Cross-sectional and Prospective Associations of Actigraphy-Assessed Sleep Regularity With Metabolic Abnormalities: The Multi-Ethnic Study of Atherosclerosis

Tianyi Huang[1] *and Susan Redline*[2]

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OBJECTIVE

To cross-sectionally and prospectively investigate the association between irregular sleep patterns, a potential marker for circadian disruption, and metabolic abnormalities.

RESEARCH DESIGN AND METHODS

In the Multi-Ethnic Study of Atherosclerosis, participants completed 7-day actigraphy at exam 5 (2010–2013) and were prospectively followed throughout exam 6 (2016 to 2017). Sleep regularity was quantified by the 7-day SD of actigraphy-assessed sleep duration and sleep onset timing. Metabolic abnormalities were defined by *1*) the National Cholesterol Education Program Adult Treatment Panel III criteria and *2*) a data-driven clustering of metabolic factors.

RESULTS

In the exam 5 cross-sectional analysis adjusted for sociodemographic and lifestyle factors (*n* = 2,003), every 1-h increase in the sleep duration SD was associated with 27% (95% CI 1.10, 1.47) higher odds of metabolic syndrome, and every 1-h increase in the sleep timing SD was associated with 23% (95% CI 1.06, 1.42) higher odds. The associations remained significant, with additional adjustment for sleep-related factors including sleep duration. In the prospective analysis (*n* = 970), the corresponding fully adjusted odds ratio (OR) (95% CI) was 1.27 (0.97, 1.65) for sleep duration and 1.36 (1.03, 1.80) for sleep timing. Compared with the cluster of few metabolic changes, every 1-h increase in sleep variability was associated with almost doubled odds for the cluster characterized by incidence of multiple metabolic abnormalities (OR 1.97 [95% CI 1.18, 3.30] for sleep duration and OR 2.10 [95% CI 1.25, 3.53] for sleep timing).

CONCLUSIONS

Increased variability in sleep duration and timing was associated with higher prevalence and incidence of metabolic abnormalities even after considering sleep duration and other lifestyle factors.

[1]*Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA*

[2]*Division of Sleep and Circadian Disorders, Department of Medicine, Brigham and Women's Hospital, Beth Israel Deaconess Medical Center, and Harvard Medical School, Boston, MA*

Corresponding author: Tianyi Huang, tih541@mail.harvard.edu

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Modern environment and lifestyle, such as increased light exposure and activities during night and widespread use of electronic media and mobile devices, not only deprive humans of sufficient sleep, but also considerably disturb the regularity of sleep behaviors. An adequate amount of sleep, which is essential for global rejuvenation of the human body, plays a central role in normal functioning of metabolism and energy homeostasis (1,2). As a result, reduced quantity of sleep has been associated with higher risk of obesity, metabolic syndrome, and diabetes in numerous previous studies (3–5). However, less is known regarding the impact of irregular sleep (i.e., high day-to-day variability in sleep duration and timing), which could negatively influence metabolic health through sleep debt caused by nights of sleep deprivation not compensated for by nights of extended sleep and/or by disruption of circadian rhythms.

To date, a majority of epidemiologic studies on sleep health and cardiometabolic outcomes has examined average sleep duration, with less research on variations in sleep duration and timing. It is now well established that an inherent circadian rhythmicity is a universal mechanism underlying various biologic processes (6), including metabolism (7,8). Clear circadian patterns are exhibited from gene expressions to downstream circulating metabolites (9–12), as well as secretion of hormones involved in metabolic regulation (13,14). Metabolic alterations induced by circadian misalignment are most profound in individuals undergoing rotating night shift work or experiencing jet lag (15). By contrast, irregular sleep schedules may be the most common cause of disruption of the circadian system in the general population, potentially leading to chronic, cumulative metabolic effects. In addition to causing biologic rhythm disturbances, sleep irregularity may further desynchronize behavioral rhythms such as meal timing, which exacerbates the adverse metabolic consequences of irregular sleep (7,16,17). Emerging evidence has linked irregular sleep duration and timing, independent of sleep duration, with higher prevalence of unfavorable metabolic factors such as obesity, hypertension, and dyslipidemia (18–22).

