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INSOMNIA

Bedtime Variability and Metabolic Health in Midlife Women: The SWAN Sleep Study

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Study Objectives: Circadian misalignment, as seen in shift workers, can disrupt metabolic processes. Associations between sleep timing in nonshift workers and metabolic health are unknown. We examined sleep timing and indices of metabolic health in a community sample of midlife women.
Methods: Caucasian (n = 161), African American (n = 121) and Chinese (n = 56) non-shift-working women aged 48–58 y who were not taking insulin-related medications, participated in the Study of Women's Health Across the Nation (SWAN) Sleep Study and were subsequently examined approximately 5.39 (standard deviation = 0.71) y later. Daily diary-reported bedtimes were used to calculate four measures of sleep timing: mean bedtime, bedtime variability, bedtime delay and bedtime advance. Body mass index (BMI) and insulin resistance (homeostatic model assessment-insulin resistance, HOMA-IR) were measured at two time points. Linear regressions evaluated whether sleep timing was associated with BMI and HOMA-IR cross-sectionally and prospectively.
Results: In cross-sectional models, greater variability in bedtime and greater bedtime delay were associated with higher HOMA-IR (β = 0.128; P = 0.007, and β = 0.110; P = 0.013, respectively) and greater bedtime advance was associated with higher BMI (β = 0.095; P = 0.047). Prospectively, greater bedtime delay predicted increased HOMA-IR at Time 2 (β = 0.152; P = 0.003). Results were partially explained by shifted sleep timing on weekends.
Conclusion: Frequent shifts in sleep timing may be related to metabolic health among non-shift working midlife women.
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Significance
Studies examining the health consequences of circadian misalignment have primarily focused on chronically misaligned populations such as shift workers or have used circadian misalignment protocols in tightly controlled experimental designs. The current study is one of the first to examine individual differences and intra-individual variation in habitual sleep timing in relation to indices of metabolic health. Our study extends the literature on circadian misalignment beyond shift work to include daily behavioral routines which are relevant to all individuals in the general population. Our results demonstrate that variability in sleep timing is associated with adverse metabolic health, warranting further investigation into the health correlates of sleep timing and lifestyle regularity in general.

INTRODUCTION

Circadian alignment of sleep is important for metabolic health.[1,2] For instance, rotating and night shift work, characterized by circadian dysregulation, are associated with adverse metabolic consequences.[3] Experimentally induced circadian misalignment has also been shown to result in acute changes in metabolic functioning.[4] However it is unknown whether more subtle variations in sleep timing may also have implications for metabolic health.[5–7]

Associations between sleep/circadian timing and metabolic health have been most thoroughly explored in epidemiologic studies of permanent and rotating shift workers, which demonstrate that misaligned sleep timing (e.g., 6–12 h out of phase with the light-dark cycle) has adverse consequences for metabolic health. For instance, large cross-sectional and longitudinal studies have shown that more years spent working night or rotating shifts were associated with higher body mass index (BMI) and a greater likelihood of being overweight or obese.[8,9] Moreover, the prevalence of insulin resistance and type 2 diabetes is disproportionately high in shift workers,[10] and the number of years of shift work exposure shares a monotonic relationship with risk for development of type 2 diabetes.[3,11] The literature examining more moderate intra-individual shifts in sleep timing (e.g., staying up 2 h later than usual or having an unpredictable sleep schedule) is far more limited. However, some studies do suggest that nonshift workers with late or irregular bed times may also be at an increased risk for the development of metabolic health problems.[6,7] For instance, later bedtimes have been associated with higher obesity risk among adolescents and adults with intellectual disabilities, and with poor glycemic control among adults with type 2 diabetes.[12–15] Similarly, greater variability in bedtime has been associated with greater risk for obesity in healthy adult populations.[6,7] Moreover, several studies have shown that delayed bedtimes on the weekends relative to those on the weekdays (i.e., social jet lag) may result in circadian misalignment and adverse metabolic health profiles.[5,16,17] Sleep timing is a potentially modifiable behavior that is the focus of most interventions to improve sleep and has been shown to be independently associated with metabolic health.[7,13] To date, no studies have examined sleep timing in relation to concurrent metabolic health or prospective relationships between sleep timing and metabolic health over time in a nonshift-working population.

