-year and 30-year scores, as well as the Fuster-BEWAT (20) score, were calculated in all study participants. Additionally, to avoid the potential confounding factor of underdiagnosed OSA, a modified STOP-BANG (Snoring, Tired, Observed apnea, high blood Pressure, BMI >35 kg/m^2, Age >50, Neck circumference >43 cm in males and >41 cm in

ABBREVIATIONS AND ACRONYMS

3D = 3-dimensional
CT = computed tomography
LSD = long sleep duration
RSD = reference sleep duration
SFI = sleep fragmentation index
SSD = short sleep duration
VSSD = very short sleep duration
VUS = vascular ultrasound

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females, and male Gender) questionnaire score (mSTOP-BANG) was calculated and results were adjusted for this variable. The STOP-BANG questionnaire evaluates the risk of sleep apnea and has been proved to be a practical tool to screen for OSA (21). The clinical data from the PESA study included all of the necessary parameters to calculate the STOP-BANG score except for the neck circumference, and therefore the results of an mSTOP-BANG score were incorporated into our study.

All participants underwent a survey to complete the computerized dietary history adapted to the Spanish population, which was initially developed and validated in the EPIC-Spain study (22,23). The survey is based on a computer application and is structured according to the episodes of intake throughout the day (breakfast, midmorning, lunch, snack, dinner, and ingestion between meals) (24,25). Once the survey was completed, the software provided information on foods consumed, caloric intake, macronutrient and micronutrient intake, and different forms of food preparation, as well as specific eating habits. Regarding caffeinated drinks, participants were asked to report their daily intake in grams including coffee, tea, cola drinks, and energy drinks. Assuming an approximate density of 1 g/cm^3, results were converted to milliliters.

ASSESSMENT OF QUANTITY AND QUALITY OF SLEEP. Actigraphic and self-reported sleep durations were first analyzed as continuous variables and then divided into multiple categories to achieve groups of adequate sample sizes to reflect the possible nonlinear (U- or J-shaped) associations between sleep duration and risk outcomes. The quantity of sleep was assessed by triaxial accelerometry, using Acti Trainers accelerometers (Actigraph, Pensacola, Florida) placed on the participant's waist for 7 days. Based on the last scientific statement from the American Heart Association regarding the impact of sleep duration on cardiometabolic health, a sleep duration of 7 to 8 h was considered normal and participants within that range were considered as the reference sleep duration (RSD) group (26). The remaining groups included participants with very short sleep duration (VSSD) (<6 h), short sleep duration (SSD) (6 to 7 h), and long sleep duration (LSD) (>8 h).

Sleep quality was assessed by the total sleep Fragmentation Index (SFI), which is defined as the sum of the movement index (MI) and the fragmentation index (FI). MI is the percentage of epochs with y-axis counts >0 in the sleep period. FI is the percentage of 1-min periods of sleep versus all periods of sleep during the sleep period (27). Study participants were divided into quintiles according to sleep fragmentation and those with less fragmented sleep (first quintile) were considered to be the reference group. Additionally, participants completed the Sleep Habits Questionnaire, which was developed and validated by the Sleep Heart Health Study (28).

PSYCHOSOCIAL EVALUATION. The presence of depressive symptoms was evaluated by the Center for Epidemiological Studies-Depression (CES-D) scale. It has been translated and validated in the Spanish population (29), and has demonstrated high sensitivity and specificity for the identification of depressive symptoms in epidemiological studies. Participants also completed the Perceived Stress Scale (PSS) (30), which is widely used for measuring nonspecific perceived stress.

ASSESSMENT OF SUBCLINICAL ATHEROSCLEROSIS. PESA participants underwent 3D VUS studies using a volumetric-linear array transducer to evaluate plaque burden in the bilateral carotid and femoral arteries. As there is currently no standard definition for plaque presence using 3D VUS, noncoronary atherosclerosis was defined as plaque presence using the Manheim criteria for 2-dimensional VUS (31), and the number of affected territories (1 to 4) was also recorded. Cumulative plaque volume (burden, in mm^3) was quantified and divided into tertiles to classify atherosclerosis as mild, moderate, or severe (32). This 3D VUS method has already proven to be accurate measuring plaque volumes in vitro and in vivo (33). Moreover, atherosclerosis assessed by 3D VUS in the PESA cohort correlates with classic cardiovascular risk factors, especially for femoral arteries (32). A 16-slice CT scan was used to quantify the Agatston coronary calcium score (CACS), which was categorized as 0, <1, 1 to 100, 101 to 400, and >400 (34).

All performed imaging tests were blind, and the Centro Nacional de Investigaciones Cardiovasculares conducted the analysis.

ASSESSMENT OF INFLAMMATORY BIOMARKERS. The assessed inflammatory biomarkers included neutrophil count, P selectin, high-sensitivity C-reactive protein (hs-CRP), and vascular cell adhesion molecule (VCAM).