One notable limitation of prior studies on sleep regularity and metabolic factors is the cross-sectional design, precluding the ability to address the directionality of the association and imply potential causality. Also, previous studies did not take full account of factors closely related to both sleep regularity and metabolic functions, such as diet and sleep-disordered breathing, which may confound the observed associations. Given the high prevalence of irregular sleep and metabolic syndrome, elucidating their associations may help inform public health recommendations for healthy sleep. Therefore, we conducted the current study to examine cross-sectional and prospective associations between actigraphy-assessed sleep regularity and metabolic syndrome in men and women participating in the Multi-Ethnic Study of Atherosclerosis (MESA). We hypothesized that individuals with greater variation in nightly sleep duration and variation in sleep onset would have greater prevalence and incidence of metabolic syndrome and that these associations would persist after adjusting for average sleep duration.

RESEARCH DESIGN AND METHODS

Study Population

MESA is a prospective, multicenter, community-based study initiated between 2000 and 2002 to investigate the prevalence and progression of subclinical cardiovascular disease. A total of 6,814 men and women (aged 45–84 years; 38% white, 28% African American, 22% Hispanic, and 12% Chinese American) who were free of clinical cardiovascular disease at the baseline examination were recruited from six field centers across the U.S. Multiple waves of follow-up examinations were conducted to collect health-related information and identify incident disease diagnoses. At exam 5 (2010–2013), 3,789 eligible participants who reported no regular use of oral devices, nocturnal oxygen, or positive airway pressure devices were invited to participate in the MESA-Sleep Ancillary study, which included one-night at-home polysomnography, 7-day wrist actigraphy, and assessment of sleep habits through questionnaires (23). A total of 2,261 participants (59.7% participation rate) completed at least one component of the sleep study, including 2,156 with actigraphy data. Compared with participants in the sleep study, those who did not participate were slightly more likely to be older, white, have ever smoked, and have a history of hypertension or chronic obstructive pulmonary disease, as reported previously (23). After excluding those with <5 days of actigraphic measurements (n = 21), missing data on one or more metabolic factors (n = 33), or potentially implausible outlying sleep variability measures (i.e., the 7-day SD of sleep onset timing >4 h; n = 99), the cross-sectional analysis included 2,003 participants; a subset of 970 participants who did not meet the criteria for metabolic syndrome at exam 5 and had repeated measures of metabolic factors at exam 6 (2016 to 2017) were included in the prospective analysis of incident disease. The institutional review board at each study site approved the study, and all participants provided written informed consent.

Sleep Assessment

To objectively measure sleep duration and quality, participants were asked to wear the Actiwatch Spectrum wrist actigraph (Philips Respironics, Murrysville, PA) on their nondominant wrist for 7 consecutive days along with a concurrent sleep diary record. Using ActiwareSleep version 5.59 analysis software (Mini Mitter Co., Inc. Bend, OR), every 30-s epoch of actigraphic data was scored as sleep or wake, with sleep onset annotated based on changes in activity count coupled with information from the marker input by participants, environmental light, and sleep timing recorded on sleep diary. The final activity count for each epoch was generated by incorporating the activity level in the surrounding 2-min time period (i.e., $\pm$ 2 min) using a validated algorithm (24). We measured regularity in sleep duration and sleep onset timing as SD of these variables across 7 days. Given the moderate correlation between sleep duration SD and sleep onset timing SD (r = 0.48), we examined them separately in all analyses. Further, due to the strong correlation between sleep onset timing SD and sleep midpoint SD (r = 0.97), we focused on variability in sleep onset timing, which represents a directly modifiable behavioral factor.

Sleep-disordered breathing was measured by polysomnography following procedures described previously (23) and quantified by the apnea-hypopnea index (AHI) as the average number of

all obstructive apneas plus hypopneas associated with 4% oxygen desaturation per hour of sleep. The sleep questionnaire queried multiple validated measures for sleep-related traits, including the five-item Women's Health Initiative Insomnia Rating Scale (25) for insomnia symptoms (defined as Women's Health Initiative Insomnia Rating Scale >10), the Epworth Sleepiness Scale (26) for excessive daytime sleepiness (defined as Epworth Sleepiness Scale >10), and the modified Horne-Östberg Morningness-Eveningness Questionnaire (MEQ) (27) for chronotype (defined as MEQ ≥18 for morningness and MEQ ≤11 for eveningness). Usual work schedule was reported from options including "day shift," "afternoon shift," "night shift," "split shift," "irregular shift/on-call," "rotating shifts," and "do not work" and was further categorized as "day shift," "other shift," and "do not work."

