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ORIGINAL RESEARCH

# Sleep Irregularity and Subclinical Markers of Cardiovascular Disease: The Multi-Ethnic Study of Atherosclerosis

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**BACKGROUND:** Sleep irregularity has been linked to incident cardiovascular disease. Less is known about associations of sleep regularity with atherosclerosis. We examined cross-sectional associations of actigraphy-assessed sleep duration and sleep timing regularity with subclinical atherosclerosis in the community-based MESA (Multi-Ethnic Study of Atherosclerosis).

**METHODS AND RESULTS:** MESA Sleep Ancillary Study participants (N=2032; mean age, 68.6±9.2 years; 37.9% White) completed 7-day wrist actigraphy. Participants underwent assessments of coronary artery calcium, carotid plaque presence, carotid intima-media thickness, and the ankle-brachial index. Sleep regularity was quantified by the 7-day within person SD of sleep duration and sleep onset timing. Relative risk regression models were used to calculate prevalence ratios and 95% CIs. Models are adjusted for demographics, cardiovascular disease risk factors, and other objectively assessed sleep characteristics including obstructive sleep apnea, sleep duration, and sleep fragmentation. After adjustment, compared with participants with more regular sleep durations (SD ≤60 minutes), participants with greater sleep duration irregularity (SD >120 minutes) were more likely to have high coronary artery calcium burden (>300; prevalence ratio, 1.33 [95% CI, 1.03–1.71]) and abnormal ankle-brachial index (<0.9; prevalence ratio, 1.75 [95% CI, 1.03–2.95]). Compared with participants with more regular sleep timing (SD ≤30 minutes), participants with irregular sleep timing (SD >90 minutes) were more likely to have high coronary artery calcium burden (prevalence ratio, 1.39 [95% CI, 1.07–1.82]). Associations persisted after adjustment for cardiovascular disease risk factors and average sleep duration, obstructive sleep apnea, and sleep fragmentation.

**CONCLUSIONS:** Sleep irregularity, particularly sleep duration irregularity, was associated with several measures of subclinical atherosclerosis. Sleep regularity may be a modifiable target for reducing atherosclerosis risk. Future investigation into cardiovascular risk reduction interventions targeting sleep irregularity may be warranted.

**Key Words:** cardiovascular disease ■ circadian rhythms ■ lifestyle ■ risk factors

Poor sleep, including poor quality, abnormal quantity, and fragmented sleep, is associated with cardiovascular risk factors, incident cardiovascular disease (CVD), and CVD-related mortality.<sup>1–6</sup> Questions remain about which dimensions of sleep may drive the pathophysiologic development of CVD<sup>7</sup> and be promising intervention targets for improving cardiovascular health.<sup>1</sup> To explore mechanisms through which poor sleep may lead to CVD development, researchers have examined

associations of various dimensions of sleep with noninvasive measures of atherosclerosis, which have shown to be strongly associated with incident CVD.<sup>8–12</sup> There is a consistent line of cross-sectional<sup>13–15</sup> and prospective<sup>14,16</sup> evidence to suggest adults with abnormal sleep characteristics are more likely to have significant subclinical atherosclerosis.

An emerging area of interest is whether sleep irregularity, estimated by variation in sleep durations and

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## CLINICAL PERSPECTIVE

### What Is New?

- In this large, racially and ethnically diverse, community-based cohort, sleep duration irregularity (variation in sleep duration >120 minutes in a week) was associated with measures of subclinical atherosclerosis.
- Our findings suggest that irregular sleep patterns may play a role in the pathophysiologic development of cardiovascular disease.

### What Are the Clinical Implications?

- Encouraging regular sleep schedules may be an important part of clinical lifestyle recommendations for the prevention of cardiovascular disease.

## Nonstandard Abbreviations and Acronyms

<b>cIMT</b>	carotid intima-media thickness
<b>MESA</b>	Multi-Ethnic Study of Atherosclerosis
<b>OSA</b>	obstructive sleep apnea
<b>PR</b>	prevalence ratio

sleep timing across nights,<sup>1,17</sup> is associated with CVD risk. Irregular sleep patterns and night-to-night variations in sleep timing may be indicators of circadian misalignment, or desynchronization of sleep–wake timing, which has been linked to cardiometabolic risk factors.<sup>18–20</sup> Initial studies on regularity of sleep patterns and CVD risk were focused on nurses and shift workers with pronounced variations in sleep schedules.<sup>21–23</sup> However, recent evidence has connected irregular sleep patterns to cardiovascular health in the general population.<sup>20,24–27</sup>

It remains unknown whether irregularity in sleep durations and timing plays a role in the development of atherosclerosis.<sup>27</sup> The MESA (Multi-Ethnic Study of Atherosclerosis) includes objectively measured sleep data and numerous noninvasive measures of subclinical atherosclerosis, assessed in a diverse sample of older adults. In this study, we tested the hypotheses that more irregular sleep durations and sleep timing were associated with subclinical atherosclerosis (including prevalent coronary artery calcium [CAC], prevalent carotid plaque, abnormal carotid intima-media thickness [cIMT], and abnormal ankle-brachial index [ABI]), after adjustment for cardiovascular risk factors and objectively measured obstructive sleep apnea (OSA), sleep duration, and sleep fragmentation. We were also interested in understanding whether associations were consistent across several subclinical markers.

## METHODS

Requests to access data sets from qualified researchers trained in human subject confidentiality protocols should be made through the MESA internal site at <https://mesa-nhlbi.org>.

### Study Design

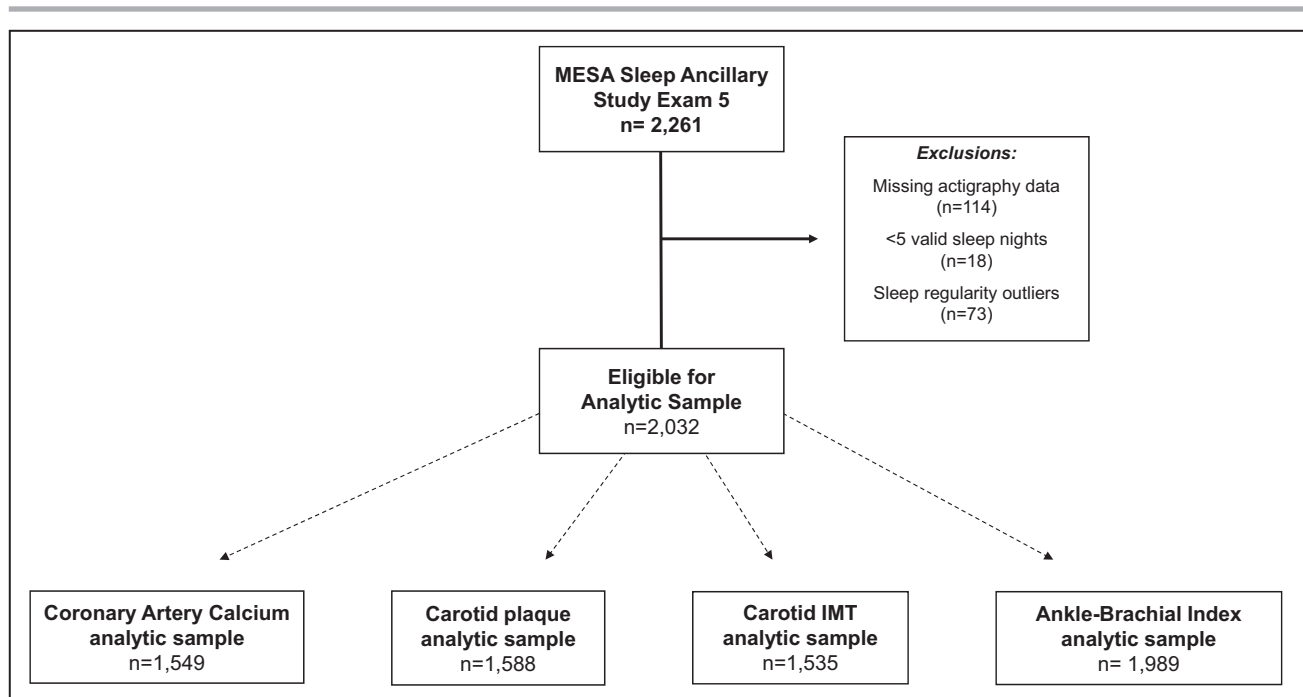
The MESA is a multisite longitudinal cohort study designed to investigate the prevalence and progression of subclinical CVD and to identify risk factors for incident CVD in a racially and ethnically diverse community-based sample.<sup>28</sup> Between 2000 and 2002, 6814 men and women aged 45 to 84 years, who identified as White, Black/African American, Hispanic American, or Chinese American and were free of clinical CVD, were recruited from 6 US communities (St. Paul, MN; Baltimore City and Baltimore County, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; and Northern Manhattan and the Bronx, NY).