STATISTICAL ANALYSIS. Statistical analyses were performed with SPSS software version 21.0 (IBM, Armonk, New York). The population baseline characteristics of the study are presented as percentages for categorical variables and as the mean and SD for continuous variables. Bonferroni (analysis of variance with multiple testing correction) was used for continuous variables, including p for trend values for the general comparison of groups and specific

TABLE 1 Baseline Characteristics and Sleep Duration Measured by Actigraph

Total Sleep Time (Actigraph)	Total	VSSD <6 h	SSD 6 to <7 h	RSD 7 to <8 h (Ref)	LSD ≥8 h	p Value*
Number of participants	3,974 (100.0)	1,071 (27.0)	1,521 (38.3)	1,222 (30.7)	160 (4.0)	
Age, yrs	45.8 ± 4.3	46.6 ± 4.3†	45.8 ± 4.4†	45.1 ± 4.0	44.5 ± 4.0	**<0.001**
Men	62.6	74.0	65.2	52.0	43.1	**<0.001**
Smoking status						**0.02**
Never	39.4	33.9	41.2	41.7	41.5	
Former	32.4	35.1	30.8	32.9	26.4	
Social	7.5	7.3	7.4	7.4	10.1	
Current	20.7	23.7	20.6	18.0	22.0	
Alcohol intake, g/day	5.8 (1.5–12.6)	7.2 (1.7–14.1)	6.3 (1.8–13.2)	4.7 (1.0–11.0)	4.1 (0.9–10.4)	**<0.001**
MVPA, min/day	46.8 ± 20.7	47.9 ± 22.0	47.2 ± 20.8	46.3 ± 19.6	40.6 ± 17.0†	0.13
Married	75.9	74.6	76.4	77.0	71.1	0.06
BMI, kg/m^2	26.1 ± 3.79	26.9 ± 3.9†	26.2 ± 3.9†	25.5 ± 3.8	24.5 ± 3.6†	**<0.001**
Systolic BP, mm Hg	116.2 ± 12.5	117.9 ± 12.3†	116.6 ± 12.2†	114.3 ± 12.6	114.0 ± 13.7	**<0.001**
Diastolic BP, mm Hg	72.4 ± 9.4	73.6 ± 9.5†	72.5 ± 9.4†	71.4 ± 9.1	71.7 ± 9.6	**<0.001**
Hypertension	12.1	13.9	12.5	10.0	10.0	**0.03**
Antihypertensive drugs	7.3	9.2	7.2	6.0	5.0	**0.02**
Fasting glucose, mg/dl	90.4 ± 13.7	92.1 ± 13.1†	90.6 ± 15.7†	88.9 ± 10.2	89.3 ± 17.3	**<0.001**
Diabetes mellitus	1.7	2.5	1.5	1.2	1.3	0.1
Antidiabetic drugs	1.5	2.1	1.2	1.2	1.2	0.31
Total cholesterol, mg/dl	200.0 ± 34.3	202.0 ± 34.3	200.0 ± 32.6	200.0 ± 33.3	203.0 ± 33.0	0.443
HDL cholesterol, mg/dl	49.2 ± 12.2	47.2 ± 11.8†	49.0 ± 11.7†	50.9 ± 12.8	50.8 ± 13.4	**<0.001**
LDL cholesterol, mg/dl	132.0 ± 29.8	134.0 ± 30.6	132.0 ± 28.8	131.0 ± 29.9	133.0 ± 31.9	0.135
Triglycerides, mg/dl	94.5 ± 57.3	100.7 ± 61.1†	94.4 ± 55.0	89.1 ± 50.7	95.5 ± 88.3	**<0.001**
Lipid-lowering drugs	6.9	8.3	8.0	4.7	4.4	**0.001**
Metabolic syndrome‡	9.5	12.6	8.8	8.0	6.9	**<0.001**
STOP-BANG score§	1.3 ± 1.1	1.6 ± 1.1†	1.3 ± 1.02†	1.1 ± 0.9	1.0 ± 1.0	**<0.001**
STOP-BANG score ≥3§	13.2	18.9	13.2	9.0	6.2	**<0.001**
CRP, mg/dl	0.10 (0.05–0.19)	0.11 (0.05–0.20)	0.09 (0.05–0.18)	0.09 (0.05–0.19)	0.09 (0.05–0.17)	0.07
VCAM, ng/ml	617 (490–765)	593 (476–747)	621 (494–769)	627 (498–772)	630 (488–774)	**0.006**
P-selectin, ng/ml	129 (104–154)	133 (108–157)	129 (104–154)	127 (102–151)	122 (96–140)	**0.002**
Neutrophil, %	57.6 (52.5–62.8)	57.8 (52.8–63.4)	57.3 (52.4–62.2)	57.6 (52.3–62.8)	58.3 (52.2–64.1)	0.23
Use of benzodiazepine and its derivatives	6.8	6.2	6.8	6.5	13.8	**0.012**

Values are n (%), mean ± SD, %, or median (quartile 1, quartile 3). **Bold** indicates statistical significance. *p values for continuous variables in this column reflect p for trend. †p<0.05 vs. RSD (reference group). ‡National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) criteria. §Modified score. Neck circumference not available.

