SLEEP TIMING AND METABOLIC HEALTH IN MIDLIFE WOMEN

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Circadian rhythms are critical to health and functioning. Circadian misalignment can result from desynchrony between sleep-wake cycles and the natural light-dark cycle, disrupting time-dependent variations in biological functioning associated with metabolism and energy homeostasis. Here, we test a chronobiological model suggesting that sleep timing may act on health outcomes via a melatonergic-metabolic pathway by gating the effect of light on circadian signaling. We evaluated associations between four measures of sleep timing and indices of metabolic health in order to assess the importance of sleep timing for healthy functioning in midlife women.

Participants were 338 Caucasian (n = 161), African American (n = 121) and Chinese (n = 56) women who participated in the SWAN Sleep Study and who were not taking insulin or other insulin-related medications. Participants reported habitual sleep-wake times in the Pittsburgh Sleep Diary for a minimum of 11 nights. From self-reported sleep-wake times, four measurements of sleep timing were calculated: average bedtime, variability in bedtime, bedtime delay, and social jetlag. Body mass index (BMI) and the homeostasis model assessment of insulin resistance (HOMA-IR) were measured at two time points (average years between time points = 5.39 ± 0.71). We expected later average bedtime, greater variability in bedtime, more bedtime delay, and more social jetlag to be associated with higher BMI and higher HOMA-IR at time one and time two.

Greater variability in bedtime was associated with higher HOMA-IR at Time 1 after controlling for race, menopausal status, sleep duration, exercise, depression, and BMI (β = .132; p = .005). Moreover, fully adjusted cross-sectional models also revealed significant positive associations between bedtime delay and both BMI (β = .128; p < .001) and HOMA-IR (β = .098;

p = .038). Average bedtime and social jetlag were unrelated to metabolic health in cross-sectional analyses and no measure of sleep timing was associated with either measure of metabolic health in prospective analyses.

These data indicate that individual differences in sleep timing are associated with metabolic health in a non-shift working population. The current findings provide support for a chronobiological model linking sleep timing with metabolic health.

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1.0 INTRODUCTION

Mounting evidence suggests that sleep and circadian misalignment are important for metabolic health. The sleep and health literature has primarily focused on the metabolic consequences of sleep disorders such as obstructive sleep apnea and insomnia while a separate literature has documented the adverse metabolic health outcomes associated with shift work due to circadian dysregulation. This work has given rise to an interest in more moderate sleep disturbances and shifts in circadian rhythms. An emerging literature on social jetlag suggests that bedtime delay on free days, relative to work days, may be similarly associated with metabolic health problems such as obesity. However, far less is known about the day-to-day timing of sleep in relation to metabolic health. Accordingly, the proposed study seeks to assess indices of sleep timing, namely average bed time, variability in bedtime, social jetlag, and intra-week bedtime delay, in relation to metabolic health in midlife women.

Sleep timing is an integral component of the two primary processes regulating sleep: homeostatic sleep drive and circadian rhythms. Under normal conditions, the need for sleep, or homeostatic sleep pressure, builds across the day and is counteracted by a circadian wake-promoting system. These two systems work dynamically and in tandem to promote distinct and consolidated periods of sleep and wake (Gillette & Sejnowski, 2005). Changes in the timing of sleep can result in desynchrony between homeostatic sleep drive and circadian rhythms, leading to sleep disturbances, including sleep fragmentation, insufficient sleep duration, and changes in perceived sleep quality (Burgess & Eastman, 2004). A strong body of literature suggests that indices of sleep disturbance are associated with metabolic disturbances including obesity, insulin resistance and type II diabetes (Hall et al., 2012; Tasali, Leproult, Ehrmann, & Van Cauter, 2008; Patterson et al., 2014; Ohkuma et al., 2013; Lucassen, Rother, & Cizza, 2012; Grandner, Jackson, Pak, & Gehrman, 2012; Choi et al., 2008; Kobayashi, Takahashi, Deshpande, Shimbo, & Fukui, 2011; Hall et al., 2008). However, sleep timing itself may have implications for

metabolic health independent of sleep disturbances by dysregulating circadian signaling, thereby creating desynchrony among physiological pacemakers.