All 4077 MESA participants who took part in exam 5 (2010–2012) were invited to participate in the MESA Sleep Ancillary Study (2010–2013). Interested participants who did not report regular use of oral devices, nocturnal oxygen, or nightly positive airway pressure devices and who did not live too far away from the MESA clinics were eligible. Of the interested and eligible participants, 2261 took part in the MESA Sleep Ancillary study (59.7%). The study protocol and procedures were approved by the institutional review board of each study field center, and all participants provided written informed consent to participate in the study.

Of the 2261 participants, 2147 had actigraphy wear and available data on at least 1 subclinical marker. We further excluded participants who had <5 days of actigraphy wear (n=18) or had extreme values for sleep duration regularity or sleep onset regularity (n=73), resulting in an available analytic sample of 2032 participants. The final analytic sample differed for each outcome on the basis of participation in subclinical measure assessment (Figure 1).

### Objective Sleep Assessment

Participants wore the Actiwatch Spectrum wrist actigraph (Philips Respironics, Murrysville, PA) on the nondominant wrist for 7 consecutive days, while concurrently completing a sleep diary over the same period. The 30-second epoch actigraph data were scored using the Actiware-Sleep version 5.59 analysis software (MiniMitter Co, Inc, Bend, OR), after technicians at the Brigham and Women's Hospital Sleep Reading Center annotated the rest periods using sleep diaries and information from light, markers, and movement.<sup>26</sup> A validated sleep/wake algorithm was used in which each epoch was classified as sleep or wake



**Figure 1.** Flow chart of MESA Sleep participants in analytic sample.

Of 2261 eligible participants, 2147 had valid actigraphy and subclinical marker data. Participants were excluded who had <5 days of actigraphy wear (n=18) and extreme sleep duration regularity or sleep onset regularity (n=73). Final sample sizes varied by subclinical marker.

on the basis of all activity counts in the surrounding 2-minute period of time (eg,  $\pm 2$  min).<sup>29</sup> The median time interval between MESA exam 5 assessment and objective sleep assessment was 1 year.

Sleep duration was estimated as the sum of the minutes classified as sleep during the main sleep period by the algorithm minus all minutes classified as wake after sleep onset. Sleep onset time was defined as the time of the first epoch classified as sleep during the main sleep period. Consistent with previous MESA analyses,<sup>30</sup> we estimated the regularity in sleep duration and sleep onset timing as the within-person SD of these variables across the 7-day wear period. Also consistent with previous MESA analyses,<sup>30</sup> participants were categorized by 30-minute increments on the basis of the data distributions in the sample ( $\leq 60$ , 61–90, 91–120, >120 minutes for sleep duration regularity and  $\leq 30$ , 31–60, 61–90, and >90 minutes for sleep timing regularity). The sleep fragmentation index is a measure of sleep continuity and estimates disruption in sleep throughout the sleep period. The fragmentation index is calculated as the sum of (1) the percentage of the sleep period with movement ( $>2$  activity counts) and (2) the percentage of the sleep period with immobile phases that are  $\leq 1$  minute.<sup>31,32</sup>

According to a previously developed protocol, participants also completed a 1-night in-home polysomnography study with the 15-channel Compumedics

Somte system (Compumedics, Abbottsville, Australia), which measures sleep-disordered breathing, sleep stages, wake after sleep onset, and heart rate.<sup>33</sup> The polysomnography recording provided quantitative assessments of levels of overnight hypoxemia, apneas and hypopneas, and sleep stage distributions. For this analysis, OSA severity was quantified using the Apnea-Hypopnea Index, composed of the sum of all obstructive apneas plus hypopneas associated with  $\geq 4\%$  oxygen desaturation. Participants with an Apnea-Hypopnea Index  $\geq 30$  events/hour were categorized as having severe OSA.<sup>34</sup>

### Subclinical Markers of CVD

Study outcomes include noninvasive measures of subclinical CVD collected at exam 5 including prevalent CAC, carotid plaque presence, abnormal cIMT, and abnormal ABI.

MESA scanning centers at all 6 sites measured CAC by cardiac computed tomography, using a standardized protocol.<sup>35</sup> A cardiologist or radiologist at a central reading center (Los Angeles Biomedical Research Institute at Harbor–UCLA Medical Center), blinded to participant data, read all cardiac computed tomography scans using an interactive scoring system. The phantom adjusted Agatston score, a continuous score derived from the densities and areas of plaque in the coronary arteries,<sup>36</sup> was quantified for each

participant. This standardized measure of CAC has shown to have high intra- and interreader reproducibility in MESA ( $\kappa > 0.90$ ).<sup>35</sup> For this study, Agatston scores were categorized as  $>0$  for presence of CAC (reference 0). Agatston scores  $>300$  (reference  $\leq 300$ ) represented high CAC burden.

To measure cIMT and carotid plaque, trained technicians in each field center performed B-mode ultrasonography of the right and left near and far walls of the internal carotid and common carotid arteries. Technicians recorded artery images with the Logiq 700 ultrasound device (General Electric Medical Systems, Waukesha, WI). The recorded images were reviewed at the University of Wisconsin Atherosclerosis Imaging Research Program MESA Carotid Ultrasound Reading Center. For this analysis, cIMT was calculated as the mean of the left mean and the right mean distal common carotid artery wall thickness.<sup>15</sup> Abnormal cIMT was defined as  $>0.9$  mm. Carotid plaques in the images of the right or left walls of the internal carotid artery, common carotid arteries, or bulb were identified and scored.<sup>37</sup> Carotid plaque identified in any location indicated carotid plaque presence (1 versus 0).

The ABI, a measure of systemic atherosclerosis and stiffness in the blood vessels, is a ratio of the systolic blood pressure at the ankle to the systolic blood pressure in the arm. To derive ABI estimates, MESA technicians obtained systolic blood pressure measurements from the bilateral brachial, dorsalis pedis, and posterior tibial arteries using a hand-held Doppler instrument with a 5-MHz probe with the participant in the supine position.<sup>11</sup> For each leg, the ABI numerator was the highest pressure recorded from that leg (dorsalis pedis or posterior tibial), while the denominator was the higher of the 2 arm pressures. Abnormal ABI was defined when at least 1 leg had a value  $<0.90$ , whereas “normal” was defined when both legs had values  $0.90 \leq \text{ABI} \leq 1.40$ . Previous evidence suggests that  $\text{ABI} > 1.40$  may be associated with greater CVD risk.<sup>38</sup> Thus, those with  $\text{ABI} > 1.40$  were excluded from ABI analyses.

## Covariates

Relevant covariates were obtained from the MESA sleep questionnaire, the MESA exam 5 questionnaire, and exam 5 physiologic assessments. Covariates in this analysis included age, sex, race and ethnicity, study site, education, yearly income, work schedule, smoking status, alcohol consumption, physical activity, body mass index (BMI), systolic blood pressure, diastolic blood pressure, antihypertensive medication use, statin medication use, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and prevalent diabetes.

Interview-administered questionnaires were used to assess education, yearly income, smoking status,

alcohol consumption, and physical activity. Education was categorized as high school graduate or less, some college, or college graduate plus. Participants average yearly income was categorized as  $< \$20\,000$ ;  $\$20\,000$  to  $< \$50\,000$ ; and  $\geq \$50\,000$ . Participants were asked if they currently smoke cigarettes or drink alcohol and categorized as current, former, or never. Participants were asked the number of days (and hours and minutes per day) they participated in various physical activities (including household chores, walking, sports activities, etc) in a typical week in the past month. Total metabolic equivalent minutes of moderate to vigorous physical activity were calculated to represent weekly average physical activity. At the MESA sleep exam, participants also completed a sleep questionnaire to report sleep habits and usual work schedules. Usual work schedule was grouped as “do not work,” “day shift,” and “other shift” that included responses of “afternoon shift,” “night shift,” “split shift,” “irregular shift/on-call,” and “rotating shifts.”

Trained staff collected height, weight, blood pressure, and fasting blood measures. BMI was calculated as weight (kilogram) divided by height (meter) squared. Blood pressure was measured 3 times in the seated position using a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon, Tampa, FL), and the final 2 measurements were averaged. Participants taking antihypertensive medications were coded as 1 for antihypertensive medication use (0: no antihypertensive medications). Participants taking statin medications were coded as 1 for statin medication use (0: no statin medication use). Serum assays were processed (Fairview University Medical Center, Minneapolis, MN), and high-density lipoprotein cholesterol was assessed in EDTA plasma using the cholesterol oxidase method (Roche Diagnostics, Risch-Rotkreuz, Switzerland). Low-density lipoprotein cholesterol was calculated in plasma specimens using the Friedewald formula. Prevalent diabetes was defined as fasting blood glucose concentration  $\geq 126$  mg/dL, nonfasting glucose concentration  $\geq 200$  mg/dL, self-reported physician diagnosis, or pharmacological treatment for diabetes.

## Statistical Analysis

Means and proportions of participant characteristics were calculated and compared according to categories of sleep duration regularity and sleep timing regularity.