BMI = body mass index; BP = blood pressure; CRP = C-reactive protein, HDL = high-density lipoprotein; LDL = low-density lipoprotein; LSD = long sleep duration; MVPA = moderate to vigorous physical activity; RSD = reference sleep duration; STOP-BANG = Snoring, Tired, Observed apnea, high blood Pressure, BMI >35 kg/m^2, Age >50, Neck circumference >43 cm in males and >41 cm in females, and male Gender; SSD = short sleep duration; VCAM = vascular cell adhesion molecule; VSSD = very short sleep duration.

p values when compared with the reference group. The chi-square test was used for categorical variables.

The degree of agreement between actigraphic and self-reported sleep duration was quantified by computing a concordance correlation coefficient. Associations between actigraphic sleep parameters (fragmentation index and sleep duration) and cardiometabolic risk outcomes or inflammation markers were evaluated by multivariable ordinal regression models adjusted for age, sex, physical activity, BMI, smoking status, alcohol consumption, systolic blood pressure, education level, fasting glucose, total cholesterol, total kcal per day, marital status, CES-D/PSS, and mSTOP-BANG questionnaire scores. Moreover, to obtain p values for the overall adjusted association between sleep parameters and atherosclerosis variables, we performed a likelihood-ratio test comparing the final models and the model including all variables other than the predictive variable in each analysis.

As sex has been reported to modify the association between sleep and cardiometabolic parameters (35), associations were additionally explored separately in men and women when a test for significance of effect modification by sex showed a p value <0.05.

RESULTS

A total of 2,488 men (62.6%) and 1,486 women (37.4%) underwent actigraphic analysis to evaluate

TABLE 2 Cardiovascular Risk Scales According to Sleep Duration and Fragmentation

Total Sleep Time (Actigraph)	Total	VSSD <6 h	SSD 6 to <7 h	RSD 7 to <8 h (Ref)	LSD ≥8 h	p Value*
CVD risk scales						
FRS 10%	5.9 ± 4.4	6.9 ± 4.8†	5.9 ± 4.3†	5.0 ± 3.8	5.1 ± 4.6	**<0.001**
FRS 30%	17.7 ± 11.8	20.9 ± 12.7†	17.7 ± 11.4†	15.2 ± 10.6	15.6 ± 12.3	**<0.001**
Fuster-BEWAT score						**<0.001**
Poor	6.5	9.3	5.6	5.5	4.4	
Intermediate	60.1	63.4	62.2	55.6	51.6	
Ideal	33.4	27.3	32.2	38.9	44.0	
Sleep Fragmentation Index (Actigraph)	**Quintile 1 (Ref) 0.23–2.88**	**Quintile 2 2.88–4.04**	**Quintile 3 4.04–5.29**	**Quintile 4 5.29–7.38**	**Quintile 5 7.39–43.43**	
CVD risk scales						
FRS 10%	5.0 ± 3.8	5.4 ± 3.9	5.9 ± 4.4†	6.3 ± 4.9†	6.8 ± 4.7†	**<0.001**
FRS 30%	15.2 ± 10.3	16.6 ± 10.9	17.5 ± 11.4†	18.8 ± 12.6†	20.4 ± 12.8†	**<0.001**
Fuster-BEWAT score						**<0.001**
Poor	4.5	5.8	6.2	7.2	9.0	
Intermediate	57.8	59.8	59.7	58.3	64.8	
Ideal	37.7	34.4	34.1	34.5	26.2	

Values are mean ± SD or %. Post hoc Bonferroni analysis. **Bold** indicates statistical significance. *p values for continuous variables in this column reflect p for trend. †p < 0.05 compared with reference group.

FRS = Framingham risk score; Ref = reference.

sleep duration and quality. The proportion of participants with RSD was 30.7%, whereas SSD or VSSD accounted for 65.3% of cases. Only 4% of participants presented LSD (**Table 1**). Regarding sleep fragmentation, each of the quintiles comprised 774 to 786 participants (Online Table 1).

There was a significant but weak correlation between actigraphic and self-reported sleep duration among the study participants (Pearson correlation coefficient: 0.35; p < 0.001). Moreover, the 3,899 subjects who answered the questionnaires overestimated their sleep duration as compared with the accelerometer results (Online Figure 1).

CLINICAL PROFILE AND SLEEP PARAMETERS. Baseline characteristics according to actigraphy-measured sleep duration are presented in **Table 1**. Increased age, higher systolic and diastolic blood pressure hypertension, BMI, lower HDL cholesterol, and metabolic syndrome were significantly more prevalent in participants with VSSD or SSD compared to RSD (7 to 8 h) (**Table 1**). Similar to VSSD and SSD, participants in the higher quintile for SFI were significantly older and had an increased prevalence of smoking and hypertension (Online Table 1).