The associations between sleep timing and circadian rhythms have been most thoroughly explored through the epidemiological work in permanent and rotating shift workers. More recently, several studies have found that non-shift workers with late or irregular sleep times may also be at an increased risk for developing metabolic health problems (Logue, Scott, Palmieri, & Dudley, 2014a; Bailey et al., 2014a). Experimental chronobiology studies have supported these observational findings by identifying specific aspects of metabolic physiology that undergo acute changes in response to circadian dysregulation conditions (Buxton et al., 2012; Scheer, Hilton, Mantzoros, & Shea, 2009). Taken as a whole, the current literature provides compelling support for an evaluation of sleep timing as a more naturalistic index of circadian alignment which may be relevant for metabolic health and functioning.

1.1 SLEEP TIMING AND METABOLIC HEALTH

1.1.1 Epidemiology of metabolic health disturbance among shift workers

Shift work is characterized by abnormal sleep/wake patterns. Permanent night shift workers are often 12 hours out of phase with the light/dark cycle while rotating shift workers experience abrupt shifts in their sleep/wake routines as frequently as every few days. Obesity is a common health problem for men and women in both types of shift work (Zimberg, Fernandes Junior, Crispim, Tufik, & de Mello, 2012; Wang, Armstrong, Cairns, Key, & Travis, 2011; Szosland, 2010). A cross-sectional study of roughly 10,000 female nurses in Korea showed a linear trend between the prevalence of overweight/obesity and duration of shift work exposure (Kim, Lee, & Duffy, 2013). Moreover, rotating shift work was independently associated with significant increases in BMI relative to day-working matched controls in a 14 year, longitudinal study (Suwazono et al., 2008).

The prevalence of insulin resistance and type II diabetes are also disproportionately high in shift workers. A longitudinal analysis showed that rotating shift work was associated with a 1.35 odds ratio (OR) for new onset of diabetes in a sample of 3,203 day workers and 2,426 rotating shift workers (Suwazono et al., 2006). The Nurse's Health Study I and II (NHS I and NHS II) also found associations between shift work and type II diabetes in a large sample (N =

177,000) of young and midlife women (Pan, Schernhammer, Sun, & Hu, 2011). Pooled hazard ratios revealed a monotonic relationship between years of shift work exposure and risk for type II diabetes. Taken as a whole, the epidemiological literature in shift workers provides large-scale observational evidence to support the link between circadian misalignment and metabolic health disturbances. Though sleep timing is an inherent characteristic of circadian misalignment in shift workers, it is rarely evaluated for its independent contribution to health outcomes.

1.1.2 Observational studies in non-shift workers

Sleep timing is an understudied dimension of sleep in the general population as well. To our knowledge, only three studies have evaluated bedtime in relation to metabolic health in non-shift workers. A cross-sectional study of 2,200 Australian adolescents found that later bedtime was associated with increased BMI (Vanhelst, Bui-Xuan, Fardy, & Mikulovic, 2013; Golley, Maher, Matricciani, & Olds, 2013). In this sample, teens with a later bedtime were 1.5 times more likely to be obese compared to teens with an earlier bedtime after controlling for sleep duration and physical activity levels (Golley et al., 2013). Late bedtime has also been associated with overweight status among adults with intellectual disabilities after controlling for sleep duration (Mikulovic, Dieu, Fardy, Bui-Xuan, & Vanhelst, 2014). Finally, a cross-sectional study among adults with type II diabetes found that early bedtime was strongly associated with better glycemic control after adjusting for diet, physical activity, and other measures of sleep (Reutrakul et al., 2013).