A series of progressively adjusted relative risk regression models were run to examine associations between categories of sleep duration regularity and sleep timing regularity with each subclinical marker of CVD. Prevalence ratios (PRs) and 95% CIs according to sleep regularity categories were calculated using

**Table 1. MESA Sleep Participant Characteristics by Categories of Sleep Duration Regularity (N=2032)**

	Overall	Sleep duration regularity (nightly within-person SD)				P value
		≤60 min	61–90 min	91–120 min	>120 min	
		n=696	n=558	n=420	n=358	
Demographics						
Age, y	68.6±9.2	68.8±8.9	68.1±9.1	69.0±9.6	68.5±9.4	0.44
Female sex, n (%)	1090 (53.6)	357 (51.3)	320 (57.3)	228 (54.3)	185 (51.7)	0.19
Race and ethnicity, n (%)						<0.001
White	770 (37.9)	346 (49.7)	197 (35.3)	129 (30.7)	98 (27.4)	
Chinese American	226 (11.1)	78 (11.2)	53 (9.5)	49 (11.7)	46 (12.8)	
Black, African American	561 (27.6)	132 (19.0)	153 (27.4)	152 (36.2)	124 (34.6)	
Hispanic American	475 (23.4)	140 (20.1)	155 (27.8)	90 (21.4)	90 (25.1)	
Education, n (%)						0.04
≤HS graduate	613 (30.2)	188 (27.0)	198 (35.5)	122 (29.0)	105 (29.3)	
Some college	615 (30.3)	204 (29.3)	163 (29.2)	137 (32.6)	111 (31.0)	
College graduate plus	800 (39.4)	302 (43.4)	197 (35.3)	160 (38.1)	141 (39.4)	
Average yearly income						<0.01
<\$20000	383 (18.8)	101 (14.5)	115 (20.6)	85 (20.2)	82 (22.9)	
\$20000 to <\$50000	502 (24.7)	167 (24.0)	139 (24.9)	99 (23.6)	97 (27.1)	
≥\$50000	1086 (53.4)	408 (58.6)	290 (52.0)	224 (53.3)	164 (45.8)	
Work schedule, n (%)						0.01
Do not work	1148 (56.5)	406 (58.3)	295 (52.9)	235 (56.0)	212 (59.2)	
Day shift	617 (30.4)	213 (30.6)	189 (33.9)	134 (31.9)	81 (22.6)	
Other shift	246 (12.1)	74 (10.6)	68 (12.2)	47 (11.2)	57 (15.9)	
Lifestyle characteristics						
Current smoker, n (%)	142 (7.0)	35 (5.0)	35 (6.3)	36 (8.6)	36 (10.1)	0.02
Current alcohol consumer, n (%)	881 (43.4)	335(48.1)	235 (42.1)	177 (42.1)	134 (37.4)	0.02
MVPA, MET min/wk	5380±6220	5300±4850	5440±6120	5680±8320	5080±5890	0.39
BMI, kg/m <sup>2</sup>	28.8±5.6	28.0±5.1	29.2±5.7	29.0±5.8	29.4±5.8	<0.01
Cardiovascular risk factors						
Systolic blood pressure, mmHg	123.0±20.0	121.0±19.1	124.0±20.7	124.0±19.1	125.0±21.6	0.02
Diastolic blood pressure, mmHg	68.3±9.8	67.3±9.5	68.6±9.9	68.7±9.2	69.4±10.8	0.01
Antihypertensive medication use, n (%)	1090 (53.6)	358 (51.4)	293 (52.5)	230 (54.8)	209 (58.4)	0.18
Statin medication use, n (%)	775 (38.1)	278 (39.9)	200 (35.8)	158 (37.6)	139 (38.8)	0.51
LDL-C, mg/dL	106.0±32.4	105.0±31.3	108.0±31.4	107.0±35.3	105.0±32.7	0.39
HDL-C, mg/dL	55.6±16.5	55.5±15.4	56.9±17.3	55.4±16.8	54.0±16.8	0.10
Prevalent diabetes, n (%)	397 (19.5)	102 (14.7)	100 (17.9)	97 (23.1)	98 (27.4)	<0.001
Severe obstructive sleep apnea, n (%)	386 (19.0)	112 (16.1)	102 (18.3)	83 (19.8)	89 (24.9)	0.17
Average sleep fragmentation	20.2±7.0	18.8±6.6	20.1±7.0	20.9±6.6	22.0±7.8	<0.001

Data presented as mean±SD unless specified. P values adjusted for multiple comparisons using false discovery rate method. BMI indicates body mass index; HDL-C, high-density lipoprotein cholesterol; HS, high school; LDL-C, low-density lipoprotein cholesterol; MESA, Multi-Ethnic Study of Atherosclerosis; MET, metabolic equivalent; and MVPA, moderate to vigorous intensity physical activity.

modified Poisson regression with robust error variances.<sup>39</sup> Because the outcomes investigated in this study were common, we considered this relative risk regression approach more appropriate than calculating prevalence odds ratios.<sup>40</sup>

Progressive model adjustments included adjustment for basic demographics in model 1, including

age, sex, race and ethnicity, and site. Model 2 included additional adjustments for lifestyle characteristics that are potential confounders of the examined association, including education, yearly income, work schedule, smoking status, alcohol consumption, physical activity, and BMI. To further evaluate whether the associations persisted after adjustment for known CVD risk

**Table 2. Average Subclinical Atherosclerosis Measures by Sleep Regularity Categories: the MESA Sleep Study (2010–2013)**

	Sleep duration regularity (nightly within-person SD)				
	≤60 min n=696	61–90 min n=558	91–120 min n=420	>120 min n=358	P value
Subclinical measures, median (IQR)					
CAC, Agatston Score	22.79 (213.95)	30.86 (209.37)	35.16 (290.60)	69.16 (315.16)	0.16
Carotid IMT, mm	0.81 (0.24)	0.81 (0.22)	0.85 (0.24)	0.83 (0.22)	0.13
Ankle-brachial index	1.13 (0.15)	1.13 (0.13)	1.13 (0.14)	1.12 (0.15)	0.32
	Sleep timing regularity (nightly within-person SD)				
	≤30 min n=420	31–60 min n=713	61–90 min n=443	>90 min n=456	P value
Subclinical measures, median (IQR)					
CAC, Agatston Score	37.38 (253.12)	24.30 (208.90)	35.01 (203.29)	36.46 (287.76)	0.44
Carotid IMT, mm	0.85 (0.27)	0.81 (0.22)	0.83 (0.23)	0.82 (0.21)	0.15
Ankle-brachial index	1.12 (0.15)	1.13 (0.15)	1.13 (0.14)	1.12 (0.15)	0.09

P values calculated with Kruskal–Wallis rank-sum test. CAC indicates coronary artery calcium; IMT, intima-media thickness; IQR, interquartile range; and MESA, Multi-Ethnic Study of Atherosclerosis.

factors, model 3 included additional adjustments for systolic blood pressure, diastolic blood pressure, antihypertensive medication use, statin medication use, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and prevalent diabetes.

We performed a series of sensitivity analyses. Because sleep duration,<sup>3</sup> OSA,<sup>41</sup> and sleep fragmentation<sup>13</sup> are also associated with CVD risk, we assessed if the association between sleep irregularity and atherosclerosis remained after adjusting for these other relevant dimensions of sleep health. We reran all models separately, excluding participants who had prevalent CVD (n=107), those with severe OSA (n=386), and those who identified as other shift workers (n=246). Because of the potential influence of seasonality on our exposure, we explored the additional adjustment for season of actigraphy data collection. We also examined sleep regularity defined by variation in only weekday sleep duration. Finally, we explored potential effect modification by adding an age\*sleep regularity and sex\*sleep regularity cross-product term to the models.

## RESULTS

Table 1 presents the participant characteristics of the 2032 participants in the eligible sample overall and by categories of sleep duration regularity. The mean age of participants was 68.6 (±9.2) years. Just over half of the participants were women (53.6%), and 37.9% identified as White, 11.1% as Chinese American, 27.6% as Black or African American, and 23.4% as Hispanic American. Approximately 40% of participants had a college degree, and 53% had an average yearly income ≥\$50 000. Over 56% of the sample reported not currently working, while 12.1% (n=246) reported working a shift other than a day shift, of whom 12% (n=30)

reported night shift work. For OSA severity, 15% of the sample had normal breathing during sleep, 31% had mild OSA, 25% moderate OSA, and 19% severe OSA.

Across the 7-day data collection period, ≈38% of participants had sleep duration SD >90 minutes, and 18% of those participants had sleep duration SD >120 minutes. Participants with more irregular sleep durations (SD >120 minutes) were more likely to be non-White, have lower average yearly incomes, were more likely to not work or work other shift schedules (including afternoon, night, split, irregular, or rotating shifts), and were more likely to be current smokers with higher average BMI. Participant characteristics are also presented by categories of sleep timing regularity (Table S1).