The current study assessed four indices of sleep timing: mean bedtime, variability in bedtime, bedtime delay, and bedtime advance. Bedtime delay is a novel construct measuring divergences in sleep timing later than one standard deviation beyond the mean bedtime. Bedtime delay quantifies the amount of time one "stays up late", beyond the typical range of variability, operationalized as the mean and standard deviation

(SD) in bedtime. The bedtime delay variable was constructed to assess whether the divergences beyond one's typical range of bedtimes would be associated with metabolic consequences. For instance, people may demonstrate extreme deviations from their normal bedtimes on so-called 'free days', or days on which sleep is not restricted by occupational or social obligations. In the literature, deviation in sleep on free days relative to nonfree days is referred to as social jet lag, due to the jet lag-like consequences that may result from drastic shifts in sleep schedule.[5] The novel measure of bedtime delay captures drastic deviations in sleep timing irrespective of free versus nonfree days. Given the novelty of the bedtime delay variable, we conducted additional exploratory analyses using the inverse of bedtime delay (i.e., bedtime advance) to determine if delayed and advanced bedtimes were differentially associated with metabolic health.

We hypothesized that sleep timing would be related to metabolic health cross-sectionally and prospectively, using longitudinal data across an average of 5.39 (SD = 0.71) y. Sleep timing was evaluated in relation to BMI and insulin resistance in midlife women. We hypothesized that later mean bedtime, greater variability in bedtime, and greater bedtime delay would each be associated with higher BMI and greater insulin resistance in both cross-sectional and prospective analyses. Given the lack of literature on bedtime advance, we have no specific hypotheses regarding the association between bedtime advance and metabolic health.

METHODS

Participants and Protocol

Participants were drawn from the SWAN Sleep Study, an ancillary project to the Study of Women's Health Across the Nation (SWAN). The SWAN project enrolled a multiethnic cohort of midlife women from seven different sites across the United States with participants completing an in-person interview, blood draw, and anthropometry annually. Four sites (Pittsburgh, PA; Detroit, MI; Oakland, CA; and Chicago, IL) participated in the Sleep Study with a targeted enrollment of 100 participants for the Pittsburgh, Detroit and Chicago sites (50 Caucasian and 50 African American each) and a target enrollment of 130 for the Oakland site (50 Caucasian, 80 Chinese). The final population consisted of 370 Caucasian, African American, and Chinese women. The study included self-report questionnaires and up to 35 days of sleep diary data collection conducted between 2002 and 2005. The following analyses use sleep diary data from the Sleep Study to cross-sectionally examine indices of metabolic health measured during the annual SWAN visit that occurred closest to the sleep assessment (Time 1) and prospectively predict metabolic health measured during the most recent core SWAN visit (Time 2), conducted between 2010 and 2011. Participants also completed 3 nights of in-home polysomnography (PSG) during sleep diary data collection; however, because the focus of this study was habitual sleep timing and its variability, PSG data were not considered as informative as sleep diary data. Several indices of sleep, as measured by PSG, were evaluated as potential covariates (described in the following paragraphs).

All women in the SWAN Sleep Study were between the ages of 48–58 y. Participants provided written informed consent in accordance with guidelines put forth by the institutional review boards at each participating institution. Exclusion criteria for the SWAN Sleep Study were use of hormone replacement therapy, participation in night or shift work, active chemotherapy or radiation therapy, oral corticosteroid use, regular alcohol consumption of more than four drinks per day, or noncompliance with the core SWAN protocol.

Of the 370 Sleep Study participants, all had complete BMI data and 367 had complete homeostatic model assessment-insulin resistance (HOMA-IR) data. Ten women were excluded from analysis due to missing or insufficient sleep diary data (< 11 days; n = 10) and 22 participants were excluded for taking insulin or medications for type 2 diabetes. Therefore, cross-sectional analyses were performed using a total sample size of 338 and 335 for BMI and HOMA-IR, respectively. Participants who were excluded from analyses (n = 32) were more likely to be employed for at least 20 h/w ($\chi^2 = 5.212$; P = 0.022), report less time engaging in moderate to vigorous exercise ($F(1, 363) = 7.959$; P = 0.009), have more self-reported symptoms of depression ($F(1, 367) = 7.614$; P = 0.046) and consume fewer daily servings of alcohol ($F(1, 363) = 4.716$; P = 0.028).