Measurement of Metabolic Abnormalities

All metabolic factors were measured at MESA exam 5 and 6. We used the criteria from the National Cholesterol Education Program Adult Treatment Panel III report, including *1*) central obesity (waist circumference ≥102 cm in men or ≥88 cm in women); *2*) hypertriglyceridemia (serum triglycerides ≥150 mg/dL); *3*) low HDL cholesterol (HDL cholesterol <40 mg/dL in men or <50 mg/dL in women); *4*) high blood pressure (systolic/diastolic blood pressure ≥130/85 mmHg or treatment for hypertension); or *5*) hyperglycemia (fasting blood glucose ≥100 mg/dL or treatment for diabetes). According to the National Cholesterol Education Program Adult Treatment Panel III criteria, our primary outcome considered participants with three or more of these metabolic components as having the metabolic syndrome. Secondarily, we used a data-driven approach to identify clustering patterns of metabolic abnormalities (see later in text).

Statistical Analyses

In the cross-sectional analysis, multivariable logistic regression was used to estimate the prevalence odds ratio (OR) and 95% CI for the associations of metabolic syndrome with sleep regularity measures, which were evaluated as a continuous variable (per hour). To identify potential metabolic unhealthy sleep variability levels, we also categorized the SD of sleep duration as <60 min (reference), 61–90 min, 91–120 min, and >120 min and the SD of sleep onset timing as <30 min (reference), 31–60 min, 61–90 min, and >90 min; these cutoffs were selected for approximately balanced comparison groups. The basic model (model 1) adjusted for age, sex, study site, race/ethnicity, education, and work schedules. In the primary model (model 2), we further adjusted for several common lifestyle factors that may impact metabolic health, including smoking, physical activity, total caloric intake, number of meals/snacks per day, and depressive symptoms. In the sensitivity analysis (model 3), we additionally considered other sleep-related traits closely related to sleep regularity (28), including average sleep duration, insomnia symptoms, chronotype, daytime sleepiness, and AHI. We also used multinomial logistic regression to explore the associations between sleep regularity and the number of altered metabolic factors and tested for trend by using the number of metabolic factors as an ordinal outcome. In the prospective analysis, we conducted similar analyses to estimate the OR (95% CI) of developing metabolic syndrome at exam 6 according to sleep regularity measures among participants who did not meet the criteria for metabolic syndrome at exam 5. We considered the same baseline covariates at exam 5 as described above in the multivariable adjustment.

For both cross-sectional and prospective analysis, we conducted subgroup analyses to explore variations in the associations by age, sex, and race/ethnicity. Likelihood ratio tests comparing the models with versus without the cross-product interaction were used to evaluate the heterogeneity in the associations. We also performed a sensitivity analysis excluding participants reporting any shift work schedules. As social jetlag, the phenomenon of changes in sleep schedules between weekdays and weekend, may contribute to 7-day sleep variability and has previously been linked to unfavorable metabolic factors (29,30), we repeated both cross-sectional and prospective analysis restricting to sleep variability on weekdays.

Considering the interrelationships of metabolic factors, we conducted a data-driven cluster analysis using latent class analysis (LCA), with the optimal number of clusters determined by the Akaike information criterion (31). LCA was performed separately for the cross-sectional and prospective sample, and multinomial logistic regression was used to examine the associations between sleep regularity measures and identified metabolic clusters. Secondarily, to address potential heterogeneity by metabolic components, we also examined the associations with individual metabolic factors. All analyses were performed in SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Of 2,003 MESA participants, the average number of nights with actigraphic measurements was 7.0 (SD 0.4), with a mean sleep duration of 429 min and sleep onset timing of 11:40 P.M.; 1,311 (65.5%) had a 7-day SD of sleep duration >60 min, and 898 (44.8%) had a 7-day SD of sleep onset timing >60 min. Compared with participants with a sleep duration SD ≤60 min, those with a larger SD were more likely to be African Americans, work non–day shift schedules, currently smoke, and have shorter sleep duration and higher depressive symptoms, total caloric intake, and AHI (Table 1). Participants with higher day-to-day sleep duration variability were more likely to self-report as evening types and less likely as morning types. Increasing sleep duration SD was associated with unfavorable metabolic profiles, including lower HDL cholesterol and higher BMI, waist circumference, blood pressure, total triglycerides, and fasting glucose. Similar characteristics were observed across categories of sleep onset timing SD (Supplementary Table 1).

