

ORIGINAL INVESTIGATIONS

# Sleep Irregularity and Risk of Cardiovascular Events

## The Multi-Ethnic Study of Atherosclerosis

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### ABSTRACT

**BACKGROUND** The cardiovascular system exhibits strong circadian rhythms to maintain normal functioning. Irregular sleep schedules, characterized by high day-to-day variability in sleep duration or timing, represent possibly milder but much more common and chronic disruption of circadian rhythms in the general population than shift work.

**OBJECTIVES** This study aimed to prospectively examine the association between sleep regularity and risk of cardiovascular disease (CVD).

**METHODS** In MESA (Multi-Ethnic Study of Atherosclerosis), 1,992 participants free of CVD completed 7-day wrist actigraphy for sleep assessment from 2010 to 2013 and were prospectively followed through 2016. The study assessed sleep regularity using the SD of actigraphy-measured sleep duration and sleep-onset timing across 7 days. Incident CVD included nonfatal and fatal cardiovascular events. A Cox proportional hazards model was used to estimate hazard ratios (HRs) for incident CVD according to SD of sleep duration and timing, adjusted for traditional CVD risk factors (including CVD biomarkers) and other sleep-related factors (including average sleep duration).

**RESULTS** During a median follow-up of 4.9 years, 111 participants developed CVD events. The multivariable-adjusted HRs (95% confidence intervals) for CVD across categories of sleep duration SD were 1.00 (reference) for  $\leq 60$  min, 1.09 (0.62 to 1.92) for 61 to 90 min, 1.59 (0.91 to 2.76) for 91 to 120 min, and 2.14 (1.24 to 3.68) for  $>120$  min ( $p$  trend = 0.002). Similarly, compared with participants with a sleep timing SD  $\leq 30$  min, the HRs (95% confidence intervals) for CVD were 1.16 (0.64 to 2.13) for 31 to 60 min, 1.52 (0.81 to 2.88) for 61 to 90 min, and 2.11 (1.13 to 3.91) for  $>90$  min ( $p$  trend = 0.002). Exclusion of current shift workers yielded similar results.

**CONCLUSIONS** Irregular sleep duration and timing may be novel risk factors for CVD, independent of traditional CVD risk factors and sleep quantity and/or quality. (J Am Coll Cardiol 2020;75:991-9) © 2020 by the American College of Cardiology Foundation.



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## ABBREVIATIONS AND ACRONYMS

**AHI** = apnea-hypopnea index  
**CHD** = coronary heart disease  
**CI** = confidence interval  
**CVD** = cardiovascular disease  
**HR** = hazard ratio  
**REM** = rapid eye movement  
**WASO** = wake after sleep onset

The longstanding clinical observations that adverse cardiovascular events occur at a higher frequency in the morning suggest the existence of circadian mechanisms in the pathogenesis of cardiovascular disease (CVD) (1-3). Almost all major cardiovascular functions, including heart rate, blood pressure, vascular tone, and endothelial functions, display tightly regulated circadian patterns (4-8). Previous studies have linked certain forms of disrupted

circadian rhythms to increased CVD risk. For example, shift work has been associated with a modestly increased risk of coronary heart disease (CHD) and stroke after accounting for CVD risk factors (9,10). Several studies reported 4% to 29% higher incidence of myocardial infarction following transition to daylight savings time (11), which represents a combination of circadian phase shift and sleep loss by 1 h.

It is now increasingly recognized that circadian disruption may be a ubiquitous phenomenon that is not restricted to specific settings (e.g., in shift workers) and may accumulate over time (12,13), particularly considering increased day-to-day exposures to factors that can disrupt circadian rhythms (e.g., light exposure at night, media device use in the bedroom, and so on). However, the impact of such ubiquitous exposures to chronic circadian disruption on cardiovascular health has not been addressed at the population level. Irregular sleep schedules, characterized by high day-to-day variability in sleep duration or timing, may represent milder but chronic disruption of the circadian clock that is broadly relevant across the population. Specifically, individuals who frequently alter their sleep duration or sleep timing on a night-to-night basis may have higher cardiometabolic risk due to disrupted circadian functions. Assessment of sleep regularity requires assessment of sleep timing and duration across multiple nights and is often quantified by use of actigraphy over several days (14-19).

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A large amount of experimental and epidemiological evidence also supports the importance of adequate sleep duration for cardiovascular health (20,21). Although adequacy of sleep duration is often evaluated using measures of average, or habitual, sleep duration, this measure may not capture individuals with high sleep duration variability, in whom intermittent periods of sleep deprivation may not be fully compensated for by sleeping longer on other nights. In support of a role of sleep variability in

cardiometabolic health, recent literature demonstrates that higher variability in sleep duration or timing is associated with unfavorable metabolic profiles, such as higher blood pressure, dysregulated blood lipids, and insulin resistance (14-19). Because these adverse metabolic factors are precursors and strong predictors for CVD (22), irregular sleep may increase CVD risk through influencing metabolic health, in addition to its direct impact on the inherent rhythmicity of the cardiovascular system. Using 7-day actigraphic measurements of sleep collected under habitual settings, we hypothesized that both irregular sleep duration and timing at baseline were associated with increased incidence of CVD over 5 years, and that these associations were partly explained by worse baseline metabolic profiles among irregular sleepers.