Sleep Timing

Participants recorded sleep/wake times daily for a minimum of 11 nights (maximum of 14 nights, mean (SD) = 13.86 ± 0.48 nights) using the Pittsburgh Sleep Diary.[18] Fourteen days of sleep diary data were used to standardize the window of observation for all participants. Mean bedtime was calculated as the mean time at which participants reported turning out the lights across the first 14 nights of data collection (11–13 d were used for n = 10 participants). Variability in bedtime was quantified as the SD from an individual's mean sleep time, such that high variability in bedtime was indicated by high SDs across the same time period. Two additional indices of sleep timing, namely bedtime delay and bedtime advance, were calculated to establish whether deviations from the mean bedtime in a delayed or advanced direction would be differentially associated with metabolic health. Bedtime delay was calculated as the sum of minutes spent awake and out of bed beyond 1 SD after one's mean bedtime. For example, if a woman's average bedtime was 23:00 with a SD of 30 min and she stayed up until 24:00 twice in a given week, she would have a cumulative bedtime delay of 60 min. Similarly, bedtime advance was calculated as the sum of minutes spent in bed prior to 1 SD (in minutes) earlier than one's mean bedtime. Both bedtime delay and bedtime advance were normalized by dividing the summed values by the number of diary nights used. Correlations among sleep timing variables are presented in Table 1. Variability in bedtime, bedtime delay, and bedtime advance were square root transformed due to skewness.

Body Mass Index

BMI was calculated as weight in kilograms divided by height in meters squared from measurements taken during core SWAN annual visits. BMI was measured at the SWAN visit coincident with the Sleep Study and at the most recent SWAN visit (mean time between visits = 5.39 ± 0.71 y).

Insulin Resistance

Insulin resistance was assessed using the HOMA[19] method. HOMA-IR was calculated from blood samples that were also taken at the SWAN visit coincident with the Sleep Study and at the most recent SWAN visit (mean time between visits = 5.39 ± 0.71 y). The most recent method (HOMA2) was used for assessing HOMA-IR.[20] The HOMA model provides estimates of insulin resistance that are comparable to those obtained by the euglycemic-hyperinsulinemic clamp method ($r = 0.88$) for both diabetic and nondiabetic individuals.[19] In all analyses, HOMA-IR was adjusted using a natural log transformation due to skewness.

Table 1—Pearson correlation coefficients among sleep timing variables (n = 338).

	Mean Bedtime	Bedtime Variability	Bedtime Delay	Bedtime Advance
Mean bedtime	–	0.285[a]	0.114[c]	0.034
Bedtime variability		–	0.356[a]	0.163[b]
Bedtime delay			–	−0.207[b]
Bedtime advance				–

[a]P < 0.001, [b]P < 0.001, [c]P < 0.05.

Sample Characteristics and Candidate Covariates

Sample characteristics were derived from the core SWAN assessment closest to the Sleep Study or from the Sleep Study itself via self-report questionnaires. Potential covariates were evaluated prior to inclusion in analyses (see the following paragraphs). Potential covariates included sociodemographic characteristics such as age, race, marital status, education, and employment. Other candidate covariates were variables known to affect indices of metabolic health including symptoms of depression, exercise, intake of alcohol and caffeine, menopausal status, and indices of sleep and sleep disordered breathing. Symptoms of depression were assessed using the 16-item version of the Inventory of Depressive Symptoms (IDS).[21] The frequency of moderate- or vigorous-intensity exercise, daily servings of alcohol and caffeine, chronic health conditions affecting metabolic health, and frequency of sleep-affecting medication usage were self-reported. Menopausal status was based on menstrual bleeding patterns outlined by the World Health Organization criteria.[22] Sleep variables included sleep disordered breathing, as measured by apnea-hypopnea index (AHI), measured using in-home PSG on the first night of the Sleep Study and average self-reported sleep duration measured via the Pittsburgh Sleep Diary[23] over the course of 2 w. Self-reported sleep quality was measured by the Pittsburgh Sleep Quality Index (PSQI).[24]

Statistical Analysis

Descriptive Statistics and Covariate Evaluation

Pearson correlations were used to identify significant bivariate associations between potential covariates and outcome variables. In order to maximize the available degrees of freedom, only variables with significant bivariate associations ($P < 0.05$) with either of the primary outcome variables were adjusted for in the final statistical models. Ultimately, the covariates included in analyses were race, menopausal status, diary-assessed sleep duration, exercise, and depressive symptoms. Age, marital status, education, employment, intake of alcohol and caffeine, and AHI were not included as covariates as they were statistically unrelated to outcome variables in this sample. Analyses involving HOMA-IR were additionally adjusted for BMI.