The Framingham risk score for 10 and 30 years estimated a significantly higher cardiovascular risk in participants with VSSD or SSD compared with RSD as well as in those included in the 3 higher quintiles of sleep fragmentation. The same findings were observed with the recently described Fuster-BEWAT score (20) (**Table 2**). No differences were found regarding psychosocial characteristics according to sleep duration and fragmentation (Online Table 2).

ASSOCIATION OF SLEEP DURATION AND QUALITY WITH SUBCLINICAL ATHEROSCLEROSIS. Three-dimensional VUS in carotid and femoral territories was available for analysis in 3,804 participants (Online Table 3). When adjusted for age, sex, moderate to vigorous physical activity (MVPA), BMI, smoking status, alcohol consumption, systolic blood pressure, education level, fasting glucose, total cholesterol, total kcal per day, marital status, CES-D, PSS, and mSTOP-BANG questionnaire scores, VSSD was independently associated with an increased plaque burden compared with the reference group (sleep duration 7 to 8 h) (odds ratio [OR] of being in the highest tertile of plaque burden: 1.27; 95% confidence interval [CI]: 1.06 to 1.52; p = 0.008) (**Table 3, Central Illustration**). The ordinal regression analysis considering tertiles for 3D plaque burden and number of diseased territories also showed that participants who slept <6 h presented a trend toward a more extensive atherosclerosis with a higher number of affected vascular territories, but the differences were not significant (OR of presenting more affected territories: 1.21; 95% CI: 1.02 to 1.45; p = 0.03, but overall test p value = 0.18). The association between subclinical atherosclerosis and sleep duration was also investigated using the Sleep Habits Questionnaire. In this case, no statistically significant differences in plaque burden or CAC score were observed between the different sleep groups in the overall association tests

TABLE 3 Atherosclerotic Plaque Burden and Number of Affected Territories Measured by 3D Echocardiography and Sleep Duration: Comparison Between Self-Reported Sleep and Actigraphy

	Actigraph						Sleep Habits Questionnaire					
	Noncoronary Plaque Burden			Number of Territories Affected (1–4)			Noncoronary Plaque Burden (mm^3)			Number of Territories Affected (1–4)		
	OR	95% CI	p Value	OR	95% CI	p Value	OR	95% CI	p Value	OR	95% CI	p Value
Total sleep duration, h			0.045*			0.18*			0.33*			0.20*
<6	1.27	1.06–1.52	0.008	1.21	1.02–1–45	0.03	0.99	0.79–1.24	0.92	0.92	0.74–1.16	0.50
6–7	1.10	0.94–1.30	0.25	1.07	0.90–1.26	0.40	1.13	0.98–1.31	0.10	1.13	0.98–1.31	0.09
7–8	1.00	Reference		1.00	Reference		1.00	Reference		1.00	Reference	
>8	1.31	0.92–1.85	0.13	1.13	0.79–1.13	0.50	0.91	0.78–1.34	0.50	1.03	0.78–1.34	0.86
Men sleep duration, h			0.32*			0.41*			0.27*			0.22*
<6	1.21	0.98–1.49	0.08	1.14	0.93–1.41	0.21	1.15	0.88–1.50	0.32	1.06	0.81–1.39	0.69
6–7	1.13	0.93–1.38	0.23	1.04	0.85–1.27	0.71	1.23	1.03–1.46	0.02	1.21	1.02–1.44	0.03
7–8	1.00	Reference		1.00	Reference		1.00	Reference		1.00	Reference	
>8	0.96	0.59–1.56	0.87	1.13	0.79–1.13	0.44	0.99	0.69–1.43	0.96	1.08	0.75–1.55	0.68
Women sleep duration, h			0.02*			0.11*			0.37*			0.33*
<6	1.48	1.06–2.07	0.02	1.38	1.00–1.93	0.053	0.69	0.44–1.07	0.10	0.68	0.44–1.05	0.08
6–7	1.01	0.76–1.36	0.90	1.04	0.85–1.27	0.44	0.94	0.72–1.23	0.66	0.97	0.74–1.26	0.81
7–8	1.00	Reference		1.00	Reference		1.00	Reference		1.00	Reference	
>8	1.83	1.12–3.01	0.02	1.65	1.01–2.72	0.05	0.77	0.51–1.18	0.23	0.89	0.59–1.35	0.59

Odds ratios (ORs) and 95% confidence intervals (CIs) of total plaque burden measured by 3-dimensional echocardiography (carotid and femoral territories) and affected territories in the different groups according to sleep duration compared with the reference group (7 to 8 h of sleep). Ordinal regression model adjusted for age, sex, moderate to vigorous physical activity, body mass index, smoking status, alcohol consumption, systolic blood pressure, education level, fasting glucose, total cholesterol, total kcal/day, marital status, Center for Epidemiological Studies-Depression, Perceived Stress Scale, and mSTOP-BANG questionnaire scores. Total plaque burden was divided into no plaque and tertiles (men: 0, 1.09 to 31.98, 31.99 to 105.62, and 106.53 to 1,241.98 mm^3; women: 0, 1.19 to 14.83, 15.02 to 38.89, and 40.69 to 536.34 mm^3). *p values for the overall adjusted associations for each analysis (likelihood-ratio test). The other p values correspond to pairwise comparisons with the reference group.