## METHODS

**STUDY POPULATION.** We used the data from the MESA (Multi-Ethnic Study of Atherosclerosis) cohort, a prospective study of clinical and subclinical risk factors for progression of atherosclerosis (23). In 2000 to 2002, 6,814 white (38%), African American (28%), Hispanic (22%), and Chinese American (12%) participants aged 45 to 84 years who were free of clinical CVD were enrolled from 6 field centers across the United States (Baltimore City and Baltimore County, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; Northern Manhattan and the Bronx, New York; and St. Paul, Minnesota) and completed a baseline examination. Five follow-up examinations were performed throughout 2018 to update information on disease diagnoses, medication use, and lifestyle factors. Of 3,789 eligible participants who were invited to the MESA Sleep Ancillary Study at MESA Exam 5 (2010 to 2013), 2,261 (59.7%) participated in and completed the sleep examination, which included 7-day wrist actigraphy, 1 night of at-home polysomnography, and questionnaire-based sleep assessment (24). Compared with sleep study participants, those who did not participate were slightly older and more likely to be white, had ever smoked, and had a history of hypertension or chronic obstructive pulmonary disease (24). We further excluded participants with pre-existing CVD at the sleep study, with missing CVD event follow-up after the sleep study, or who had <5 days of actigraphic recordings, leaving 1,992 participants available for analysis. The institutional review board at each study site approved the study, and all participants provided written informed consent.

## SLEEP ASSESSMENT

Participants wore the Actiwatch Spectrum wrist actigraph (Philips Respironics, Murrysville, Pennsylvania) on their nondominant wrist for 7 consecutive days, while also indicating their sleep and wake times in the accompanying sleep diary. The actigraphic signals were scored as wake or sleep for each 30-s epoch according to increases or decreases in activity count, in combination with the event marker input by the participants, self-recorded sleep diary, and environmental light changes. The data were processed by a certified technician at the Sleep Reading Center of Brigham and Women's Hospital using Actiware-Sleep version 5.59 analysis software (Mini Mitter Co., Inc. Bend, Oregon). The interscorer reliability (based on subsamples of re-scored data) was 0.96 for sleep-onset timing and 0.89 for wake timing. We considered 2 SD measures to quantify sleep regularity: 1) 7-day SD in sleep duration; and 2) 7-day SD in sleep-onset timing. Because of their moderate correlation ( $r = 0.48$ ), we examined their associations with CVD risk separately in all analyses.

At-home polysomnography was performed for 1 night using the Compumedics Somte system (Compumedics, Abbotsville, Australia) according to the protocol developed previously (25); it measures sleep-disordered breathing, sleep stages (including rapid eye movement [REM] sleep and stage N3 sleep), wake after sleep onset (WASO), and heart rate. Sleep-disordered breathing was measured by the apnea-hypopnea index (AHI), which included all obstructive apneas plus hypopneas associated with  $\geq 4\%$  oxygen desaturation. There was a moderate agreement between actigraphy-measured and polysomnography-measured sleep duration on the same night (weighted kappa statistic = 0.30), which was mainly due to underestimation of WASO by actigraphy (26).

Participants also completed a sleep questionnaire to report their sleep habits and sleep-related traits, including insomnia symptoms measured by the Women's Health Initiative Insomnia Rating Scale ( $>10$  for elevated insomnia symptoms [27]), daytime sleepiness measured by the Epworth Sleepiness Scale ( $>10$  for excessive daytime sleepiness [28]), and chronotype measured by the modified Horne-Ostberg Morningness-Eveningness Questionnaire ( $\geq 18$  for morning type and  $\leq 11$  for evening type [29]). 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."

## ASSESSMENT OF CARDIOVASCULAR ENDPOINTS.

Incident cardiovascular events were identified at each MESA follow-up examination, as well as by telephone interviews conducted every 9 to 12 months. An estimated 98% of self-reported hospitalized cardiovascular events were adjudicated by expert review of medical records or death certificates, and 95% of out-of-hospital cardiovascular deaths were confirmed by next-of-kin (30). The primary endpoint was pre-defined as incident total CVD events, which included myocardial infarction, CHD death, resuscitated cardiac arrest, angina followed by revascularization, stroke, stroke death, and other atherosclerotic or CVD deaths, consistent with the previous study (31). The secondary endpoint was incidence of a hard CVD outcome that consisted of fatal and nonfatal CHD and stroke.