Cross-Sectional Analyses

Hierarchical linear regression models were used to test the hypothesis that later bedtime, greater variability in bedtime, and greater bedtime delay were cross-sectionally associated with higher BMI and HOMA-IR. Hierarchical linear regression was also used to conduct exploratory analyses evaluating the association between bedtime advance and metabolic health. Relevant covariates were entered into step one for each model. Separate regression models were used for each independent predictor, resulting in eight regression analyses. Due to the multiple comparisons, a more conservative statistical significance level was used ($P \leq 0.01$).

Prospective Analyses

Hierarchical linear regression models were used to test the hypothesis that later bedtime, greater variability in bedtime, and greater bedtime delay were prospectively associated with higher BMI and HOMA-IR at Time 2 while controlling for BMI and HOMA-IR at Time 1. Again, hierarchical linear regression was also used to conduct exploratory analyses evaluating the association between bedtime advance and metabolic health at Time 2. All covariates from the cross-sectional analyses were carried over and entered into step 1 of the prospective model along with BMI and HOMA-IR values from Time 1. Prospective analyses were also adjusted for time (in months) between Time 1 and Time 2. Again, separate linear regression models were used for each sleep variable (i.e., mean bedtime, variability in bedtime, bedtime delay, and bedtime advance). Again, due to the multiple comparisons, a more conservative statistical significance level was used ($P \leq 0.01$).

Sensitivity Analyses

Antihypertensive medications (i.e., beta-blockers) can have adverse effects on glucose metabolism.[25] Therefore, a sensitivity analysis was performed to determine if results remained stable when women taking such medications were omitted from analyses. Based on studies of social jet lag that have demonstrated a significant association between delayed sleep timing on weekends relative to weekdays and BMI,[5] an additional sensitivity analysis was conducted to determine if any significant associations between sleep timing variables and metabolic health were being driven by changes in sleep timing on the weekends. To address this, we recalculated mean, SD, and both delay and advanced variables excluding weekend bedtimes (i.e., Friday and Saturday night) and repeated analyses.

RESULTS

Cross-sectional analyses were performed on a sample of 161 Caucasian, 121 African American, and 56 Chinese women

(n = 338; age 52.12 ± 2.10 y). Sociodemographic, health, and sleep characteristics are presented in Table 2. On average, the sample was overweight (BMI = 29.55 ± 7.57 kg/m^2) with a mean HOMA-IR value of 1.73 ± 1.29 (Table 2). Based on HOMA-IR data from the National Health and Nutrition Examination Survey (NHANES), 11.8% of the women in our sample met criteria for insulin resistance (HOMA-IR values > 2.73).[26]

Table 2—Sample characteristics (n = 338).

Demographic characteristics	
Age, y	52.12 ± 2.10
Marital status: Married/living w/partner, n (%)	219 (65.75)
Education: ≥ college degree, n (%)	174 (52.29)
Employment: Unemployed or < 20 h/w, n (%)	68 (18.96)
Menopausal status: Perimenopause/early perimenopausal, n (%)	211 (63.00)
Health characteristics	
BMI, kg/m^2	29.55 ± 7.57
HOMA-IR (n = 335)	1.73 ± 1.29
Current smoker, n (%)	34 (10.06)
Caffeine use, servings/day	1.57 ± 1.37
Alcohol use, servings/day	0.29 ± 0.50
Moderate/vigorous-intensity exercise, % of days	20.84 ± 23.89
IDS	4.65 ± 2.78
Sleep characteristics	
Average sleep duration, min	398.07 ± 50.33
Average wakefulness after sleep onset, min	15.08 ± 14.56
Average sleep onset latency	15.49 ± 11.97
PSQI, 0–21	5.64 ± 3.06
AHI, events/h	8.05 ± 9.07
Sleep-affecting medication use, % of days	25.70 ± 42.58
Mean bedtime, min prior to midnight	30.00 ± 59.27
Bedtime variability, min	56.34 ± 32.22
Bedtime delay, min	68.08 ± 48.93
Bedtime advance, min	42.08 ± 35.66

Data are expressed as mean ± standard deviation or as n (%), as appropriate. AHI, apnea-hypopnea index; BMI, body mass index; HOMA-IR, homeostatic model assessment of insulin resistance; PSQI, Pittsburgh Sleep Quality Index.