Abbreviations as in Table 1.

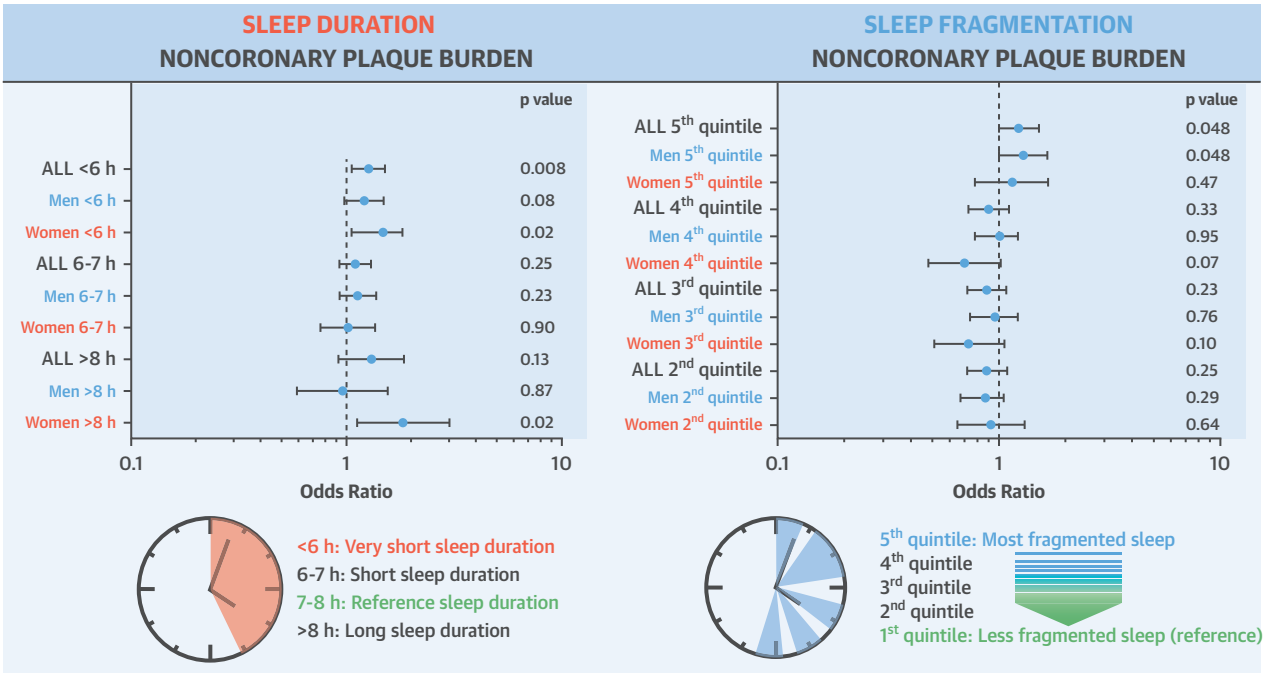
(Table 3), further highlighting the importance of objective sleep data for these kinds of studies. The same analysis was performed to evaluate the impact of sleep fragmentation on plaque burden. We found that the whole cohort and more specifically male participants with a more fragmented sleep (fifth quintile) presented a higher number of affected territories compared to the reference group (first quintile) (Central Illustration). A subanalysis excluding subjects with an mSTOP-BANG score ≥3 (n = 450; 11.8% of study participants with available 3D VUS) was conducted and showed similar results regarding VSSD and noncoronary atherosclerosis (Online Table 4). Moreover, in this case, participants with LSD showed a higher noncoronary plaque burden, although this difference was specifically observed in women (OR: 1.95; 95% CI: 1.20 to 3.19; p = 0.007 vs. OR: 1.07; 95% CI: 0.64 to 1.80; p = 0.80 in men).

Next, we investigated the relationship between sleep patterns and CACS. Coronary CT was available for analysis in 3,899 participants. Patients in the VSSD and SSD groups, as well as those with more disrupted sleep (fifth quintile), were associated with a higher CACS (Online Table 5). Adjusting for the aforementioned confounding factors, CACS was not significantly higher in SSD, VSSD, or LSD participants regardless of the method used for the evaluation of sleep habits (Online Table 4). Similarly, no significant association was observed between sleep quality and CACS in the variable-adjusted analysis or after excluding subjects with an mSTOP-BANG score ≥3 (Figure 1, Online Table 6).