In the cross-sectional analysis, 707 out of 2,003 participants (35.3%) met the criteria for metabolic syndrome at exam 5. After adjusting for age, sex, race/ethnicity, education, work schedules, study site, and multiple behavioral factors, the OR (95% CI) of prevalent metabolic syndrome across categories of sleep duration SD was 1.00 (reference) for ≤60 min, 1.27 (0.99, 1.63) for 61–90 min, 1.41 (1.07, 1.85) for 91–120 min, and 1.57 (1.18, 2.09) for >120 min (OR per 1 h: 1.27 [95% CI 1.10, 1.47]; *P* trend = 0.0009) (Table 2). Similarly, compared with sleep onset timing SD ≤30 min, the multivariable-adjusted OR (95% CI) was 0.98 (0.75, 1.28) for 31–60 min, 1.14 (0.84, 1.53) for 61–90 min, and 1.58

Table 1—Characteristics of the study population by SDs of sleep duration across 7 days

	SD of 7-day actigraphy-based sleep duration			
	≤60 min	61–90 min	91–120 min	>120 min
N	692	558	406	347
Sociodemographic factors				
Age, years	69.7 (8.9)	69.0 (9.2)	70.0 (9.6)	69.5 (9.2)
Male, %	48	43	45	50
Race/ethnicity, %				
White	50	35	32	27
African American	19	27	35	33
Hispanic	20	28	21	25
Chinese	12	9	11	14
Work schedule, %				
Day shift	31	34	32	24
Other shift	11	12	11	15
Do not work	58	54	57	62
Education, %				
High school or less	28	35	29	30
Some college	29	29	33	31
College graduate	22	18	19	18
Graduate school	21	17	19	21
Lifestyle factors				
Current smokers, %	5	6	9	11
Physical activity, MET-h/week	87.4 (80.1)	90.8 (101.9)	94.5 (140.0)	85.3 (100.2)
CES-D	7.1 (6.5)	8.3 (7.5)	8.9 (8.2)	8.9 (7.7)
Number of meals/snacks per day	3.8 (1.1)	3.6 (1.1)	3.5 (1.1)	3.6 (1.1)
Total caloric intake, kcal	1,662 (758)	1,674 (758)	1,703 (816)	1,721 (859)
Sleep-related factors				
Sleep duration, h	7.6 (1.2)	7.2 (1.3)	6.9 (1.5)	6.5 (1.4)
AHI	18.2 (15.5)	20.5 (18.4)	21.1 (19.2)	22.6 (18.5)
Insomnia, %[1]	21	23	29	24
Excessive daytime sleepiness, %[2]	10	14	16	17
Chronotype, %[3]				
Evening type	6	7	8	9
Intermediate type	38	41	45	44
Morning type	56	52	48	46
Metabolic factors				
BMI, kg/m^2	28.0 (5.1)	29.2 (5.6)	29.0 (5.9)	29.4 (6.0)
Waist circumference, cm	97.9 (13.5)	100.5 (15.1)	99.9 (15.0)	101.3 (14.9)
Diastolic blood pressure, mmHg	67.3 (9.4)	68.5 (10.0)	68.6 (9.3)	69.3 (10.8)
Systolic blood pressure, mmHg	121.2 (19.3)	123.7 (20.5)	123.3 (18.9)	124.8 (21.9)
Total triglycerides, mg/dL	108.5 (60.7)	109.8 (60.9)	107.7 (59.1)	120.0 (80.9)
HDL cholesterol, mg/dL	55.5 (15.3)	56.9 (17.2)	55.5 (16.7)	53.7 (16.9)
Fasting glucose, mg/dL	98.4 (18.8)	101.0 (29.7)	104.2 (29.0)	106.7 (34.0)

CES-D, Center for Epidemiologic Studies Depression Scale; MET, metabolic equivalent. [1]Defined as the Women's Health Initiative Insomnia Rating Scale >10. [2]Defined as the Epworth Sleepiness Scale >10. [3]Defined as the modified Horne-Östberg Morningness-Eveningness Questionnaire score 4–11 for evening type, 12–17 for intermediate type, and 18–25 for morning type.

(1.17, 2.14) for >90 min (OR per 1 h: 1.23 [95% CI 1.06, 1.42]; *P* trend = 0.005). Adjustment for several sleep-related factors (particularly AHI and daytime sleepiness) moderately attenuated these associations; each additional hour of variability was associated with 20% (95% CI 1.03, 1.39; *P* trend = 0.02) higher odds of prevalent metabolic syndrome for sleep duration and 19% (95% CI 1.01, 1.39; *P* trend = 0.03) higher odds for sleep onset timing.