### Sleep Duration Regularity

Compared with participants with regular sleep durations (SD <60 minutes), those with more irregular sleep durations had higher CAC scores and greater cIMT values, though differences were not statistically significant when these outcomes were explored as continuous measures (Table 2).

Participants with more irregular sleep durations (SD >120 minutes) were 1.40 (95% CI, 1.09–1.81) times more likely to have high CAC burden (>300) compared with participants with regular sleep durations (SD ≤60 minutes), after adjustment for demographics, lifestyle characteristics, and BMI (Table 3). This association persisted after additional adjustment for prevalent CVD risk factors that may be mediators of the association (PR, 1.33 [95% CI, 1.03–1.71]). Compared with participants with regular sleep durations (SD ≤60 minutes), those with irregular sleep durations (SD >120 minutes) were also more likely to have carotid plaque (PR, 1.12 [95% CI, 1.01–1.23]) and abnormal ABI (PR, 1.91 [95%

**Table 3. Sleep Duration Regularity and Associations With Subclinical Markers of CVD: the MESA Sleep Study (2010–2013)**

	Sleep duration regularity (nightly within-person SD)			
	≤60 min	61–90 min	91–120 min	>120 min
Prevalence ratio (95% CI)				
Coronary artery calcium (>0)				
n (%)	363 (65.5)	273 (65.5)	211 (66.1)	180 (69.5)
Model 1	(Reference)	1.06 (0.97–1.16)	1.04 (0.95–1.14)	1.10 (1.00–1.21)*
Model 2	(Reference)	1.05 (0.97–1.15)	1.03 (0.94–1.13)	1.08 (0.98–1.19)
Model 3	(Reference)	1.06 (0.98–1.16)	1.03 (0.94–1.13)	1.07 (0.98–1.18)
Coronary artery calcium (>300)				
n (%)	113 (20.4)	84 (20.1)	78 (24.4)	67 (25.9)
Model 1	(Reference)	1.16 (0.91–1.47)	1.28 (1.01–1.61)*	1.42 (1.10–1.84)*
Model 2	(Reference)	1.19 (0.94–1.51)	1.28 (1.01–1.62)*	1.40 (1.09–1.81)*
Model 3	(Reference)	1.26 (0.99–1.59)	1.32 (1.05–1.67)*	1.33 (1.03–1.71)*
Carotid plaque				
n (%)	356 (64.1)	289 (67.5)	230 (69.3)	192 (70.3)
Model 1	(Reference)	1.10 (1.01–1.20)*	1.10 (1.00–1.21)*	1.14 (1.03–1.25)*
Model 2	(Reference)	1.09 (1.00–1.20)*	1.09 (0.99–1.19)	1.12 (1.01–1.23)*
Model 3	(Reference)	1.10 (1.01–1.20)*	1.09 (0.99–1.20)	1.09 (0.99–1.21)
Carotid IMT (>0.9)				
n (%)	183 (34.1)	133 (32.2)	119 (36.6)	98 (37.5)
Model 1	(Reference)	1.04 (0.87–1.23)	1.03 (0.86–1.22)	1.09 (0.91–1.31)
Model 2	(Reference)	1.00 (0.84–1.19)	0.99 (0.82–1.18)	1.07 (0.89–1.29)
Model 3	(Reference)	0.99 (0.83–1.18)	0.99 (0.83–1.18)	1.03 (0.85–1.25)
Ankle-brachial index (<0.9)				
n (%)	24 (3.5)	26 (4.8)	28 (6.8)	25 (7.3)
Model 1	(Reference)	1.37 (0.80–2.35)	1.64 (0.97–2.75)	1.85 (1.09–3.15)*
Model 2	(Reference)	1.43 (0.83–2.44)	1.62 (0.96–2.73)	1.91 (1.12–3.26)*
Model 3	(Reference)	1.50 (0.86–2.59)	1.62 (0.98–2.70)	1.75 (1.03–2.95)*

Coronary artery calcium, n=1549; carotid plaque, n=1588; carotid IMT n=1535; ankle-brachial index, n=1989. Model 1: age, sex, race and ethnicity, site; model 2: M1+ education, income, work schedule, smoking status, alcohol consumption, physical activity, and body mass index; model 3: M2+systolic blood pressure, diastolic blood pressure, antihypertension medication use, statin medication use, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, prevalent diabetes. CVD indicates cardiovascular disease; IMT, intima-media thickness; and MESA, Multi-Ethnic Study of Atherosclerosis.

\*P value <0.05.

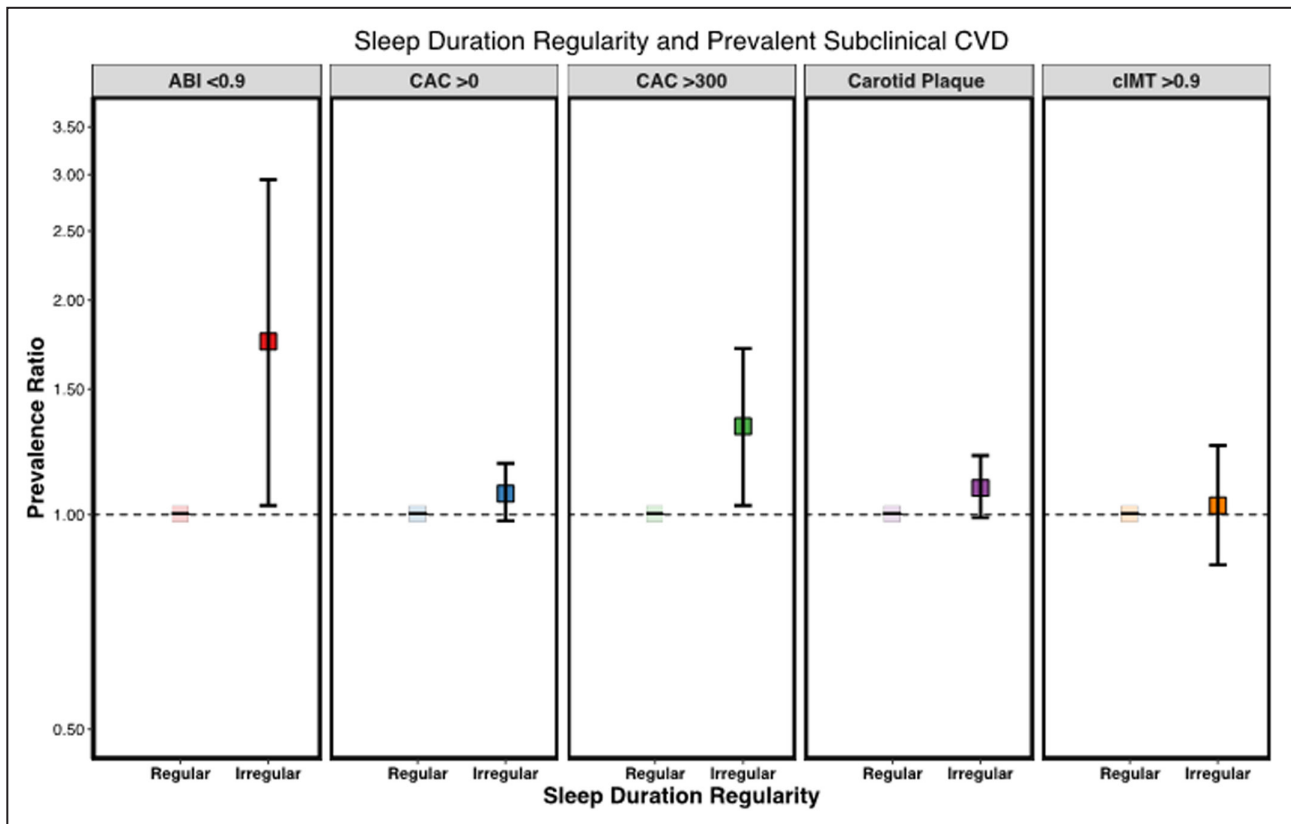
CI, 1.12–3.26]) after adjustment for demographics, lifestyle characteristics, and BMI. These associations were only slightly attenuated after additional adjustment for CVD risk factors (Figure 2). There was no association found between sleep duration regularity and abnormal cIMT.