ASSOCIATION OF DIETARY INTAKE AND INFLAMMATION WITH SLEEP PARAMETERS. No differences were observed between the different sleep duration groups when the quantity of nutrients was adjusted to grams in 2,000 kcal/day (Online Table 7). However, participants in the VSSD group presented a higher daily intake of alcohol, and those included in the VSSD and SSD groups presented a higher intake of caffeine compared with participants in the RSD group (Online Table 7). Similarly, participants in the higher quintile of SFI presented a higher intake of alcohol and caffeine compared with the reference group, and also an increased total energy intake (Online Table 8).

We next investigated the association between inflammation markers and sleep patterns. P-selectin and hs-CRP were significantly higher in VSSD participants (Table 1) and hs-CRP values were significantly higher in the higher quintile of FI compared with the lower quintile (Online Table 1). However, neither VSSD nor SSD were associated with a higher level

CENTRAL ILLUSTRATION **Sleep Duration and Quality Versus Subclinical Atherosclerotic Burden**



Domínguez, F. et al. J Am Coll Cardiol. 2019;73(2):134–44.

Forest plots showing the odds ratios (ORs) and confidence intervals (CIs) of total plaque burden measured by 3D echocardiography (carotid and femoral territories) in the different groups according to actigraphic sleep duration and fragmentation compared with the reference group (7 to 8 h of sleep, quintile 1). Ordinal regression model adjusted for age, sex, moderate to vigorous physical activity, body mass index, smoking status, alcohol consumption, systolic blood pressure, education level, fasting glucose, total cholesterol, total kcal/day, marital status, Center for Epidemiological Studies-Depression scale, Perceived Stress Scale, and mSTOP-BANG (modified Snoring, Tired, Observed apnea, high blood Pressure, BMI >35 kg/m^2, Age >50, Neck circumference >43 cm in males and >41 cm in females, and male Gender) questionnaire scores. The p values (**bold** indicates statistical significance) for the overall adjusted association between sleep parameters and atherosclerosis variables correspond to: sleep duration versus noncoronary plaque burden: **p = 0.045** (men: p = 0.32; women: **p = 0.02**); sleep fragmentation versus noncoronary plaque burden: **p = 0.004** (men: **p = 0.02**; women: p = 0.09). Total plaque burden divided in no plaque and tertiles (men: 0, 1.09 to 31.98, 31.99 to 105.62, and 106.53 to 1241.98 mm^3; women: 0, 1.19 to 14.83, 15.02 to 38.89, and 40.69 to 536.34 mm^3). Sleep fragmentation index values fifth quintile: 7.39 to 43.43; fourth quintile: 5.29 to 7.38; third quintile: 4.04 to 5.29; second quintile: 2.88 to 4.04; first quintile (reference group): 0.23 to 2.88. 3D = 3-dimensional; CT = computed tomography; LSD = long sleep duration; RSD = reference sleep duration; SFI = sleep fragmentation index; SSD = short sleep duration; VSSD = very short sleep duration; VUS = vascular ultrasound.

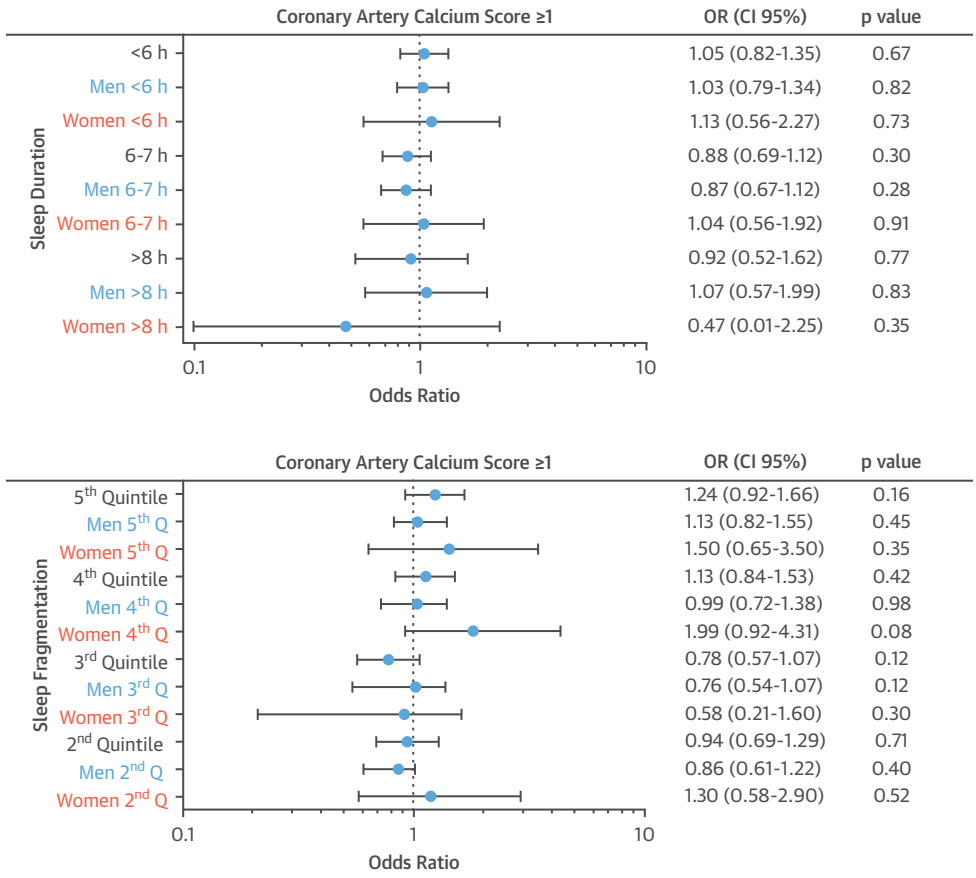
of inflammatory markers in the adjusted model (Online Table 9).