Higher variability in sleep duration and timing was associated with a greater number of altered metabolic factors (Supplementary Table 2). Compared with no metabolic abnormalities, the OR (95% CI) associated with a 1-h increase in sleep duration SD was 1.10 (0.85, 1.42) for one altered metabolic factor, 1.10 (0.85, 1.42) for two factors, 1.26 (0.97, 1.64) for three factors, 1.50 (1.10, 2.04) for four factors, and 2.11 (1.47, 3.05) for five factors (*P* trend <0.0001). A similar positive trend was observed between sleep onset timing variability and the number of altered metabolic factors (*P* trend <0.0001). When examining the associations with individual components of metabolic syndrome, sleep duration variability was associated with all metabolic components except high blood pressure, whereas sleep timing variability was associated with central obesity, low HDL cholesterol, and high fasting glucose (Supplementary Table 3). The cross-sectional associations did not differ significantly by age, sex, or race/ethnicity (Supplementary Table 4). Exclusion of participants reporting any shift work schedules resulted in similar associations (data not shown). We observed slightly smaller sleep variability on weekdays compared with 7-day sleep variability. The mean SD measure was 77 min for weekday sleep duration variability (compared with 82 min for 7-day sleep duration variability) and 58 min for weekday sleep onset timing variability (compared with 64 min for 7-day sleep onset timing variability). However, there were similar positive associations of weekday variability in sleep duration and sleep onset timing with prevalent metabolic abnormalities (Supplementary Table 5).

In the prospective analysis, 181 out of 970 participants (18.7%) who did not meet the criteria for metabolic syndrome at exam 5 developed metabolic syndrome at exam 6 during a median follow-up of 6.3 years. All metabolic syndrome components, except for total triglycerides and diastolic blood pressure, on average worsened from exam 5 to exam 6 (Supplementary Table 6). Overall, the prospective associations between measures of sleep regularity and incident metabolic syndrome were similar to the cross-sectional associations, although the estimates were less precise. In the primary model (model 2), every 1-h increase in sleep duration SD and sleep onset timing SD was associated with 27% (95% CI 0.99, 1.64; *P* trend = 0.06) higher odds of incident metabolic syndrome (Table 3). The results remained similar after further adjustment for other sleep-related factors. Of all metabolic components, higher sleep variability at exam 5 was most strongly associated with incidence of high triglycerides at exam 6 (Supplementary Table 7). In subgroup analysis (Supplementary Table 4), the prospective associations were potentially stronger in participants ≥70 years versus <70 years, although the test for interaction was not significant. Similar

Table 2—Cross-sectional associations of variability in sleep duration and timing with metabolic syndrome at MESA exam 5 (*n* = 2,003)

	Cases/*N*	Prevalence (%)	Model 1	Model 2	Model 3
SD of sleep duration					
≤60 min	205/692	29.6	1.00 (reference)	1.00 (reference)	1.00 (reference)
61–90 min	205/558	36.7	1.28 (1.00, 1.64)	1.27 (0.99, 1.63)	1.22 (0.95, 1.57)
91–120 min	154/406	37.9	1.44 (1.10, 1.88)	1.41 (1.07, 1.85)	1.30 (0.98, 1.72)
>120 min	143/347	41.2	1.62 (1.23, 2.15)	1.57 (1.18, 2.09)	1.41 (1.05, 1.90)
Per 1 h			1.30 (1.13, 1.49)	1.27 (1.10, 1.47)	1.20 (1.03, 1.39)
P trend			0.0003	0.0009	0.02
SD of sleep onset timing					
≤30 min	132/399	33.1	1.00 (reference)	1.00 (reference)	1.00 (reference)
31–60 min	226/710	31.8	0.97 (0.74, 1.27)	0.98 (0.75, 1.28)	0.94 (0.71, 1.24)
61–90 min	159/459	34.6	1.13 (0.84, 1.52)	1.14 (0.84, 1.53)	1.09 (0.80, 1.48)
>90 min	190/435	43.7	1.66 (1.23, 2.23)	1.58 (1.17, 2.14)	1.45 (1.05, 2.00)
Per 1 h			1.27 (1.10, 1.46)	1.23 (1.06, 1.42)	1.19 (1.01, 1.39)
P trend			0.001	0.005	0.03

Data are OR (95% CI) unless otherwise indicated. Model 1: adjusted for age, sex, study site, race/ethnicity, education, and work schedules. Model 2: model 1 plus adjusted for smoking status, physical activity, total caloric intake, number of meals/snacks per day, and depressive symptoms. Model 3: model 2 plus adjusted for average sleep duration, insomnia symptom scores, chronotype, Epworth Sleepiness Scale score, and AHI.

positive associations were observed across sex and race/ethnic groups other than African Americans. We observed similar associations after excluding participants reporting any shift work schedules (data not shown). Restricting the analysis to sleep variability on weekdays resulted in somewhat stronger prospective associations for sleep duration SD and similar associations for sleep onset timing SD (Supplementary Table 5).