### Sleep Timing Regularity

Compared with participants with regular sleep timing (SD ≤30 minutes), participants with more irregular sleep timing (SD >90 minutes) were 1.43 (95% CI, 1.10–1.86) times more likely to have high CAC burden (>300) after adjustment for demographics, lifestyle characteristics, and BMI (Table 4). This association remained in the model adjusting for potential mediators (PR, 1.39 [95% CI, 1.07–1.82]) (Figure 3). There was little evidence that sleep timing regularity was associated with other

subclinical markers of CVD. In sensitivity analyses, the observed association of sleep duration regularity with high CAC burden and abnormal ABI persisted after additional adjustment for severe OSA, average nightly sleep duration, and average sleep fragmentation index (Table 5). Of note, when sleep duration was added to the model, all participants with more irregular sleep durations (SD >60 minutes) were more likely to have high CAC burden (>300) compared with participants with regular sleep durations (SD ≤60 minutes). When participants with prevalent CVD were excluded, results were slightly attenuated but remained mostly unchanged (Table S2). When participants with severe OSA were excluded, results remained unchanged (Table S3). All results remained unchanged when participants who reported other shift work, including night shift work, were excluded (data not shown). Adding additional adjustment for season of actigraphy data collection





**Figure 2.** Sleep duration regularity and prevalent subclinical CVD in the MESA sleep study.

Adjusted for age, sex, race and ethnicity, site, education, yearly income, work schedule, smoking status, alcohol consumption, physical activity, body mass index, systolic blood pressure, diastolic blood pressure, antihypertensive medication use, statin medication use, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and prevalent diabetes; regular sleep duration:  $\leq 60$  minutes; irregular sleep duration:  $>120$  minutes. ABI indicates ankle-brachial index; CAC, coronary artery calcium; cIMT, carotid intima-media thickness; CVD, cardiovascular disease; and MESA, Multi-Ethnic Study of Atherosclerosis.

had no substantive impact on results (Table S4). When sleep regularity was calculated across weekdays only, fewer participants had a weekday sleep duration SD  $>90$  minutes (33% versus 38% when compared with 7-day SD) and a weekday sleep timing SD  $>60$  minutes (36% versus 44% when compared with 7-day SD). A similar association was observed between irregular weekday sleep duration and carotid plaque and abnormal ABI; however, the association with high CAC burden was attenuated and no longer statistically significant (Table S5). We found no meaningful interactions between sleep duration regularity or sleep timing regularity and any subclinical markers by age (all  $P > 0.05$ ), or sex (all  $P > 0.05$ ).

## DISCUSSION

In this racially and ethnically diverse sample of older adults, participants with greater sleep duration irregularity were more likely to have a high burden of atherosclerosis as measured across several subclinical

markers, specifically higher CAC and an abnormally low ABI. These associations persisted after adjusting for BMI and prevalent CVD risk factors. When we examined sleep timing regularity, we observed an association between greater sleep timing irregularity and high CAC burden but not with other measures of subclinical CVD. Importantly, the associations observed also persisted after adjustment for severe OSA, average sleep duration, and sleep fragmentation. These results suggest that sleep regularity may have a unique etiologic link to subclinical CVD.

Sleep regularity has recently received increased attention as a relatively unexplored but relevant dimension of sleep health.<sup>27</sup> Day-to-day variations in sleep patterns appear to be prevalent in the general population,<sup>42,43</sup> with greater variation found across some racial and ethnic subgroups.<sup>44</sup> In our sample, more than one-third of older adults had a sleep duration SD  $>90$  minutes across a 7-day period. While it is common for sleep patterns to change as adults age,<sup>45</sup> the proportion of the general population with irregular sleep

**Table 4. Sleep Timing Regularity and Associations With Subclinical Markers of CVD: the MESA Sleep Study (2010–2013)**

	Sleep timing regularity (nightly within-person SD)			
	≤30 min	31–60 min	61–90 min	>90 min
Prevalence ratio (95% CI)				
Coronary artery calcium (>0)				
n (%)	234 (69.0)	348 (64.1)	223 (66.0)	222 (67.5)
Model 1	(Reference)	1.02 (0.94–1.12)	1.04 (0.94–1.15)	1.08 (0.98–1.19)
Model 2	(Reference)	1.03 (0.94–1.12)	1.04 (0.94–1.15)	1.06 (0.96–1.17)
Model 3	(Reference)	1.04 (0.95–1.14)	1.04 (0.94–1.14)	1.05 (0.95–1.16)
Coronary artery calcium (>300)				
n (%)	76 (22.4)	114 (21.0)	72 (21.3)	80 (24.3)
Model 1	(Reference)	1.19 (0.93–1.52)	1.15 (0.88–1.50)	1.39 (1.07–1.82)*
Model 2	(Reference)	1.24 (0.97–1.57)	1.19 (0.91–1.57)	1.43 (1.10–1.86)*
Model 3	(Reference)	1.29 (1.01–1.65)*	1.23 (0.93–1.62)	1.39 (1.07–1.82)*
Carotid plaque				
n (%)	240 (70.8)	361 (64.6)	230 (66.3)	236 (68.8)
Model 1	(Reference)	0.98 (0.90–1.07)	1.01 (0.91–1.11)	1.05 (0.96–1.16)
Model 2	(Reference)	0.97 (0.89–1.06)	1.00 (0.91–1.11)	1.04 (0.94–1.14)
Model 3	(Reference)	0.98 (0.90–1.07)	1.00 (0.90–1.10)	1.02 (0.92–1.13)
Carotid IMT (>0.9)				
n (%)	129 (39.6)	176 (32.3)	120 (35.7)	108 (32.8)
Model 1	(Reference)	0.92 (0.77–1.09)	0.96 (0.80–1.16)	0.89 (0.73–1.08)
Model 2	(Reference)	0.90 (0.76–1.07)	0.92 (0.76–1.11)	0.87 (0.71–1.06)
Model 3	(Reference)	0.93 (0.78–1.10)	0.94 (0.78–1.13)	0.85 (0.69–1.05)
Ankle-brachial index (<0.9)				
n (%)	18 (4.4)	31 (4.4)	21 (4.9)	33 (7.4)
Model 1	(Reference)	1.13 (0.64–1.99)	1.23 (0.67–2.26)	1.68 (0.97–2.93)
Model 2	(Reference)	1.08 (0.61–1.90)	1.25 (0.69–2.27)	1.72 (0.98–3.01)
Model 3	(Reference)	1.12 (0.64–1.98)	1.18 (0.64–2.17)	1.58 (0.92–2.74)

Coronary artery calcium, n=1549; carotid plaque n=1588; carotid IMT, n=1535; ankle-brachial index, n=1989. Model 1: age, sex, race and ethnicity, site. Model 2: M1+ education, income, work schedule, smoking status, alcohol consumption, physical activity, and body mass index; model 3: M2+systolic blood pressure, diastolic blood pressure, antihypertension medication use, statin medication use, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, prevalent diabetes. CVD indicates cardiovascular disease; IMT, intima-media thickness; and MESA, Multi-Ethnic Study of Atherosclerosis.

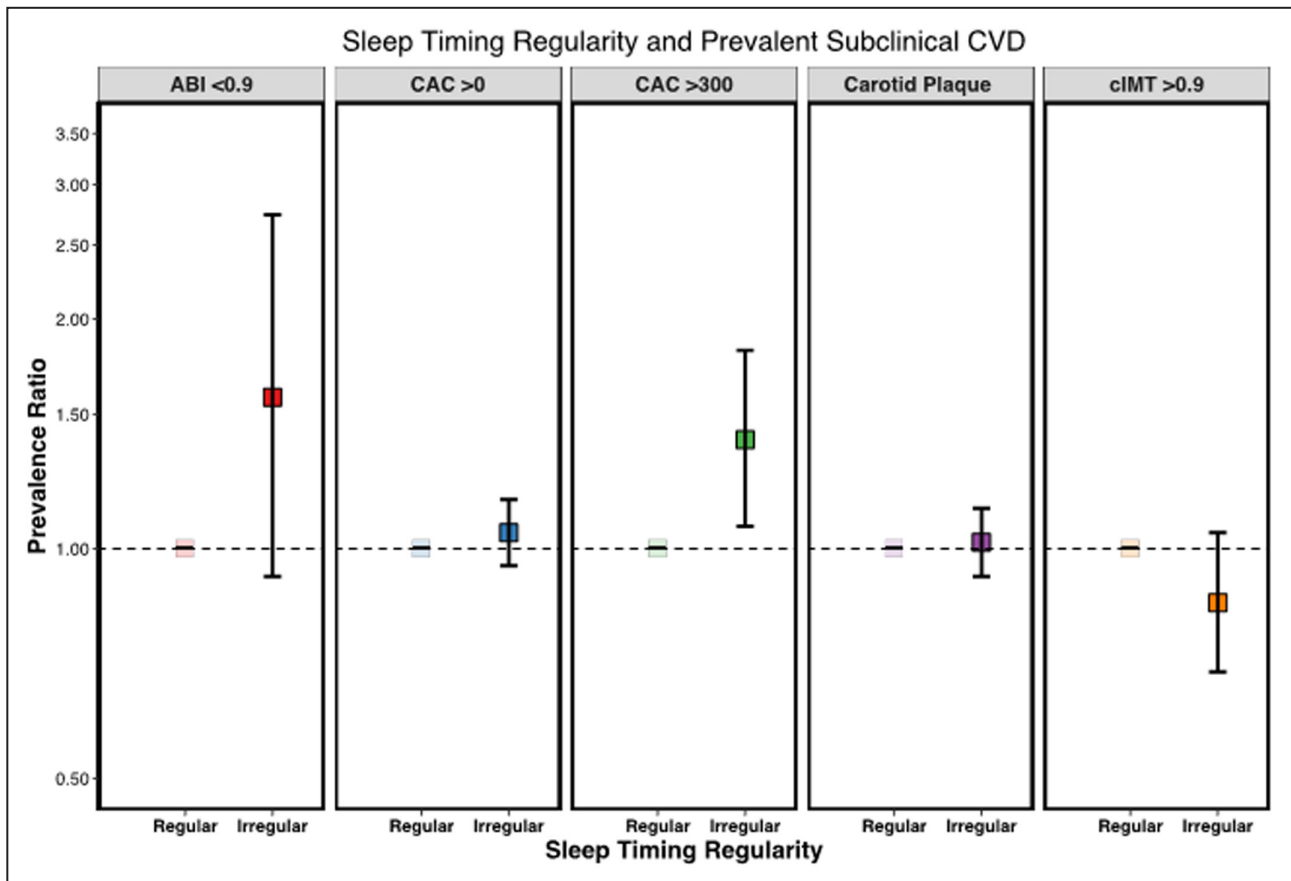
\*P value <0.05.

patterns, who are not shift workers, may be concerning given the growing evidence linking sleep irregularity with CVD risk.