DISCUSSION

Our study shows that objectively assessed sleep duration and sleep fragmentation are independently associated with subclinical atherosclerosis after adjusting for cardiovascular risk factors and OSA risk. Unlike previous studies, the atherosclerotic plaque burden was accurately assessed by 2 imaging techniques including 3D VUS and coronary CT. Because various vascular territories were evaluated, this is the first study to report the impact of actigraphic sleep parameters on multiterritorial atherosclerosis, and is the biggest cohort with objectively measured sleep in this regard published to date. Furthermore, subjects diagnosed with obstructive sleep OSA were excluded, and the results were adjusted for the potential presence of OSA based on an mSTOP-BANG questionnaire score, thereby avoiding the confounding effect of this sleep disorder on our analysis.

We observed that participants sleeping <6 h/night (VSSD group) present a higher burden of noncoronary atherosclerosis and those with most fragmented sleep (fifth FI quintile) show in addition a higher number of affected territories measured by 3D VUS, independently of the presence of conventional CVD risk factors. Furthermore, LSD was related to a higher atherosclerotic burden specifically in women.

FIGURE 1 **Coronary Artery Calcium Score Versus Actigraphic Sleep Duration and Fragmentation Index**



Forest plot showing the odds ratios and confidence intervals of coronary artery calcium (CAC) scores in the different groups according to sleep duration fragmentation compared to the reference groups (7 to 8 h and first quintile, respectively). CAC score was divided into the following groups according to Agatston score: <1, 1 to 100, 100 to 400, >400. Ordinal regression model adjusted for age, sex, moderate to vigorous physical activity, body mass index (BMI), smoking status, alcohol consumption, systolic blood pressure, education level, fasting glucose, total cholesterol, total kcal/day, marital status, Center for Epidemiological Studies-Depression, Perceived Stress Scale, and mSTOP-BANG (modified Snoring, Tired, Observed apnea, high blood Pressure, BMI >35 kg/m^2, Age >50, Neck circumference >43 cm in males and >41 cm in females, and male Gender) questionnaire scores. The p values for the overall adjusted association between sleep parameters and CAC score correspond to (**bold** indicates statistical significance): sleep duration versus CAC score ≥1: p = 0.44 (men: p = 0.47; women: p = 0.70); sleep fragmentation versus CAC score ≥1: **p = 0.02** (men: p = 0.12; women: p = 0.08). Total plaque burden divided in no plaque and tertiles (men: 0, 1.09 to 33.70, 33.71 to 107.69, 108.03 to 1,241.98, and >1,241.98 mm^3; women: 0, 1.19 to 16.32, 16.56 to 45.24, 45.49 to 536.34, and >536.34 mm^3). Sleep fragmentation index values fifth quintile: 7.39 to 43.43; fourth quintile: 5.29 to 7.38; third quintile: 4.04 to 5.29; second quintile: 2.88 to 4.04; and first quintile (reference group): 0.23 to 2.88. CI = confidence interval; OR = odds ratio.

However, we did not find that sleep duration and quality had an effect on CACS or inflammation biomarkers in our study population.

In our study, participants with SSD or VSSD presented a higher prevalence of classical cardiovascular risk factors, which is consistent with previously published data (3,6,36-38). Consequently, individuals with poorer sleep presented higher scores in various cardiovascular risk scales (**Table 2**). Moreover, participants with VSSD, SSD, and a more fragmented sleep (fourth and fifth quintiles) were more overweight (>26 kg/m^2) and those with LSD and non-fragmented sleep presented with lower BMI values (**Table 1**, Online Table 1).