In cluster analysis, LCA identified four distinct metabolic groups in the cross-sectional sample (Supplementary Table 8) characterized by few metabolic abnormalities (cluster 1), hypertension without dyslipidemia (cluster 2), multiple metabolic abnormalities (cluster 3), and metabolically abnormal obese diabetes (cluster 4). Compared with cluster 1, the OR (95% CI) for cluster 4 was 1.43 (1.12, 1.84) for 1-h increase in sleep duration variability and 1.45 (1.11, 1.89) for 1-h increase in sleep timing variability (Table 4). In the prospective sample, four metabolic clusters were also identified (Supplementary Table 9), including few metabolic changes (cluster 1), primarily incident high blood pressure (cluster 2), primarily incident high fasting glucose (cluster 3), and incidence of multiple metabolic abnormalities (cluster 4). The odds for incidence of multiple metabolic abnormalities (cluster 4) versus few metabolic changes (cluster 1) were almost doubled for 1-h increase in sleep duration SD (OR 1.97 [95% CI 1.18, 3.30]) or sleep timing SD (OR 2.10 [95% CI 1.25, 3.53]).

CONCLUSIONS

The current study confirmed and extended existing cross-sectional evidence by showing that irregular sleep duration and timing was associated with higher incidence of multiple metabolic disturbances over a median follow-up of 6.3 years. In addition to the concrete biologic evidence from experimental studies, the consistent patterns between cross-sectional and prospective associations in humans collectively support a detrimental effect of irregular sleep on metabolic regulation. More importantly, the observed

Table 3—Associations of incident metabolic syndrome at MESA exam 6 with variability in sleep duration and sleep onset timing among individuals who did not have metabolic syndrome at exam 5 (*n* = 970)

	Cases/*N*	Incidence (%)	Model 1	Model 2	Model 3
SD of sleep duration					
≤60 min	64/371	17.3	1.00 (reference)	1.00 (reference)	1.00 (reference)
61–90 min	47/266	17.7	0.93 (0.61, 1.43)	0.95 (0.62, 1.45)	0.93 (0.60, 1.44)
91–120 min	34/187	18.2	1.01 (0.62, 1.62)	1.02 (0.63, 1.65)	1.01 (0.61, 1.66)
>120 min	36/146	24.7	1.47 (0.91, 2.37)	1.53 (0.94, 2.49)	1.51 (0.90, 2.52)
Per 1 h			1.25 (0.97, 1.60)	1.27 (0.99, 1.64)	1.27 (0.97, 1.65)
P trend			0.08	0.06	0.08
SD of sleep onset timing					
≤30 min	31/188	16.5	1.00 (reference)	1.00 (reference)	1.00 (reference)
31–60 min	60/370	16.2	0.97 (0.60, 1.58)	0.98 (0.60, 1.59)	0.90 (0.55, 1.48)
61–90 min	51/230	22.2	1.43 (0.85, 2.40)	1.48 (0.88, 2.49)	1.52 (0.89, 2.60)
>90 min	39/182	21.4	1.38 (0.80, 2.39)	1.41 (0.81, 2.46)	1.46 (0.81, 2.62)
Per 1 h			1.26 (0.98, 1.61)	1.27 (0.99, 1.64)	1.36 (1.03, 1.80)
P trend			0.07	0.06	0.03

Data are OR (95% CI) unless otherwise indicated. Model 1: adjusted for age, sex, study site, race/ethnicity, education, and work schedules. Model 2: model 1 plus adjusted for smoking status, physical activity, total caloric intake, number of meals/snacks per day, and depressive symptoms. Model 3: model 2 plus adjusted for average sleep duration, insomnia symptom scores, chronotype, Epworth Sleepiness Scale score, and AHI.