Even less is understood about variability in bedtime, due to very limited research and inconsistent findings. Data collected from an urban family medical center indicated that stable bedtimes were an important correlate of obesity in adult men and women (Logue, Scott, Palmieri, & Dudley, 2014b). Using the Sleep Timing Questionnaire (Monk & Buysse, 2003), Logue and colleagues (2014) showed that greater variability in bedtime during both the week and the weekend was associated with an increased risk for being obese (OR = 2.3; p = 008 and OR = 1.8; p = .04, respectively). Another study measured sleep timing for seven days using actigraphy and sleep diaries in young, adult women (Bailey et al., 2014b). This study showed that greater variability in bedtime was associated with increased percentage of body fat (β = .13; p = .017) and BMI (β = .11; p = .041). In these studies, neither average bedtime nor sleep duration was

associated with health outcomes. These studies indicate that day-to-day variability in sleep timing may be an overlooked risk factor for metabolic health problems. However, a separate epidemiological study of men and women found that sleep timing was not consistently associated with obesity, but that variability in sleep duration predicted a 1.63 and 1.22 fold increase in the risk for being obese in men and women, respectively (Patel et al., 2014). Longitudinal assessments are needed in order to understand whether sleep timing may be causally related to the trajectory of metabolic health. As of yet, no prospective studies have assessed the relationship between indices of sleep timing and changes in metabolic health over time.

Social jetlag is an additional index of sleep timing that has recently entered the public health arena (Roenneberg, Allebrandt, Merrow, & Vetter, 2012; Touitou, 2013; Garaulet et al., 2013). Social jetlag is the discrepancy between sleep time on free days and sleep time on work/school days, which can be similar to shifts in sleep and circadian rhythms associated with cross-meridian travel (i.e., "jetlag"). Social jetlag is thought to result from a discrepancy between endogenous circadian timing and social timing, which may not only result in sleep loss, but also desynchrony among internal pacemakers. This desynchrony may affect energy homeostasis through down-stream circadian signaling cascades. Based on data from a large European sample, Roenneberg and colleagues (2012) examined social jetlag in relation to BMI and found that 69% of the represented population reported at least one hour of social jetlag each week, which in turn, was predictive of being overweight (BMI $\geq$ 25). This finding was robust after adjusting for sleep duration. Only two subsequent studies have examined social jetlag in relation to metabolic health; however, these studies reported null associations between social jetlag and both BMI (Rutters et al., 2014) and homeostasis model assessment of insulin resistance (HOMA-IR; Kantermann, 2014). These studies were characterized by small sample sizes and heterogeneous samples, suggesting that more work is needed to understand whether weekly shifts in sleep timing may be a prominent risk factor for metabolic health, independent of factors such as average sleep duration.

1.1.3 Manipulations of sleep timing & metabolic functioning

Mechanisms to explain the link between circadian desynchrony and metabolic health have been explored. Potential mechanisms have included metabolic dysregulation due to insufficient sleep, the influence of sleep deprivation on dietary preference, and reduced physical activity and availability of healthy foods during nighttime hours compared to daytime hours (Ekmekcioglu & Touitou, 2011). Although it is clear that dietary behavior and a positive energy balance (i.e., more calories consumed than expended) contribute to weight gain within the context of circadian misalignment, the independent effects of sleep timing on metabolic health are less clear and are often confounded by changes in sleep duration.

Buxton and colleagues (2012) systematically assessed the effect of circadian misalignment on metabolic physiology (Buxton et al., 2012). Participants in this study were placed on an imposed schedule of sleeping, waking, fasting and feeding that was delayed by four hours each day over three weeks. After one week, participants were sleeping during the day and awake at night. Allowed sleep time was also limited to 5.6 hours per 24 hours. By the end of five weeks, participants' resting metabolic rate had reduced by 8% and pancreatic insulin secretion had dropped by approximatley 33%. This finding suggested that dramatic delays in both sleep and eating time contributed to metabolic dysfunction, potentially by decreasing energy expenditure and the body's ability to metabolize glucose.

Pancreatic insulin secretion may be particularly sensitive to changes in circadian rhythms, independent of sleep. Scheer and colleagues (2009) found that following a circadian misalignment protocol, participants demonstrated impaired pancreatic insulin production and higher glucose, independent of changes in sleep efficiency. Studies of sleep restriction in the absence of circadian misalignment have reported on reduced insulin sensitivity despite no changes in pancreatic insulin secretion (Buxton et al., 2010). These studies indicate that misaligned sleep-wake cycles may have detrimental effects on metabolic health, independent of sleep duration and efficiency, and that sleep timing may uniquely act on a chronobiological pathway specific to pancreatic insulin functioning.