Cross-Sectional Associations between Sleep Timing and BMI

Greater variability in bedtime and bedtime advance were associated with increased BMI at Time 1 in unadjusted models (β = 0.190; P < 0.001 and β = 0.189; P < 0.001, respectively; Table 3). After adjusting for covariates, bedtime advance remained associated with BMI at the level of P < 0.05 (β = 0.095; P = 0.047). Bedtime advance explained an additional 0.9% of the variance in BMI above and beyond other variables in the model. Mean bedtime and bedtime delay were not related to BMI before or after covariate adjustment.

Cross-Sectional Associations between Sleep Timing and HOMA-IR

Variability in bedtime and bedtime delay exhibited significant, positive associations with HOMA-IR after adjusting for race, menopausal status, sleep duration, exercise, depressive symptoms, and BMI (β = 0.128; P = 0.007 and β = 0.110; P = 0.013, respectively; Table 3). Variability in bedtime and bedtime delay explained an additional 1.4% and 1.2% of the variance in HOMA-IR above and beyond other variables in the model. Greater bedtime advance was associated with higher HOMA-IR before adjustment (β = 0.125; P = 0.05). Mean bedtime was unrelated to HOMA-IR before and after covariate adjustment.

Prospective Associations between Sleep Timing and Metabolic Health

Of the 338 women included in cross-sectional analyses, 20 were lost to follow-up, 65 women were missing HOMA-IR data at Time 2, and 12 started taking insulin-related medication. Therefore,

Table 3—Summary of regression analyses examining cross-sectional associations between sleep timing variables and body mass index, and homeostatic model assessment of insulin resistance.

	Unadjusted			Adjusted[a]			Adjusted[b]		
Variable	**ΔR2**	**β**		**ΔR2**	**β**		**ΔR2**	**β**	
BMI (n = 338)									
Mean bedtime	0.009	0.096		0.001	0.035		–	–	
Bedtime variability	0.036	0.190	***	0.001	0.036		–	–	
Bedtime delay	0.002	0.047		0.000	−0.010		–	–	
Bedtime advance	0.036	0.189	***	0.009	0.095	*	–	–	
HOMA-IR (n = 335)									
Mean bedtime	0.006	0.077		0.000	0.000		0.000	−0.021	
Bedtime variability	0.071	0.266	***	0.019	0.152	**	0.014	0.128	**
Bedtime delay	0.018	0.132	*	0.011	0.104	*	0.012	0.110	*
Bedtime advance	0.016	0.125	*	0.003	0.053		0.000	−0.005	

Sleep timing variables are measured in minutes. [a]Adjusted for race, menopausal status, exercise, depressive symptoms, and sleep duration. [b]Further adjusted for BMI. *P < 0.05, **P < 0.01, ***P < 0.001. BMI, body mass index; HOMA-IR, homeostatic model assessment of insulin resistance.

Table 4—Summary of regression analyses examining prospective associations between sleep-timing variables and body mass index and homeostatic model assessment of insulin resistance.

	Unadjusted			Adjusted[a]			Adjusted[b]		
Variable	**ΔR2**	**β**		**ΔR2**	**β**		**ΔR2**	**β**	
BMI (n = 306)									
Mean bedtime	0.018	0.136		0.000	0.012		0.000	0.013	
Bedtime variability	0.022	0.148	**	0.000	−0.005		0.000	−0.001	
Bedtime delay	0.000	−0.010		0.003	−0.057		0.000	0.012	
Bedtime advance	0.035	0.188	***	0.007	0.085		0.000	−0.007	
HOMA-IR (n = 241)									
Mean bedtime	0.001	−0.025		0.003	−0.058		0.005	−0.071	
Bedtime variability	0.003	0.058		0.000	0.002		0.000	−0.017	
Bedtime delay	0.019	0.137	*	0.022	0.150	**	0.023	0.152	**
Bedtime advance	0.008	0.088		0.002	−0.045		0.002	−0.048	