Table 4—Cross-sectional and prospective associations of metabolic clusters with every 1-h increase of variability in sleep duration and sleep onset timing

	Sleep duration variability		Sleep onset timing variability	
	Model 1	Model 2	Model 1	Model 2
Cross-sectional sample				
Cluster 1: few metabolic abnormalities	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Cluster 2: hypertension without dyslipidemia	1.10 (0.92, 1.32)	1.09 (0.91, 1.32)	1.13 (0.94, 1.37)	1.15 (0.94, 1.41)
Cluster 3: multiple metabolic abnormalities	1.13 (0.92, 1.38)	1.08 (0.87, 1.33)	1.08 (0.87, 1.34)	1.03 (0.82, 1.30)
Cluster 4: metabolically abnormal obese diabetes	1.58 (1.24, 2.00)	1.43 (1.12, 1.84)	1.56 (1.23, 1.98)	1.45 (1.11, 1.89)
Longitudinal sample				
Cluster 1: few metabolic changes	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Cluster 2: incident high blood pressure	1.22 (0.95, 1.56)	1.16 (0.89, 1.51)	1.12 (0.87, 1.44)	1.07 (0.81, 1.41)
Cluster 3: incident high fasting glucose	1.34 (0.98, 1.83)	1.33 (0.95, 1.85)	1.18 (0.86, 1.61)	1.17 (0.83, 1.67)
Cluster 4: incidence of multiple metabolic abnormalities	1.99 (1.25, 3.16)	1.97 (1.18, 3.30)	1.97 (1.25, 3.09)	2.10 (1.25, 3.53)

Data are OR (95% CI). Model 1: adjusted for age, sex, study site, race/ethnicity, education, and work schedules. Model 2: model 1 plus adjusted for smoking status, physical activity, total caloric intake, number of meals/snacks per day, depressive symptoms, average sleep duration, insomnia symptom scores, chronotype, Epworth Sleepiness Scale, and AHI.

associations were independent of multiple sociodemographic, lifestyle, and sleep-related factors, corroborating the importance of considering sleep duration and timing regularity for metabolic health beyond sleep duration, sleep disorders, and other lifestyle factors.

Only a limited number of cross-sectional studies have examined the associations between irregular sleep schedules and metabolic dysregulation. In the Osteoporotic Fractures in Men Study and the Study of Osteoporotic Fractures, higher night-to-night variability in sleep duration was associated with greater odds of obesity, independent of sleep duration (18). The cross-sectional analysis in the Rush Memory and Aging Project reported that irregularity of 24-h activity rhythms measured by 7-day actigraphy was adversely associated with all four metabolic factors examined, including high BMI, hypertension, dyslipidemia, and diabetes (19). Another study of 338 middle-aged women based on daily sleep diary found that higher variability in bedtime was associated with insulin resistance (20). In the pediatric population, irregular sleep duration and timing were also associated with higher prevalence of obesity and unfavorable profiles of metabolic biomarkers through synergistic interaction with short sleep duration (21). Based on the same sample from the MESA-Sleep Ancillary study, Lunsford-Avery et al. (22) recently validated a Sleep Regularity Index that was cross-sectionally associated with obesity, hypertension, diabetes, and predicted 10-year cardiovascular risk. Although Sleep Regularity Index integrated regularity in both sleep timing and sleep duration and considered multiple sleep periods per day, its complexity may limit the ability to be translated into clinical practice or help shape healthy sleep guidelines. In addition, prior studies have documented metabolic dysregulation associated with social jetlag, which focused on discrepancies in sleep timing between weekdays and weekend (29,30). While social jetlag is one of the contributing factors to 7-day sleep variability, our measures of sleep regularity based on variability across the entire week may additionally identify adverse sleep health experienced on a night-to-night basis. Higher sleep variability on weekdays alone was similarly associated with increased prevalence and incidence of metabolic abnormalities. Taken together, our cross-sectional results were consistent with prior studies, expanding prior analyses with inclusions of a racially/ethnically diverse sample of men and women from multiple geographic areas. Moreover, the prospective results identified that variation in sleep preceded the development of metabolic dysfunction, providing temporal evidence supporting a causal link between irregular sleep and metabolic dysfunction.