**STATISTICAL ANALYSIS.** Participants contributed person-time of follow-up from the date of sleep study until occurrence of a cardiovascular event (including cardiovascular death), other death, or the date of last follow-up. Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for incident CVD in relation to measures of sleep regularity. The primary sleep regularity measure was 7-day SD of sleep duration or sleep-onset timing, divided into 4 groups in 30-min increments to allow sufficient numbers of CVD cases in each group. Due to the different data distributions, the categories were  $\leq 60$ , 61 to 90, 91 to 120, and  $>120$  min for sleep duration SD and  $\leq 30$ , 31 to 60, 61 to 90, and  $>90$  min for sleep-onset timing SD. The secondary sleep regularity measure included the continuous SD measures (per hour) and the binary measures of  $>90$  versus  $\leq 90$  min (for both SD measures), a pre-defined cutoff that was associated with metabolic abnormalities in the previous investigation (14). The proportional hazards assumption was tested by examining the interactions between the continuous sleep regularity measures and the follow-up time and was found not to be violated ( $p$  interaction = 0.58 for sleep duration SD and 0.29 for sleep-onset timing SD).

All analyses were stratified by study site and adjusted for age at sleep study, sex, race/ethnicity, education, and work schedules (model 1). To evaluate whether the associations with sleep regularity were independent of known CVD risk factors, the multivariable model (model 2) adjusted for cigarette smoking, physical activity, depressive symptoms (measured by Center for Epidemiologic Studies Depression scale), body mass index, diabetes status, systolic blood pressure, high-density lipoprotein

**TABLE 1** Age-Standardized Characteristics of the Study Sample by Sleep Regularity Measures at MESA Sleep Ancillary Study

|                                         | Sleep Duration SD      |                      |          | Sleep-Onset Timing SD  |                      |          |
|-----------------------------------------|------------------------|----------------------|----------|------------------------|----------------------|----------|
|                                         | <90 min<br>(n = 1,206) | ≥90 min<br>(n = 786) | p Value* | <90 min<br>(n = 1,482) | ≥90 min<br>(n = 510) | p Value* |
| Age, yrs                                | 69.1 ± 9.0             | 69.5 ± 9.5           | 0.31     | 69.4 ± 9.1             | 68.8 ± 9.6           | 0.19     |
| Male                                    | 45                     | 46                   | 0.60     | 45                     | 47                   | 0.50     |
| Race/ethnicity                          |                        |                      | <0.001   |                        |                      | <0.001   |
| White                                   | 43                     | 29                   |          | 41                     | 28                   |          |
| Chinese American                        | 11                     | 13                   |          | 11                     | 12                   |          |
| African American                        | 23                     | 35                   |          | 24                     | 38                   |          |
| Hispanic                                | 24                     | 23                   |          | 24                     | 22                   |          |
| Work schedules                          |                        |                      | 0.01     |                        |                      | <0.001   |
| Day shift                               | 33                     | 27                   |          | 32                     | 27                   |          |
| Other shift                             | 11                     | 15                   |          | 11                     | 18                   |          |
| Do not work                             | 56                     | 58                   |          | 57                     | 55                   |          |
| Education                               |                        |                      | 0.80     |                        |                      | 0.23     |
| HS or less                              | 31                     | 31                   |          | 31                     | 31                   |          |
| Some college                            | 29                     | 30                   |          | 29                     | 31                   |          |
| Bachelor                                | 20                     | 19                   |          | 21                     | 17                   |          |
| Graduate school                         | 20                     | 20                   |          | 19                     | 22                   |          |
| Body mass index, kg/m <sup>2</sup>      | 28.5 ± 5.4             | 29.1 ± 6.0           | 0.02     | 28.5 ± 5.5             | 29.4 ± 6.1           | 0.005    |
| Current smoker                          | 5                      | 10                   | <0.001   | 6                      | 12                   | <0.001   |
| Physical activity, MET-h/week           | 41.4 ± 37.4            | 42.6 ± 40.0          | 0.51     | 42.1 ± 38.2            | 41.4 ± 39.2          | 0.71     |
| Depressive symptoms                     | 7.6 ± 7.0              | 9.0 ± 8.0            | <0.001   | 7.6 ± 7.0              | 9.6 ± 8.3            | <0.001   |
| Diastolic blood pressure, mm Hg         | 68.0 ± 9.7             | 69.2 ± 10.3          | 0.007    | 67.9 ± 9.6             | 70.0 ± 10.9          | <0.001   |
| Systolic blood pressure, mm Hg          | 121.9 ± 19.8           | 124.1 ± 20.9         | 0.02     | 122.2 ± 19.2           | 124.5 ± 23.0         | 0.04     |
| HDL cholesterol, mg/dl                  | 56.4 ± 16.2            | 55.0 ± 16.7          | 0.05     | 56.2 ± 16.3            | 54.9 ± 16.7          | 0.11     |
| Total cholesterol, mg/dl                | 185.4 ± 35.2           | 184.4 ± 37.8         | 0.57     | 185.7 ± 36.0           | 182.9 ± 36.8         | 0.13     |
| Diabetes                                | 15                     | 24                   | <0.001   | 16                     | 25                   | <0.001   |
| Average sleep duration, h†              | 7.4 ± 1.3              | 6.7 ± 1.5            | <0.001   | 7.4 ± 1.2              | 6.3 ± 1.6            | <0.001   |
| Insomnia‡                               | 21                     | 26                   | 0.01     | 23                     | 24                   | 0.67     |
| Excessive daytime sleepiness‡           | 12                     | 18                   | <0.001   | 13                     | 18                   | 0.01     |
| Chronotype‡                             |                        |                      | <0.001   |                        |                      | <0.001   |
| Evening type                            | 6                      | 9                    |          | 6                      | 10                   |          |
| Intermediate type                       | 38                     | 44                   |          | 38                     | 47                   |          |
| Morning type                            | 55                     | 47                   |          | 55                     | 43                   |          |
| Apnea-hypopnea index§                   | 19.0 ± 16.9            | 21.4 ± 19.1          | 0.001    | 19.4 ± 17.0            | 21.5 ± 19.9          | 0.005    |
| WASO, min§                              | 86.0 ± 58.7            | 105.0 ± 71.6         | <0.001   | 89.7 ± 60.8            | 104.5 ± 74.1         | <0.001   |
| %REM sleep§                             | 18.5 ± 6.3             | 17.4 ± 6.9           | 0.001    | 18.1 ± 6.3             | 18.0 ± 7.4           | 0.78     |
| %Stage N3 sleep§                        | 10.4 ± 9.0             | 10.0 ± 9.2           | 0.32     | 10.4 ± 9.0             | 9.9 ± 9.2            | 0.29     |
| Average heart rate in sleep, beats/min§ | 63.6 ± 8.9             | 65.0 ± 9.8           | 0.002    | 63.6 ± 9.0             | 65.5 ± 10.0          | 0.005    |