Importantly, we found a statistically significant association between sleep duration regularity and subclinical measures of atherosclerosis, even after adjustment for CVD risk factors, and objectively measured severe OSA, sleep duration, and sleep fragmentation. In previous MESA analyses, severe OSA was associated with prevalent CAC<sup>13</sup> but not with high CAC burden or abnormal ABI.<sup>14</sup> Additionally, MESA investigators reported associations between short (<6 hours) and long (>8 hours) sleep durations and an abnormal ABI,<sup>14</sup> but not CAC.<sup>13</sup> In the context of these prior findings, the consistency of the associations between greater sleep duration irregularity and high CAC burden and reduced ABI are compelling. The persistence of these associations after accounting for

BMI, prevalent CVD risk factors, and objectively measured sleep duration and severe OSA suggests that sleep duration irregularity may have a unique etiologic role in atherosclerosis. Given that these associations are cross sectional, more research is warranted to better understand the role of sleep irregularity in the development of CVD.

Sleep regularity may be a modifiable dimension of sleep that can be targeted to reduce CVD risk in aging adults.<sup>20</sup> In fact, maintaining a regular sleep schedule and decreasing variability in sleep is a key component of clinical sleep hygiene recommendations.<sup>46</sup> Our findings suggest that these recommendations—that were developed to improve sleep—also may be useful as a cardiovascular health promotion strategy. Clinical trials, testing the role of interventions aimed at improving sleep duration regularity as a lifestyle component for CVD risk reduction intervention are warranted.



**Figure 3. Sleep timing regularity and prevalent subclinical CVD in the MESA Sleep Study.**

Adjusted for age, sex, race and ethnicity, site, education, yearly income, work schedule, smoking status, alcohol consumption, physical activity, body mass index, systolic blood pressure, diastolic blood pressure, antihypertensive medication use, statin medication use, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and prevalent diabetes; regular sleep timing:  $\leq 30$  minutes; irregular sleep timing:  $> 90$  minutes. ABI indicates ankle-brachial index; CAC, coronary artery calcium; cIMT, carotid intima-media thickness; CVD, cardiovascular disease; and MESA, Multi-Ethnic Study of Atherosclerosis.

Several mechanisms have been suggested to explain the association between sleep regularity and atherosclerosis. It is hypothesized that irregular sleep patterns, including night-to-night variability in sleep duration and sleep timing, can cause desynchronization of sleep–wake timing and circadian disruption.<sup>46</sup> Almost all major cardiovascular functions, including heart rate, blood pressure, vascular tone, and endothelial functions, are regulated by circadian clock genes.<sup>47,48</sup> Disruption or misalignment of circadian rhythms can interrupt these important cardiovascular functions, resulting in the promotion of chronic inflammation, alterations in glucose metabolism, heightened sympathetic nervous system activation, and increases in arterial pressures, all predisposing to the risk of atherosclerosis progression.<sup>22</sup> These hypotheses are further supported by previous studies that have reported increased inflammatory markers, including interleukin-6 and high-sensitivity C-reactive protein, in individuals with irregular sleep patterns<sup>49,50</sup>

and increased white blood cell count in individuals with excessive sleep disruption.<sup>51</sup> It is also plausible that irregular sleep patterns may be a marker of irregular health behaviors in general, including irregular timing of meals or exercise, which may contribute to circadian disruption.<sup>20,52</sup>

Strengths of this study include the objective assessment of sleep over a 7-day period and the inclusion of several complementary noninvasive measures of subclinical CVD. Further, the MESA cohort includes a diverse representation of older adults, extending the generalizability of our study findings. Studies show that sleep characteristics differ across racial and ethnic groups.<sup>34,53</sup> Diverse representation in study samples is necessary to better understand associations between poor sleep and CVD across the population. Unfortunately, this study is cross sectional and observational and inferences regarding causality need to be confirmed in future studies. However, our results are novel and support the further investigation of sleep

**Table 5. Sleep Duration Regularity and Subclinical Markers of CVD With Additional Adjustment for Severe OSA, Average Sleep Duration, and Sleep Fragmentation Index**

	Sleep duration regularity (nightly within-person SD)			
	≤60 min	61–90 min	91–120 min	>120 min
Prevalence ratio (95% CI)				
Coronary artery calcium (>0)				
Model 3	(Reference)	1.06 (0.98–1.16)	1.03 (0.94–1.13)	1.07 (0.98–1.18)
Model 3+OSA	(Reference)	1.06 (0.96–1.16)	1.01 (0.91–1.11)	1.09 (0.99–1.20)
Model 3+sleep duration	(Reference)	1.06 (0.97–1.16)	1.02 (0.93–1.13)	1.06 (0.97–1.17)
Model 3+fragmentation	(Reference)	1.05 (0.97–1.15)	1.01 (0.92–1.11)	1.05 (0.96–1.16)
Model 3+all sleep	(Reference)	1.04 (0.95–1.15)	0.99 (0.89–1.09)	1.06 (0.96–1.17)
Coronary artery calcium (>300)				
Model 3	(Reference)	1.26 (0.99–1.59)	1.32 (1.05–1.67)*	1.33 (1.03–1.71)*
Model 3+OSA	(Reference)	1.25 (0.98–1.61)	1.29 (1.00–1.67)*	1.34 (1.02–1.76)*
Model 3+sleep duration	(Reference)	1.28 (1.01–1.62)*	1.35 (1.07–1.71)*	1.39 (1.07–1.81)*
Model 3+fragmentation	(Reference)	1.24 (0.97–1.57)	1.28 (1.01–1.62)*	1.27 (0.98–1.65)
Model 3+all sleep	(Reference)	1.26 (0.98–1.62)	1.29 (0.99–1.68)*	1.37 (1.03–1.82)*
Carotid plaque				
Model 3	(Reference)	1.10 (1.01–1.20)*	1.09 (0.99–1.20)	1.09 (0.99–1.21)
Model 3+OSA	(Reference)	1.10 (1.00–1.21)*	1.08 (0.98–1.20)	1.10 (0.99–1.22)
Model 3+sleep duration	(Reference)	1.10 (1.01–1.21)*	1.09 (0.99–1.20)	1.10 (0.99–1.22)
Model 3+fragmentation	(Reference)	1.10 (1.00–1.20)*	1.08 (0.98–1.19)	1.08 (0.98–1.20)
Model 3+all sleep	(Reference)	1.10 (1.00–1.20)*	1.08 (0.97–1.19)	1.09 (0.98–1.22)
Carotid IMT (>0.9)				
Model 3	(Reference)	0.99 (0.83–1.18)	0.99 (0.83–1.18)	1.03 (0.85–1.25)
Model 3+OSA	(Reference)	1.01 (0.84–1.22)	1.03 (0.86–1.24)	1.05 (0.85–1.28)
Model 3+sleep duration	(Reference)	1.00 (0.84–1.19)	1.00(0.84–1.20)	1.06 (0.87–1.29)
Model 3+fragmentation	(Reference)	0.99 (0.83–1.18)	0.99 (0.82–1.18)	1.03 (0.85–1.26)
Model 3+all sleep	(Reference)	1.02 (0.84–1.23)	1.04 (0.86–1.26)	1.07 (0.87–1.32)
Ankle-brachial index (<0.9)				
Model 3	(Reference)	1.50 (0.86–2.59)	1.62 (0.98–2.70)	1.75 (1.03–2.95)*
Model 3+OSA	(Reference)	1.36 (0.76–2.44)	1.52 (0.89–2.59)	1.74 (1.00–3.04)*
Model 3+sleep duration	(Reference)	1.50 (0.87–2.61)	1.64 (0.98–2.74)	1.77 (1.05–2.97)*
Model 3+fragmentation	(Reference)	1.49 (0.86–2.59)	1.62 (0.97–2.70)	1.74 (1.03–2.95)*
Model 3+all sleep	(Reference)	1.37 (0.76–2.47)	1.54 (0.89–2.65)	1.77 (1.02–3.07)*

Model 3: age, sex, race and ethnicity, site, education, income, work schedule, smoking status, alcohol consumption, physical activity, body mass index, systolic blood pressure, diastolic blood pressure, antihypertension medication use, statin medication use, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, prevalent diabetes. CVD indicates cardiovascular disease; IMT, intima-media thickness; and OSA, obstructive sleep apnea.