Sleep timing variables are measured in minutes. [a]Adjusted for BMI or HOMA-IR at Time 1. [b]Further adjusted for race, menopausal status, exercise, depressive symptoms, sleep duration, and months between Time 1 and Time 2. *P < 0.05, **P < 0.01, ***P < 0.001. BMI, body mass index; HOMA-IR, homeostatic model assessment of insulin resistance.

prospective analyses were performed using 306 and 241 participants for BMI and HOMA-IR outcomes, respectively. There was a statistically significant but small increase in BMI from Time 1 to Time 2 (28.95 ± 7.22 to 29.40 ± 7.29; $t(305) = -3.414$, P = 0.001). Conversely, there was no significant within-participant change in HOMA-IR over time (1.51 ± 0.93 to 1.49 ± 1.41; $t(240) = 0.288$, P = 0.773). Compared to participants who were included in the longitudinal analyses, participants who were included in cross-sectional analyses only had significantly higher BMI and HOMA-IR values ($t(318) = 2.852$, P = 0.005 and $t(315) = 2.640$, P = 0.009, respectively). Sleep timing variables and sociodemographic variables, with the exception of race, were not significantly different between the cross-sectional and longitudinal samples. A significantly lower proportion of Chinese women were analyzed in cross-sectional analyses only compared to Caucasian or African American participants.

Greater bedtime delay at Time 1 predicted increased HOMA-IR after full adjustment for race, menopausal status, sleep duration, exercise, depressive symptoms, months between Time 1 and Time 2 and HOMA-IR at Time 1 (β = 0.152; P = 0.003). Bedtime delay explained an additional 2.3% of the variance in prospective measures of HOMA-IR above and beyond other variables in the model. Unadjusted prospective associations were found between variability in bedtime, bedtime advance, and BMI at Time 2 (Table 4). However, after adjusting for race, menopausal status, sleep duration, exercise, depressive symptoms, months between Time 1 and Time 2 and BMI at Time 1, prospective associations were no longer significant. All other sleep timing variables were unrelated to prospective measures of metabolic health before and after covariate adjustment.

Sensitivity Analysis 1: Do Beta-Blockers Influence Results?

When participants taking antihypertensive medications (i.e., beta-blockers) were excluded, results from both cross-sectional and prospective analyses remained unchanged (see Tables S1 and S2, supplemental material).

Sensitivity Analysis 2: Are Associations Driven by Weekend Bedtimes?

When only weekday bedtimes were considered, all cross-sectional and prospective associations with HOMA-IR were attenuated and were not statistically significant in fully adjusted models. The cross-sectional association between bedtime advance and BMI remained when only weekday bedtimes were considered (β = 0.101; P = 0.039) and, although the association between bedtime variability and BMI was unrelated in original cross-sectional analyses (β = 0.036; P = 0.482), greater variability in bedtime during weekdays only was associated with higher BMI at Time 1 after fully adjusting for covariates (β = 0.137; P = 0.006).

DISCUSSION

Epidemiological studies of shift work[3,27] and experimental phase shift protocols[4,28,29] have demonstrated that circadian sleep misalignment (e.g., 6- to 12-h shifts in sleep timing) has adverse consequences for metabolic health. To our knowledge, this is the first study to demonstrate that moderate intraindividual variations in sleep timing (e.g., staying up 2 h later than usual) are also associated with concurrent and prospective metabolic health in a community-dwelling sample of middle-aged women. Fully adjusted cross-sectional analyses revealed a significant association between day-to-day variability in bedtime and insulin resistance, such that greater variability was associated with higher HOMA-IR values. Moreover, fully-adjusted cross-sectional analyses also showed that greater bedtime delay was also associated with greater HOMA-IR. Greater bedtime advance was also associated with higher BMI at Time 1. In prospective analyses, greater bedtime delay predicted increased HOMA-IR 5 y later, after adjusting for covariates and for HOMA-IR values at Time 1. Finally, a sensitivity analysis showed that when weekend bedtimes (i.e., bedtimes on Fridays and Saturdays) were removed, associations between sleep timing and metabolic health were attenuated and were nonsignificant in fully adjusted models, suggesting that

weekend shifts in sleep timing account for the associations presented here. Conversely, findings from the sensitivity analysis also indicate that greater variability in bedtime on weekdays only was significantly associated with higher BMI at Time 1. These results indicate that sleep timing may be associated with metabolic health in a nonshift-working population and extend the literature on individual and intraindividual differences in sleep timing in relation to metabolic health.