Values are mean ± SD or %. \*p Values were calculated using the Student's t-test for continuous variables and the chi-square test for categorical variables. †Based on 7-day actigraphy. ‡Based on sleep questionnaire. §Based on 1-night polysomnography.

HDL = high-density lipoprotein; HS = high school; MESA = the Multi-Ethnic Study of Atherosclerosis; REM = rapid eye movement; WASO = wake after sleep onset.

cholesterol, and total cholesterol, all collected at MESA Exam 5. Because multiple sleep traits (e.g., sleep duration [20], sleep apnea [32], insomnia symptoms [33], and so on) were also shown to predict CVD risk, we further controlled for several sleep-related factors in the final fully-adjusted model (model 3), including average sleep duration (from actigraphy), insomnia symptoms, self-reported chronotype, excessive daytime sleepiness, and sleep apnea (by the AHI).

We performed subgroup analyses to explore whether associations with sleep regularity differed by age, sex, race/ethnicity, average sleep duration, and

work schedules. Stratum-specific associations were estimated for the continuous sleep regularity measures (per hour), and a likelihood ratio test that compared the models with versus without the multiplicative interaction terms was used to assess statistical significance. We also conducted several sensitivity analyses to test the robustness of the results. First, to address the potential reverse causation that certain preclinical symptoms of CVD may disturb sleep patterns, we conducted a series of lagged analyses by excluding incident CVD cases diagnosed within the first 6, 12, and 18 months after the sleep

study. Second, we repeated the analysis that evaluated associations with hard CVD outcomes, the secondary endpoint. Third, we examined the associations between sleep regularity measures on weekdays and incident total CVD. All analyses were conducted in SAS 9.4 (SAS Institute, Cary, North Carolina), and 2-sided p values <0.05 were considered statistically significant.

## RESULTS

Of 1,992 MESA participants free of known CVD at the time of the sleep study, 786 (39.5%) had sleep duration SD >90 min and 510 (25.6%) had sleep-onset timing SD >90 min (Table 1). Metabolic and sleep-related parameters were in general worse when we compared participants with higher (>90 min) versus lower (≤90 min) sleep duration SD, including higher levels of body mass index, blood pressure, diabetes prevalence, AHI, insomnia symptoms, daytime sleepiness, as well as longer WASO, shorter average sleep duration, less REM sleep, and higher heart rate during sleep. Compared with those with regular sleep, participants with more irregular sleep were more likely to be African Americans, had nonday shift work, were current smoker, reported higher depressive symptoms, and identified themselves as evening or intermediate chronotype and less likely as morning chronotype. We observed similar differences by sleep-onset timing SD.