\**P* value <0.05.

regularity in other samples with prospective assessment of CVD risk.

This study is one of the first studies to provide evidence that irregular sleep duration and timing are associated with measures of subclinical atherosclerosis. The development of atherosclerosis is a long process, allowing time for intervention before plaques have formed and hardened and can cause severe stenosis or rupture. Encouraging maintenance of regular sleep schedules with consistent sleep durations may be an important part of lifestyle recommendations provided in clinical practice for the prevention of CVD.

## ARTICLE INFORMATION

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### Supplemental Material

Appendix S1

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# **Supplemental Material**

**Table S1. MESA Sleep participant characteristics by categories of sleep timing regularity (N=2032)**

	<b>Sleep Timing Regularity</b>				
	<i>(Nightly within- Person Standard Deviations)</i>				
	<b>Overall</b>	$\leq 30$ mins n=420	31 – 60 mins n=713	61 – 90 mins n=443	>90 mins n=456
<b>Demographics</b>					
Female sex, n (%)	1090 (53.6)	219 (52.1)	402 (56.4)	237 (53.5)	232 (50.9)
<b>Race-ethnicity, n (%)</b>					
White	770 (37.9)	217 (51.7)	282 (39.6)	145 (32.7)	126 (27.6)
Chinese-American	226 (11.1)	34 (8.1)	84 (11.8)	58 (13.1)	50 (11.0)
Black, African-American	561 (27.6)	66 (15.7)	176 (24.7)	140 (31.6)	179 (39.3)
Hispanic	475 (23.4)	103 (24.5)	171 (24.0)	100 (22.6)	101 (22.1)
<b>Education, n (%)</b>					
< HS grad	613 (30.2)	129 (30.7)	229 (32.1)	124 (28.0)	131 (28.7)
Some college	615 (30.3)	118 (28.1)	206 (28.9)	135 (30.5)	156 (34.2)
College graduate plus	800 (39.4)	173 (41.2)	277 (38.8)	182 (41.1)	168 (36.8)
<b>Avg. Yearly Income*</b>					
<\$20,000	383 (18.8)	73 (17.4)	118 (16.5)	92 (20.8)	100 (21.9)
\$20,000 - <\$50,000	502 (24.7)	102 (24.3)	192 (26.9)	104 (23.5)	104 (22.8)
$\geq$ \$50,000	1086 (53.4)	233 (55.5)	379 (53.2)	242 (54.6)	232 (50.9)
<b>Work Schedule, n (%)</b>					
No Work	1148 (56.5)	266 (63.3)	404 (56.7)	228 (51.5)	250 (54.8)
Day shift	617 (30.4)	115 (27.4)	229 (32.1)	150 (33.9)	123 (27.0)
Other shift	246 (12.1)	37 (8.8)	72 (10.1)	60 (13.5)	77 (16.9)
<b>Lifestyle characteristics</b>					
Current Smoker, n (%)*	142 (7.0)	16 (3.8)	42 (5.9)	32 (7.2)	52 (11.4)
Current Alcohol Consumer, n (%)*	881 (43.4)	181 (43.1)	316 (44.3)	200 (45.1)	184 (40.4)
MVPA, MET mins/week*	5380 $\pm$ 6220	4760 $\pm$ 4230	5600 $\pm$ 6200	5790 $\pm$ 8230	5190 $\pm$ 5440
BMI, kg/m <sup>2</sup> *	28.8 $\pm$ 5.6	28.2 $\pm$ 5.2	28.7 $\pm$ 5.5	28.7 $\pm$ 5.4	29.6 $\pm$ 6.0
<b>Cardiovascular risk factors</b>					
Systolic blood pressure, mm Hg*	123.0 $\pm$ 20.0	124.0 $\pm$ 20.2	121.0 $\pm$ 18.4	124.0 $\pm$ 18.9	125.0 $\pm$ 22.9
Diastolic blood pressure, mm Hg*	68.3 $\pm$ 9.8	66.9 $\pm$ 9.7	67.3 $\pm$ 9.4	69.6 $\pm$ 9.3	70.0 $\pm$ 10.7
Anti-hypertensive medication use, n (%)	1090 (53.6)	224 (53.3)	367 (51.5)	239 (54.0)	260 (57.0)
Statin medication use, n (%)	775 (38.1)	182 (43.3)	252 (35.3)	166 (37.5)	175 (38.4)
LDL-C, mg/dL*	106.0 $\pm$ 32.4	102.0 $\pm$ 30.6	109.0 $\pm$ 32.4	108.0 $\pm$ 32.4	105.0 $\pm$ 33.7



HDL-C, mg/dL*	55.6 ± 16.5	54.9 ± 14.9	56.5 ± 16.6	56.4 ± 17.9	54.2 ± 16.1
Prevalent diabetes, n (%)*	397 (19.5)	64 (15.2)	121 (17.0)	86 (19.4)	126 (27.6)
Severe obstructive sleep apnea, n (%)*	386 (19.0)	67 (16.0)	120 (16.8)	91 (20.5)	108 (23.7)
Average sleep fragmentation	20.2 ± 7.0	18.9 ± 6.6	19.8 ± 6.9	21.0 ± 7.1	21.1 ± 7.1

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Data presented as mean ± SD unless specified; HS: high school; MVPA: moderate to vigorous intensity physical activity; BMI: Body Mass Index; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol.

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**Table S2. Sleep duration regularity and associations with subclinical markers of CVD excluding participants with prevalent Cardiovascular Disease: The MESA Sleep Study (2010-2013)**

		<b>Sleep Duration Regularity</b> (Nightly within- Person Standard Deviations)			
		≤60 mins	61 – 90 mins	91 – 120 mins	>120 mins
		<b>Prevalence Ratio (95% Confidence Interval)</b>			
<b>Coronary Artery Calcium (&gt;0)</b>					
Model 3	(reference)	1.06 (0.98, 1.16)	1.03 (0.94, 1.13)	1.07 (0.98, 1.18)	
<i>Model 3 - prevalent CVD</i>	(reference)	1.07 (0.98, 1.17)	1.02 (0.92, 1.12)	1.07 (0.97, 1.18)	
<b>Coronary Artery Calcium (&gt;300)</b>					
Model 3	(reference)	1.26 (0.99, 1.59)	<b>1.32 (1.05, 1.67)</b>	<b>1.33 (1.03, 1.71)</b>	
<i>Model 3 - prevalent CVD</i>	(reference)	<b>1.12 (1.01, 1.24)</b>	1.06 (0.95, 1.19)	<b>1.13 (1.01, 1.26)</b>	
<b>Carotid plaque</b>					
Model 3	(reference)	<b>1.10 (1.01, 1.20)</b>	1.09 (0.99, 1.20)	1.09 (0.99, 1.21)	
<i>Model 3 - prevalent CVD</i>	(reference)	<b>1.09 (1.00, 1.20)</b>	1.09 (0.99, 1.21)	1.08 (0.97, 1.20)	
<b>Carotid-IMT (&gt;0.9)</b>					
Model 3	(reference)	0.99 (0.83, 1.18)	0.99 (0.83, 1.18)	1.03 (0.85, 1.25)	
<i>Model 3 - prevalent CVD</i>	(reference)	0.98 (0.82, 1.18)	0.94 (0.78, 1.14)	1.06 (0.87, 1.29)	
<b>Ankle Brachial Index (&lt;0.9)</b>					
Model 3	(reference)	1.50 (0.86, 2.59)	1.62 (0.98, 2.70)	<b>1.75 (1.03, 2.95)</b>	
<i>Model 3 - prevalent CVD</i>	(reference)	1.12 (0.62, 2.04)	1.51 (0.90, 2.54)	1.63 (0.95, 2.78)	

CAC n=1431; Carotid plaque n=1464; Carotid-IMT n=1415; ABI n=1839; Model 1: age, sex, race/ethnicity, site; Model 2: M1+ education, income, work schedule, smoking status, alcohol consumption, physical activity, and BMI; Model 3: M2 + systolic blood pressure, diastolic blood pressure, anti-hypertension medication use, statin medication use, LDL-C, HDL-C, prevalent diabetes

**Table S3. Sleep duration regularity and associations with subclinical markers of CVD excluding participants with severe obstructive sleep apnea (OSA): The MESA Sleep Study (2010-2013)**