Circadian disruption by irregular sleep schedules may promote development of metabolic syndrome through mechanisms at multiple levels (7,8,32). For example, at the cellular level, *CLOCK* (a core component of the circadian pacemaker) directly regulates transcriptional activity of genes involved in cellular metabolism through histone acetylation (33,34); loss of the circadian rhythm of histone acetylation impairs normal hepatic lipid metabolism (35). At the level of hormonal control, multiple circulating hormones play dual roles in circadian synchronization and metabolism. The circadian rhythm of cortisol facilitates variations in metabolic needs and energy utilization across the day (36,37), whereas the melatonin rhythm synchronized by light exposure modulates insulin secretion, glucose homeostasis, and diabetes risk (38,39). At the behavioral level, higher sleep variability may result in irregular patterns in breakfast consumption, eating frequency, and meal timing (7), which have been associated with weight gain and diabetes risk (40–42). Our findings indicate that irregular sleep was more strongly associated with multiple metabolic factor clustering than individual metabolic factors. In addition to enhanced measurement reliability (i.e., a multicomponent construct may reduce measurement error of individual components), this finding suggests that sleep irregularity may influence physiologic pathways that result in clusters of metabolic abnormalities. However, direct mechanistic evidence is scarce regarding the metabolic effects of habitual sleep irregularity through these pathways, and more studies are needed to define the likely interacting effects of sleep deprivation and circadian disruption on basic mechanisms that regulate metabolism.

Our findings have important clinical and public health implications. Although the majority of the population do not regularly experience such extreme circadian misalignment as rotating night shift

work or frequent jet lag, irregular sleep is a highly prevalent form of chronic circadian disruption in today's society. In our sample of older individuals, more than half showed average night-to-night variability in sleep duration >60 min; the prevalence may be even higher among younger populations due to more social demands from work or study (43). Thus, there is substantial opportunity to improve sleep regularity, with potential metabolic benefits for millions of individuals. Our results also highlight that sleep duration variability >120 min and sleep timing variability >90 min were consistently associated with metabolic syndrome in both cross-sectional and prospective analyses. These cutoffs, if confirmed in additional studies, could provide the public with simple but quantitative guidelines for healthy sleep. With advances in mobile health technologies, such measures of sleep regularity can be readily derived and tracked by wearable sensors for monitoring or behavioral intervention. Although encouraging consistency of sleep schedules is a fundamental component of sleep hygiene interventions designed to improve sleep quality, our data suggest that reducing sleep variability also has beneficial metabolic effects; this information may help further motivate patients to adhere to sleep hygiene recommendations. Given that sleep regularity represents a modifiable risk factor, future studies should evaluate effective strategies to reduce sleep variability, taking into account social and behavioral factors that may hinder sleep regularity. This is of particular relevance given the higher rates of variable sleep observed in African Americans, individuals with depressed mood, current smokers, and shift workers. Finally, clinical trials are needed to assess whether increased sleep regularity, in combination with other lifestyle modifications, improves metabolic profiles.

The study has several limitations. First, despite actigraphy-based measurement of sleep under a habitual, free-living setting, consecutive assessment over 7 days may not accurately reflect chronic sleep patterns. Repeated assessment over an extended period (e.g., several years apart) is needed to fully understand the associations of long-term sleep regularity with metabolic syndrome development. Actigraphy, while objectively assessed, only provides estimates of sleep-wake times and only agrees modestly with polysomnography-measured sleep (44). We did not have information on several lifestyle factors related to sleep regularity, such as breakfast consumption and meal timing, which may also influence metabolic health (40–42). However, these factors are more likely to be consequences of sleep regularity, thus acting as potential mediators versus unmeasured confounders. Further, adjustment for multiple major correlates of sleep variability did not appreciably alter the observed associations (45). Finally, as the analysis was based on a relatively modest sample size, the results, particularly the subgroup associations, should be interpreted cautiously. It should be noted that the estimates for the prospective associations were only marginally significant according to the conventional threshold, although the association patterns were remarkably similar compared with the cross-sectional analysis. Consortia efforts to pool multiple cohorts are warranted to confirm our findings and characterize the associations in greater detail, such as the dose-response pattern and the potential heterogeneity by age, sex, and race/ethnicity (23,46–48).

Conclusion

In a community-based sample of older men and women, irregular sleep characterized by actigraphy-assessed high day-to-day variability in sleep duration and timing was associated with increased prevalence and incidence of metabolic abnormalities, particularly a phenotype characterized by multiple metabolic risk factors. In conjunction with mechanistic experimental evidence, our results suggest that maintaining a regular sleep schedule has beneficial metabolic effects, which may enrich current prevention strategies for metabolic disease that primarily focus on promoting sufficient sleep and other healthy lifestyles. Additionally, our data support current sleep hygiene interventions that encourage regular sleep timing by showing evidence that more consistent sleep is associated with more favorable metabolic profiles. Future studies are needed to identify behavioral strategies that improve sleep consistency across population groups and to evaluate the effects of interventions on short-term or long-term improvement in the metabolic profiles.

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