A total of 111 incident total CVD events occurred after a median follow-up of 4.9 years (including 35 myocardial infarctions, 16 CHD deaths, 30 strokes, 17 other coronary events, and 13 other atherosclerotic or CVD deaths) (Online Table 1), yielding an overall incidence rate of 11.8 per 1,000 person-years. In unadjusted analysis, there was a trend toward increased incidence of CVD with more irregular sleep duration, with the CVD incidence per 1,000 person-years being 8.8, 9.1, 14.1, and 19.3 for sleep duration SD categories of ≤60, 61 to 90, 91 to 120 and >120 min, respectively (Table 2). After adjustment for CVD risk factors (model 2), the risk for incident CVD increased progressively with increasing sleep duration variability. Compared with sleep duration SD ≤60 min, the HRs (95% CIs) were 1.07 (0.61 to 1.88) for sleep duration SD 61 to 90 min, 1.54 (0.89 to 2.65) for 91 to 120 min, and 2.02 (1.20 to 3.39) for >120 min. When evaluating sleep duration SD as a continuous variable, every 1-h increase in sleep duration SD was associated with 36% higher CVD risk (95% CI: 1.07 to 1.73; p trend = 0.02). The association became somewhat stronger after further adjusting for sleep-related factors (model 3).

**TABLE 2** Associations of 7-Day Variability in Sleep Duration and Sleep-Onset Timing With Risk of Total Cardiovascular Disease

|                          |           | Model 1          | Model 2          | Model 3          |
|--------------------------|-----------|------------------|------------------|------------------|
| Cases/Person-Years       |           | HR (95% CI)      |                  |                  |
| SD of sleep duration     |           |                  |                  |                  |
| Categorical              |           |                  |                  |                  |
| ≤60 min                  | 29/3,278  | 1.00 (ref)       | 1.00 (ref)       | 1.00 (ref)       |
| 61-90 min                | 23/2,541  | 1.06 (0.61-1.85) | 1.07 (0.61-1.88) | 1.09 (0.62-1.92) |
| 91-120 min               | 26/1,842  | 1.61 (0.93-2.76) | 1.54 (0.89-2.65) | 1.59 (0.91-2.76) |
| >120 min                 | 33/1,711  | 2.18 (1.31-3.63) | 2.02 (1.20-3.39) | 2.14 (1.24-3.68) |
| Continuous               |           |                  |                  |                  |
| Per 1 h                  | 111/9,372 | 1.41 (1.12-1.79) | 1.36 (1.07-1.73) | 1.39 (1.08-1.78) |
| p value for trend        |           | 0.006            | 0.02             | 0.002            |
| Binary                   |           |                  |                  |                  |
| ≤90 min                  | 52/5,818  | 1.00 (ref)       | 1.00 (ref)       | 1.00 (ref)       |
| >90 min                  | 59/3,554  | 1.83 (1.25-2.68) | 1.72 (1.17-2.53) | 1.76 (1.18-2.63) |
| p value                  |           | 0.004            | 0.01             | 0.009            |
| SD of sleep-onset timing |           |                  |                  |                  |
| Categorical              |           |                  |                  |                  |
| ≤30 min                  | 17/1,846  | 1.00 (ref)       | 1.00 (ref)       | 1.00 (ref)       |
| 31-60 min                | 31/3,235  | 1.19 (0.66-2.16) | 1.21 (0.66-2.22) | 1.16 (0.64-2.13) |
| 61-90 min                | 25/2,022  | 1.51 (0.81-2.82) | 1.48 (0.79-2.78) | 1.52 (0.81-2.88) |
| >90 min                  | 38/2,269  | 2.05 (1.14-3.69) | 1.95 (1.08-3.54) | 2.11 (1.13-3.91) |
| Continuous               |           |                  |                  |                  |
| Per 1 h                  | 111/9,372 | 1.17 (1.06-1.30) | 1.16 (1.05-1.29) | 1.18 (1.06-1.31) |
| p value for trend        |           | 0.002            | 0.005            | 0.002            |
| Binary                   |           |                  |                  |                  |
| ≤90 min                  | 73/7,103  | 1.00 (ref)       | 1.00 (ref)       | 1.00 (ref)       |
| >90 min                  | 38/2,269  | 1.67 (1.12-2.48) | 1.58 (1.05-2.37) | 1.69 (1.10-2.61) |
| p value                  |           | 0.01             | 0.03             | 0.02             |

Model 1: Stratified by study site, and adjusted for age, sex, race/ethnicity, education, and work schedules. Model 2: Model 1 + adjusted for smoking status, physical activity, depressive symptoms, body mass index, diabetes status, systolic blood pressure, HDL cholesterol, and total cholesterol. Model 3: Model 2 + adjusted for average sleep duration, insomnia symptom scores, chronotype, Epworth Sleepiness Scale and apnea-hypopnea index. CI = confidence interval; HR = hazard ratio; other abbreviation as in Table 1.