We speculate that variability in bedtime may lead to variable exposure to light cues, inconsistent circadian signaling, and potentially, to desynchrony among circadian clocks in multiple peripheral tissues related to glucose metabolism and energy homeostasis. Van Someren and Riemersma-Van Der Lek[30] suggest that internal synchrony among peripheral clocks is achieved by sustained and regular 24-h patterns of input from environmental time cues and behavioral rhythms. Peripheral tissues demonstrate differential rates of reentrainment to new light-dark cycles, thus ensuring some degree of desynchrony with irregular patterns of light and darkness.[31]

The association between bedtime variability and insulin resistance is consistent with findings from shift work populations. Although permanent night and rotating night-shift work have both been associated with adverse health outcomes, several studies have reported that compared to permanent night-shift work, rotating shift work is associated with worse subjective well-being,[32] a higher prevalence of cardiovascular risk factors,[33–36] and greater risk for certain types of cancer.[37] Variability in the timing of behaviors such as sleep may help to explain increased relative risk among rotating shift workers as compared to permanent night shift workers, who may develop more stable sleep-wake rhythms. Future research should examine the extent to which day-to-day variability in sleep timing explains associations between shift work and adverse metabolic health outcomes.

Consistent with our hypothesis, bedtime delay was associated with greater HOMA-IR in fully adjusted cross-sectional analyses. In addition to disrupting coordination among central and peripheral pacemakers, bedtime delay may act as a behavioral proxy for extended light exposure during nighttime hours. Although we did not see an association between bedtime delay and BMI in this sample, a recent study found that later evening exposure to light above 500 lux was associated with higher BMI.[38] The authors suggest that light exposure may be associated with BMI via melatonin suppression, given melatonin's role in regulating daily rhythms in glucose tolerance and energy homeostasis.[39–42] However, if sleep timing influences metabolic health solely through melatonin suppression, advances in bedtime would be unrelated to metabolic health. Our results indicate that greater bedtime advance was associated with higher BMI in cross-sectional analyses after covariate adjustment. These results suggest that deviations in either direction (i.e., delays or advances) may have the capacity to disrupt circadian timing and, in turn, further sleep-circadian misalignment. Future studies of sleep timing and metabolic health should examine potential mechanisms including melatonin as well as other hormones that are relevant to metabolic health and sensitive to circadian misalignment, including leptin, ghrelin, and cortisol.

Mean bedtime was not associated with BMI or HOMA-IR in either cross-sectional or prospective analyses. This null finding may suggest that measures of mean bedtime underestimate the importance of day-to-day variation. Moreover, measures of mean bedtime flatten out potentially extreme shifts in sleep timing that occur across weekend and weekday nights. For instance, social jet lag, a term coined to reflect the variability in circadian timing across work/school days and nonwork/nonschool days, has been associated with higher BMI in some populations.[5] Our findings, as indicated by our sensitivity analysis, are consistent with studies of social jet lag, suggesting that when weekend sleep timing is not considered, bedtime delay is no longer associated with HOMA-IR. On average, bedtime delay on the weekends accounted for over half of total bedtime delay across data collection, indicating that participants were more likely to delay sleep on weekend nights. Systematic delays in bedtime on the weekend may have implications for metabolic health. However, our sensitivity analysis also indicated that interweekday variability is also relevant for metabolic health given that greater variability and greater bedtime advances on weekday nights only were associated with increased BMI. Taken together, our results and findings from the social jetlag literature suggest that intraindividual variations in sleep timing could be more indicative of circadian misalignment and consequences for health and functioning than the average timing of sleep.