The link between short sleep duration and higher energy intake has already been suggested (39), but the most extensive related study published to date relied on self-reported sleep measurements (40) and the only available actigraphy-based study was restricted to women (41). In our study, only subjects with the most disrupted sleep (quintile 5) presented a higher energy intake, but the fats, carbohydrates, or

proteins did not differ significantly between sleep groups. Only alcohol and caffeine consumption were higher in participants with short and disrupted sleep (Online Tables 5 and 6). Lately, coffee intake has been associated with better cardiovascular outcomes and lower mortality (42), but in our study, a higher caffeine intake seems to be related to unhealthier sleep patterns in groups with more cardiovascular risk factors.

These results support that subjects with poor sleep hygiene are clustered into groups apparently less engaged in healthy cardiovascular behaviors. However, apart from confirming the direct association of sleep duration and quality with cardiovascular risk factors and dietary habits, the current study is the first to show that objectively measured sleep is independently associated with subclinical multiterritory atherosclerosis. The fact that sleep duration and quality was objectively measured is relevant, as we have observed that self-reported sleep duration may not be reliable. In our study, while 27.1% of participants slept <6 h/day according to the accelerometer, only 10.7% reported <6 h sleep in the Sleep Habits Questionnaire. Consequently, the association of self-reported sleep with noncoronary atherosclerosis in our study is different from that seen with actigraphy, and only the subgroup of men who slept 6 to 7 h showed a trend toward a higher risk of noncoronary atherosclerosis (**Table 3**). This could be explained by the fact that these participants actually present with VSSD rather than SSD.

The largest study to date that analyzed the impact of sleep on atherosclerosis with objectively measured sleep parameters (n = 1,844) included subjects with OSA, and the clinical endpoint was peripheral artery disease measured with ankle-brachial index (14). Another study with 1,465 participants showed that poorer sleep was associated with greater coronary artery calcification (13). However, the effect of sleep patterns on subclinical atherosclerosis in a population without sleep-related disorders has not been adequately studied until now. In the present study, roughly 3,800 participants underwent coronary CT and 3D VUS in different territories. An association with CACS was discarded after adjusting for confounders, but the association with higher noncoronary atherosclerotic burden was significant. This may be explained by the fact that 3D VUS is a more sensitive technique than CACS to measure early atherosclerosis (32).

Regarding LSD, despite the result of a previous meta-analysis that found a correlation with cardiovascular outcomes (1), its effect on subclinical atherosclerosis remains unresolved due to variable results in previous studies (8). We have observed that LSD is not associated with plaque burden or CACs in the general cohort. However, the subgroup of women who slept >8 h presented with a higher burden of subclinical atherosclerosis, and similar results were observed in the general cohort after excluding participants with an mSTOP-BANG score ≥3 (Online Table 4). As the number of patients with LSD was limited, these results need validation in a bigger cohort. In any case, these findings suggest that too-long sleep duration may not be healthy either, and recommendations should be restricted to 7 to 8 h of sleep.

Overall, our findings support the potential role of healthy sleeping in protecting against atherosclerosis. Thus, recommending a good sleep hygiene should be part of the lifestyle modifications provided in our daily clinical practice.

STUDY LIMITATIONS. The PESA study cohort is relatively homogeneous and may not be representative of the general population, as it includes only middle-aged subjects with generally low cardiovascular risk and a characteristic occupation and lifestyle. Although subjects with an established OSA diagnosis were excluded, this condition is usually underdiagnosed in the general population. Thus, the results were adjusted for an mSTOP-BANG questionnaire score with the available clinical data in the PESA study. The original STOP-BANG questionnaire could not be used due to the lack of neck circumference data. A definite OSA evaluation would need a polysomnography study in all study participants, which was not available. In addition, whereas wrist actigraphy might be the preferred method for sleep evaluation, in this study we used waist actigraphy. However, previous studies have shown a good correlation between polysomnography and waist actigraphy data (43).

Furthermore, the LSD group represents only 4% of the total cohort, and results are not as generalizable as in the other groups. Finally, as follow-up data is not included in the study, the effects of sleep patterns on subclinical atherosclerosis over time are not addressed.

However, the proportion of women participants is higher than in other studies, and sleep and clinical data are well characterized in this cohort, which are both strengths of this study.

CONCLUSIONS

Sleep is an important factor influencing cardiovascular health and could have a role as a marker of subclinical atherosclerosis. Objectively measured short sleeping times and fragmented sleep are associated with an

increased risk of subclinical atherosclerosis. These results highlight the importance of healthy sleep habits for the prevention of CVD.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Metabolic syndrome is associated with abnormal sleep patterns. Short and fragmented sleep patterns are independently associated with increased atherosclerotic plaque burden in middle-aged individuals.

TRANSLATIONAL OUTLOOK: Prospective studies are needed to assess the impact of specific interventions that improve sleep hygiene on clinical ischemic events.

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KEY WORDS 3D vascular ultrasound, actigraph, cardiac computed tomography, sleep, subclinical atherosclerosis

APPENDIX For supplemental tables and a figure, please see the online version of this paper.