A similar positive association between sleep-onset timing SD and incident CVD risk was observed (Table 2). Compared with sleep-onset timing SD ≤30 min, the HRs (95% CIs) for CVD after adjusting for CVD risk factors and sleep-related factors (model 3) were 1.16 (0.64 to 2.13) for 31 to 60 min, 1.52 (0.81 to 2.88) for 61 to 90 min, and 2.11 (1.13 to 3.91) for >90 min, with 18% higher risk (95% CI: 1.06 to 1.31) for every 1-h increase in sleep-onset timing SD (p trend = 0.002). When sleep duration SD and sleep-onset timing SD were simultaneously included in the model, the association was attenuated for both sleep regularity measures; the fully-adjusted HRs (95% CIs) associated with 1-h increase in sleep variability were 1.23 (0.94 to 1.63) for sleep duration and 1.14 (1.01 to 1.28) for sleep timing.

Tests for effect modification by age, sex, race/ethnicity, average sleep duration, or work schedules were not statistically significant (p interaction >0.43) (Table 3), although a suggestion of positive



**TABLE 3 Subgroup Analysis of the Association Between Sleep Variability Per Hour and Incident Cardiovascular Disease**

|                        | Sleep Duration SD |                          | Sleep-Onset Timing SD |                          |
|------------------------|-------------------|--------------------------|-----------------------|--------------------------|
|                        | HR (95% CI)*      | p Value for Interaction† | HR (95% CI)*          | p Value for Interaction† |
| Age                    |                   | 0.63                     |                       | 0.96                     |
| <70 yrs                | 1.50 (0.99–2.27)  |                          | 1.17 (0.96–1.42)      |                          |
| ≥70 yrs                | 1.34 (0.97–1.87)  |                          | 1.19 (1.04–1.36)      |                          |
| Sex                    |                   | 0.57                     |                       | 0.44                     |
| Male                   | 1.54 (1.11–2.14)  |                          | 1.25 (1.09–1.44)      |                          |
| Female                 | 1.40 (0.90–2.19)  |                          | 1.17 (0.96–1.42)      |                          |
| Race/ethnicity         |                   | 0.43                     |                       | 0.61                     |
| White                  | 0.91 (0.57–1.46)  |                          | 1.04 (0.84–1.29)      |                          |
| African American       | 1.66 (0.93–2.95)  |                          | 1.34 (1.05–1.71)      |                          |
| Hispanic               | 2.19 (1.35–3.57)  |                          | 1.38 (1.13–1.69)      |                          |
| Chinese                | 2.41 (0.77–7.59)  |                          | 1.55 (0.96–2.51)      |                          |
| Average sleep duration |                   | 0.92                     |                       | 0.76                     |
| <7 h                   | 1.46 (0.99–2.15)  |                          | 1.22 (1.04–1.42)      |                          |
| 7–8                    | 1.40 (0.85–2.33)  |                          | 1.30 (1.06–1.59)      |                          |
| >8 h                   | 1.16 (0.66–2.04)  |                          | 1.03 (0.74–1.45)      |                          |
| Work schedules         |                   | 0.84                     |                       | 0.76                     |
| Day shift/do not work  | 1.42 (1.08–1.87)  |                          | 1.20 (1.07–1.35)      |                          |
| Other shift            | 1.66 (0.65–4.21)  |                          | 1.43 (0.93–2.20)      |                          |

\*Stratified by study site, and adjusted for age, sex, race/ethnicity, education, work schedules, smoking status, physical activity, depressive symptoms, body mass index, diabetes status, systolic blood pressure, HDL cholesterol, total cholesterol, average sleep duration, insomnia symptom scores, chronotype, Epworth Sleepiness Scale, and apnea-hypopnea index. †p value for interaction was calculated by the likelihood ratio test comparing the models the cross-product interaction term(s) with versus without the cross-product interaction term(s).  
Abbreviations as in Table 2.

associations between irregular sleep and CVD risk was observed in racial/ethnic minorities (African Americans, Hispanics, and Chinese Americans) and not in whites. The results did not alter considerably when we excluded CVD cases diagnosed in the first 6 months ( $n = 8$ ), 12 months ( $n = 24$ ), or 18 months ( $n = 36$ ) after the sleep study (Online Table 2) or when only hard CVD outcomes ( $n = 81$ ) were considered (Online Table 3). Despite a tendency toward lower sleep variability during weekdays (e.g., 34.1% had sleep duration SD >90 min and 39.8% had sleep-onset timing SD >60 min during weekdays, compared with 7-day SDs of 39.5% and 47.2%, respectively), there were similar positive associations between weekday sleep irregularity measures and CVD risk (Online Table 4).