Alternative explanations for the significant associations between indices of sleep timing variables and metabolic health should also be considered. Given that our findings are cross-sectional and directionality cannot be addressed, it is possible that indices of metabolic health may be disrupting sleep. For instance, sleep disorders and metabolic disturbances such as obesity and type 2 diabetes appear to be co-occurring conditions with potentially additive or synergistic effects.[43,44] Longitudinal studies that begin prior to the onset of any metabolic health disturbances are needed to understand causal relationships between sleep timing and metabolic health. Moreover, indices of sleep timing may be associated with delayed eating or eating on an inconsistent schedule. For instance, eating late has been associated with decreased glucose tolerance and decreased resting energy expenditure in controlled experimental studies.[45] Future studies should examine relationships between sleep timing and metabolic health within the context of meal timing and content, physical activity, and total energy balance.

Bedtime delay was the only measure of sleep timing that was prospectively associated with metabolic health. Specifically, greater bedtime delay at Time 1 was associated with increased HOMA-IR 5 y later, after controlling for indices of metabolic health at Time 1 ($\beta = 0.152$; $P = 0.003$). As indicated by the sensitivity analysis, this association was no longer present when weekend nights were not considered ($\beta = 0.004$; $P = 0.944$). Our results suggest that delayed sleep relative to average bedtime may predict future insulin dysfunction; this effect was independent of sleep duration and was particularly pronounced on weekends. No index of sleep time was prospectively associated with BMI at Time 2, which is consistent with a prior report of the SWAN Sleep Study.[46] Applehans and colleagues[46] found that shorter sleep duration was associated with

higher BMI in cross-sectional analyses; however, longitudinal associations failed to reach significance after controlling for BMI at Time 1. Our results suggest that HOMA-IR may be more sensitive to intra-individual variations in sleep timing.

Clinical recommendations based on the current findings should be made with caution given the small effect sizes found within the current set of results and the homogeneity of the sample used in this analysis. Although ethnically/racially diverse, the SWAN sample consists of middle-aged women exclusively. These findings are not generalizable to men or to women in different age groups. The small effect sizes reported here are comparable to previously published associations between sleep duration and metabolic health.[47] Limited variability in our sleep timing measures may have also prevented us from observing stronger effects. Although the clinical relevance of sleep timing requires additional examination, explaining additional variance in such important indices of metabolic health will increase our clinical ability to minimize negative health consequences.

Several limitations of the current study are worth addressing. Because the SWAN Sleep Study was ancillary to SWAN, measurements of metabolic health and sleep data were not concurrent. Although the mean interval between the core SWAN visit and the Sleep Study was brief (4.44 ± 3.57 mo), the gap in timing between visits limits our ability to draw conclusions from these analyses. Concurrent measures are needed to better understand the acute effects of sleep timing on metabolic health. Additionally, the low variability in measures and the small sample sizes of each racial group may have impaired our ability to detect differences by race or ethnicity. Moreover, future studies would benefit from collecting biological measures of circadian phase, such as melatonin onset/offset or core body temperature, in order to test whether variability in bedtime and bedtime delay are associated with metabolic health via changes in circadian phase.

The limitations of the current study are offset by several notable strengths. The SWAN Sleep Study included a diverse sample of multiethnic women, allowing us to investigate associations between sleep timing and metabolic health in a sample that is more representative of the national population. Moreover, sleep timing was measured over the course of at least 11 d (14 d in 94% of participants). Studies of habitual sleep timing have largely used single-item questionnaires to probe typical bed and wake times on work and nonwork days. The use of the Pittsburgh Sleep Diary allowed us to track sleep timing without the limitation of recall bias. Next, we used objective and continuous measures of metabolic health at multiple time points, which allowed us to look at sleep timing in relation to a continuous gradient of risk for metabolic health problems both cross-sectionally and prospectively. Last, by focusing on a potentially modifiable behavior, the results of our study could be directly applicable to interventions seeking to standardize the timing of sleep in order to target health outcomes.

In summary, the current study indicates that associations between sleep timing and metabolic health may be evident. However, due to small effect sizes and nonsignificant longitudinal findings, further research is needed in order to determine if intraindividual variability in sleep timing is a clinically relevant variable. Alignment between sleep and circadian timing is an optimal characteristic of metabolic health and functioning.[48,49] It is plausible that intraindividual differences in sleep timing may reflect temporary or occasional misalignment from endogenous rhythms and may disrupt the temporal organization of metabolic processes. If intraindividual differences in sleep timing constitute moderate circadian misalignment, sleep timing may constitute a modifiable behavior that could have profound influences on metabolic health and functioning.

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