		<b>Sleep Duration Regularity</b> (Nightly within- Person Standard Deviations)			
		≤60 mins	61 – 90 mins	91 – 120 mins	>120 mins
		<b>Prevalence Ratio (95% Confidence Interval)</b>			
<b>Coronary Artery Calcium (&gt;0)</b>					
Model 3	(reference)	1.06 (0.98, 1.16)	1.03 (0.94, 1.13)	1.07 (0.98, 1.18)	
<i>Model 3 – severe OSA</i>	(reference)	1.07 (0.97, 1.19)	1.08 (0.97, 1.20)	<b>1.14 (1.02, 1.27)</b>	
<b>Coronary Artery Calcium (&gt;300)</b>					
Model 3	(reference)	1.26 (0.99, 1.59)	<b>1.32 (1.05, 1.67)</b>	<b>1.33 (1.03, 1.71)</b>	
<i>Model 3 – severe OSA</i>	(reference)	<b>1.13 (1.01, 1.26)</b>	<b>1.18 (1.05, 1.32)</b>	<b>1.18 (1.04, 1.34)</b>	
<b>Carotid plaque</b>					
Model 3	(reference)	<b>1.10 (1.01, 1.20)</b>	1.09 (0.99, 1.20)	1.09 (0.99, 1.21)	
<i>Model 3 – severe OSA</i>	(reference)	<b>1.12 (1.02, 1.24)</b>	<b>1.14 (1.03, 1.26)</b>	1.09 (0.97, 1.22)	
<b>Carotid-IMT (&gt;0.9)</b>					
Model 3	(reference)	0.99 (0.83, 1.18)	0.99 (0.83, 1.18)	1.03 (0.85, 1.25)	
<i>Model 3 – severe OSA</i>	(reference)	1.01 (0.83, 1.22)	1.00 (0.82, 1.22)	1.03 (0.82, 1.29)	
<b>Ankle Brachial Index (&lt;0.9)</b>					
Model 3	(reference)	1.50 (0.86, 2.59)	1.62 (0.98, 2.70)	<b>1.75 (1.03, 2.95)</b>	
<i>Model 3 – severe OSA</i>	(reference)	1.68 (0.92, 3.07)	1.67 (0.93, 3.02)	1.83 (0.98, 3.42)	

CAC n=1235; Carotid plaque n=1272; Carotid-IMT n=1233; ABI n=1565; Model 1: age, sex, race/ethnicity, site; Model 2: M1+ education, income, work schedule, smoking status, alcohol consumption, physical activity, and BMI; Model 3: M2 + systolic blood pressure, diastolic blood pressure, anti-hypertension medication use, statin medication use, LDL-C, HDL-C, prevalent diabetes; OSA: Obstructive Sleep Apnea

**Table S4. Sleep duration regularity and associations with subclinical markers of CVD with additional adjustment for season of actigraphy collection: The MESA Sleep Study (2010-2013)**

		<b>Sleep Duration Regularity</b> (Nightly within- Person Standard Deviations)			
		≤60 mins	61 – 90 mins	91 – 120 mins	>120 mins
		<b>Prevalence Ratio (95% Confidence Interval)</b>			
<b>Coronary Artery Calcium (&gt;0)</b>					
Model 3	(reference)	1.06 (0.98, 1.16)	1.03 (0.94, 1.13)	1.07 (0.98, 1.18)	
Model 3 + season	(reference)	1.06 (0.97, 1.16)	1.03 (0.94, 1.13)	1.07 (0.98, 1.18)	
<b>Coronary Artery Calcium (&gt;300)</b>					
Model 3	(reference)	1.26 (0.99, 1.59)	<b>1.32 (1.05, 1.67)</b>	<b>1.33 (1.03, 1.71)</b>	
Model 3 + season	(reference)	<b>1.10 (1.00, 1.22)</b>	1.10 (0.99, 1.22)	<b>1.14 (1.02, 1.26)</b>	
<b>Carotid plaque</b>					
Model 3	(reference)	<b>1.10 (1.01, 1.20)</b>	1.09 (0.99, 1.20)	1.09 (0.99, 1.21)	
Model 3 + season	(reference)	<b>1.10 (1.01, 1.20)</b>	1.09 (0.99, 1.20)	1.09 (0.99, 1.21)	
<b>Carotid-IMT (&gt;0.9)</b>					
Model 3	(reference)	0.99 (0.83, 1.18)	0.99 (0.83, 1.18)	1.03 (0.85, 1.25)	
Model 3 + season	(reference)	1.00 (0.84, 1.19)	0.99 (0.83, 1.19)	1.04 (0.86, 1.26)	
<b>Ankle Brachial Index (&lt;0.9)</b>					
Model 3	(reference)	1.50 (0.86, 2.59)	1.62 (0.98, 2.70)	<b>1.75 (1.03, 2.95)</b>	
Model 3 + season	(reference)	1.47 (0.85, 2.55)	1.61 (0.97, 2.66)	<b>1.72 (1.02, 2.92)</b>	

CAC n=1549; Carotid plaque n=1588; Carotid-IMT n=1535; ABI n=1989; Model 1: age, sex, race/ethnicity, site; Model 2: M1+ education, income, work schedule, smoking status, alcohol consumption, physical activity, and BMI; Model 3: M2 + systolic blood pressure, diastolic blood pressure, anti-hypertension medication use, statin medication use, LDL-C, HDL-C, prevalent diabetes

**Table S5. Weekday sleep duration regularity and associations with subclinical markers of CVD: The MESA Sleep Study (2010-2013)**

<b>Weekday Sleep Duration Regularity</b> (Nightly within- Person Standard Deviations)				
	≤60 mins	61 – 90 mins	91 – 120 mins	>120 mins
<b>Prevalence Ratio (95% Confidence Interval)</b>				
<b>Coronary Artery Calcium (&gt;0)</b>				
<i>n</i> (%)	363 (65.5)	273 (65.5)	211 (66.1)	180 (69.5)
Model 1	(reference)	1.03 (0.94, 1.18)	1.00 (0.91, 1.11)	1.05 (0.96, 1.15)
Model 2	(reference)	1.02 (0.94, 1.17)	1.00 (0.90, 1.11)	1.02 (0.93, 1.12)
Model 3	(reference)	1.02 (0.94, 1.11)	0.99 (0.89, 1.09)	1.01 (0.92, 1.11)
<b>Coronary Artery Calcium (&gt;300)</b>				
<i>n</i> (%)	113 (20.4)	84 (20.1)	78 (24.4)	67 (25.9)
Model 1	(reference)	1.03 (0.94, 1.14)	1.02 (0.91, 1.14)	<b>1.12 (1.01, 1.25)</b>
Model 2	(reference)	1.03 (0.94, 1.14)	1.01 (0.90, 1.13)	1.10 (0.99, 1.23)
Model 3	(reference)	1.05 (0.95, 1.15)	1.01 (0.90, 1.13)	1.08 (0.97, 1.20)
<b>Carotid plaque</b>				
<i>n</i> (%)	356 (64.1)	289 (67.5)	230 (69.3)	192 (70.3)
Model 1	(reference)	1.04 (0.95, 1.14)	<b>1.15 (1.05, 1.26)</b>	<b>1.12 (1.02, 1.23)</b>
Model 2	(reference)	1.04 (0.95, 1.14)	<b>1.14 (1.04, 1.25)</b>	<b>1.10 (1.01, 1.21)</b>
Model 3	(reference)	1.04 (0.95, 1.14)	<b>1.13 (1.03, 1.24)</b>	1.09 (0.99, 1.20)
<b>Carotid-IMT (&gt;0.9)</b>				
<i>n</i> (%)	183 (34.1)	133 (32.2)	119 (36.6)	98 (37.5)
Model 1	(reference)	1.16 (0.94, 1.32)	1.03 (0.86, 1.24)	1.10 (0.92, 1.31)
Model 2	(reference)	1.10 (0.94, 1.31)	0.99 (0.82, 1.20)	1.08 (0.90, 1.30)
Model 3	(reference)	1.08 (0.92, 1.28)	0.95 (0.78, 1.16)	1.07 (0.89, 1.29)
<b>Ankle Brachial Index (&lt;0.9)</b>				
<i>n</i> (%)	24 (3.5)	26 (4.8)	28 (6.8)	25 (7.3)
Model 1	(reference)	1.45 (0.87, 2.42)	<b>1.69 (1.02, 2.81)</b>	<b>1.88 (1.13, 3.12)</b>
Model 2	(reference)	1.45 (0.86, 2.45)	1.61 (0.97, 2.66)	<b>1.87 (1.12, 3.10)</b>
Model 3	(reference)	1.41 (0.83, 2.38)	1.59 (0.95, 2.66)	<b>1.70 (1.01, 2.85)</b>

CAC n=1549; Carotid plaque n=1588; Carotid-IMT n=1535; ABI n=1989; Model 1: age, sex, race/ethnicity, site; Model 2: M1+ education, income, work schedule, smoking status, alcohol consumption, physical activity, and BMI; Model 3: M2 + systolic blood pressure, diastolic blood pressure, anti-hypertension medication use, statin medication use, LDL-C, HDL-C, prevalent diabetes