## DISCUSSION

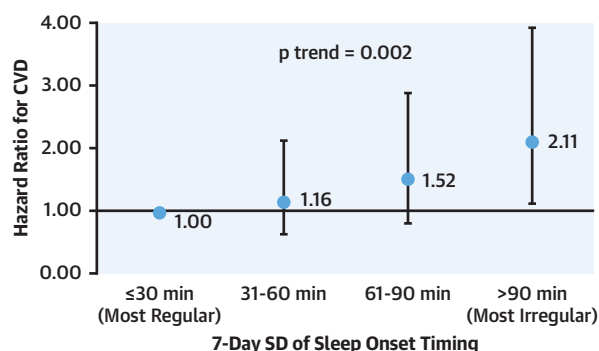
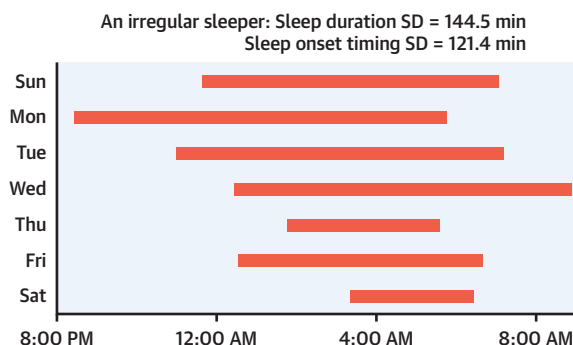
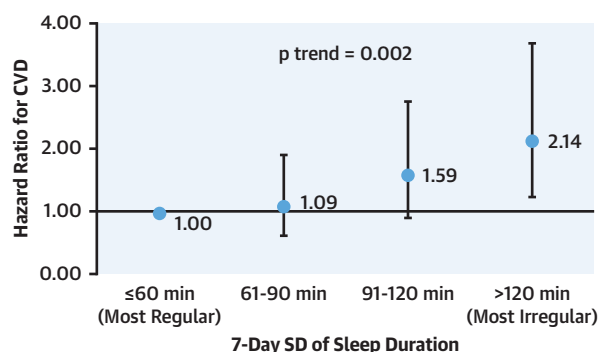
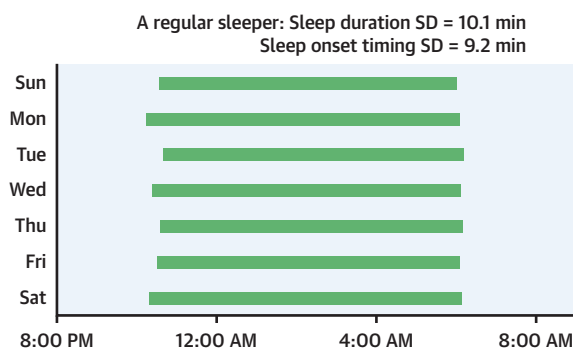
In this first prospective investigation of sleep regularity, a marker for chronic circadian disruption and intermittent sleep deprivation, with CVD incidence, participants with the most irregular sleep duration or timing had >2-fold risk of developing CVD over a median follow-up of 4.9 years compared with participants with the most regular sleep patterns (Central Illustration). This association was consistently

observed in different strata of the study sample, including subgroups defined by age, sex, race/ethnicity (except white participants), sleep duration, and work schedules. Most importantly, the results remained robust after considering multiple established CVD risk factors and conventional measures of sleep quantity and quality, which suggested that irregular sleep duration and timing might be novel and independent risk factors for CVD.

No previous studies have examined the ubiquitous exposure to chronic circadian disruption, as measured by 7-day variations in sleep duration and sleep-onset timing in relation to CVD risk. However, multiple lines of evidence have suggested that circadian disruption in specific settings could confer increased CVD risk. For example, studies from the United States and several European countries found a significant rise in heart attack and stroke in the first few days after the shift to daylight savings time in the spring (11). Elevated CVD risk was observed among rotating night shift workers or frequent intercontinental travelers, including flight crews (9,10,34,35). Social jetlag, defined as the difference in sleep timing between workdays and free days, was associated with unfavorable cardiometabolic risk factors (36,37). Although social jetlag is a major contributor to day-to-day sleep irregularity, our results indicated that irregular sleep restricted to weekdays was also associated with increased CVD risk.

Our findings were plausible because of previous research that linked actigraphy-assessed sleep regularity with metabolic risk factors that predisposed to atherosclerosis (14–19). Although we also observed that participants with irregular sleep tended to have worse cardiometabolic risk profiles at baseline, adjustment for established CVD risk factors (e.g., blood pressure, lipids, diabetes, etc.) only explained a small portion of the associations between sleep irregularity and CVD risk. This suggested that there might be other mechanisms through which irregular sleep influences CVD risk. Circadian clock genes, such as *clock*, *per2*, and *bmal1*, were shown experimentally to control a broad range of cardiovascular rhythms and functions, from blood pressure and endothelial functions to vascular thrombosis and cardiac remodeling (38–41). Circadian disruption and poor sleep also influence the rhythms of the autonomic nervous system (42,43), which directly govern normal cardiac functioning. Irregular sleep may further disturb behavioral rhythms with regard to timing and/or amount of eating or exercise, which poses even higher CVD risk to irregular sleepers, such as nocturnal food intake and skipping breakfast (44–46). However, few studies have examined the biological

# **CENTRAL ILLUSTRATION** Regular and Irregular Sleep Patterns in Relation to Cardiovascular Disease Risk



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**(Left)** Two real examples of 7-day sleep patterns measured by actigraphy: a highly regular sleeper with approximately 10 min SD for both sleep duration and sleep-onset timing and a highly irregular sleeper with >120 min for both SD measures. These 2 examples correspond to the most regular and most irregular categories in the figures on the **right**. Compared with those with the most regular sleep patterns, participants with the most irregular sleep patterns had >2-fold increased risk of developing cardiovascular events over a median follow-up of 4.9 years (p trend = 0.002 for both sleep duration SD and sleep onset timing SD). CVD = cardiovascular disease.

consequences of irregular sleep per se under a long-term habitual setting, and more studies are needed to understand the exact mechanisms linking irregular sleep and CVD risk.

Although rotating night shift work is considered as a more severe form of circadian disruption than sleep irregularity, the increased CVD risk associated with sleep irregularity in this study appeared stronger compared with previous reports of shift work and CVD (12). There are multiple potential explanations, including a healthy worker effect in published studies and the ubiquitous exposure to circadian disruption (e.g., irregular sleep schedules) among nonshift workers or short-term shift workers (12) that may mask the contrast between shift workers and nonshift workers. Our findings underscored the importance of considering sources of circadian disruption other than shift work, such as that resulting from large

night-to-night variability in sleep duration and timing, and highlighted that irregular sleep is highly prevalent in this racial/ethnically diverse community sample.

Our findings highlight the importance of sleep variability as a healthy sleep target apart from sleep duration, consistent with emerging concepts of multidimensional components of sleep health (47). Most previous large epidemiological studies focused on average sleep duration, with both short and long sleep durations associated with adverse cardiometabolic profiles (20,48). Our findings that showed increased CVD incidence with variable sleep duration or timing persisted after adjusting for average sleep duration. Further research is needed to determine the extent to which increased sleep variability influences CVD via effects on circadian disruption versus exposing individuals to

intermittent short sleep that is inadequately compensated for by oversleeping.

Our results suggested initial sleep consistency targets that could be tested for improving cardiometabolic health. A 7-day SD >90 min for either sleep duration variability or sleep-onset timing variability was consistently associated with higher CVD risk. Whether this cutoff can be generalized as a threshold target for promoting cardiometabolically healthy sleep requires studies in other populations. If confirmed, use of wearable devices or specialized mobile apps may provide opportunities to incorporate sleep consistency targets into future interventions designed to reduce CVD incidence.

**STUDY STRENGTHS AND LIMITATIONS.** The strengths of the study included the prospective study design, objectively assessed sleep variability over 7 days, expert adjudication of incident CVD outcomes, and availability of many important factors that we could control for in the analysis. The results remained robust in multiple sensitivity analyses that addressed potential reverse causality and subgroup heterogeneity, which gave additional credibility to an association of irregular sleep patterns with CVD risk.

There are also some limitations. First, the study sample was modest (but large for an actigraphy study) with relatively short follow-up. Therefore, we could not fully address potential reverse causation by introducing a longer disease induction period (e.g., 2 years); interpretation of the subgroup analysis should be cautious because of the sample size. The modest sample also precluded our ability to examine associations with individual types of CVD endpoints, such as CHD versus stroke or mortality. Second, residual and unmeasured confounding could not be excluded. Finally, there were limitations for the actigraphy data. For example, because actigraphy estimates sleep–wake times based on activity, it only modestly correlates with polysomnography-measured sleep parameters and may not perform well in individuals

with abnormal activity patterns during sleep (26,49). Nonetheless, it is a recommended tool for assessing chronic insomnia and circadian rhythm disorders in clinical settings (50).

## CONCLUSIONS

Higher day-to-day variations in sleep duration and timing are both associated with increased risk of CVD, independent of a wide range of factors including CVD risk factors, sleep duration, and sleep apnea. Because of the strong biological plausibility of our associations and previous research that implicated sleep variability with CVD risk factors, our results support considering inconsistent sleep patterns as a novel CVD risk factor and suggest the need to evaluate the role of healthy sleep practice interventions as a strategy for cardiovascular risk reduction.

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## PERSPECTIVES

### COMPETENCY IN MEDICAL KNOWLEDGE:

Irregular sleep patterns in older people without known CVD are associated with an elevated risk of developing cardiovascular events.

**TRANSLATIONAL OUTLOOK:** Because of the high prevalence of irregular sleep patterns in the population, future studies should evaluate the impact on cardiovascular health of interventions that enhance sleep pattern consistency.

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**KEY WORDS** cardiovascular disease, circadian rhythms, cohort study, risk factor, sleep patterns

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**APPENDIX** For supplemental tables, please see the online version of this paper.