1.2 CHRONOBIOLOGICAL MECHANISMS LINKING SLEEP TIMING AND METABOLIC HEALTH

Sleep timing may influence circadian signals involved in the chronobiological regulation of metabolic functioning. Energy metabolism rhythms are synchronized by a hierarchical system of internal pacemakers including a "central clock" known as the suprachiasmatic nucleus (SCN), and "peripheral clocks" located in tissues throughout the body. The SCN is a small cluster of cells located near the hypothalamus which is reset daily by exposure to light (Gillette & Tischkau, 1999; Kennaway, 1998). The SCN receives non-visual information from light-dark cycles via specialized retinal ganglion cells and projects information about the environmental photoperiod to peripheral tissues via hormonal signaling cascades (Pevet & Challet, 2011; Maywood, O'Neill, Chesham, & Hastings, 2007). When light is perceived, the SCN signals the pineal gland to suppress melatonin production, inhibiting sleep and promoting wakefulness. Melatonin is one of the most robust circadian signals, referred to as the "arm" of the circadian clock. Moreover, melatonin appears to play a prominent role in regulating rhythms of energy storage and energy expenditure.

Metabolic processes demonstrate distinct temporal organization, fluctuating between phases of energy storage (anabolic) and energy expenditure (catabolic). During the anabolic phase, carbohydrates are broken down into energy, or glucose. Glucose is converted into glycogen through a process called glycogenesis so that it can be stored in liver, adipose, and muscle tissues via insulin transport. During the catabolic phase, glycogen is converted back into glucose, through a process called glycogenolysis, to be circulated in the blood for use during periods of fasting such as sleep. The anabolic and catabolic phases of digestion rely on the temporal sequestration of glycogenesis and glycogenolysis to create rhythmic and distinct patterns of energy storage and energy expenditure, thereby achieving energy homeostasis. Glycogenesis and glycogenolysis are in synchrony with predictable rhythms of sleeping-waking, thought to reflect evolutionary behavior patterns of foraging for food during the day and fasting at night (Arble, Ramsey, Bass, & Turek, 2010).

Melatonin facilitates the temporal sequestration of the anabolic and catabolic phases of metabolism in part by regulating pancreatic insulin production. When melatonin is produced, it binds with receptors on pancreatic islets to inhibit beta-cell production of insulin. As seen in

Figure 1, decreased levels of insulin at night are necessary to initiate the catabolic phase of metabolism, allowing stored energy to be released back into the blood stream to maintain basal cellular functioning during the anticipated fasting period (i.e. sleep). However, the absence of melatonin can result in disinhibited insulin secretion at night, prolonging the energy storage phase. This becomes problematic due to the limited capacity of glycogen stores which is typically reached by the end of the day (Danforth, 1965; Chen, Williams, Cooney, & Caterson, 1992; Barclay, Eley, Buysse, Maughan, & Gregory, 2012). When glycogen stores are full and insulin is not inhibited by melatonin, glucose is directed into tissues that can no longer absorb it properly. Excess glucose either remains in circulation, contributing to a hyperglycemic state, or is transported into tissues and stored as fat (see Figure 1), both of which are risk factors for adverse metabolic health outcomes. Regular secretion of melatonin may therefore be critical for regulating patterns of energy storage and energy expenditure, and may represent a mechanistic pathway through which sleep timing may influence metabolic health and functioning.

Melatonin may also directly influence nocturnal basal energy expenditure by enhancing non-shivering thermogenesis (NST), or the conversion of energy into heat. Non-shivering thermogenesis is typically activated in response to cold, diet, or sleep, and accounts for 15-20% of total daily energy expenditure in humans (van Marken Lichtenbelt & Schrauwen, 2011). Several studies have suggested that melatonin is essential for the activation of NST in brown adipose tissue, an organ highly specialized for NST (Heldmaier & Hoffmann, 1974; Skilling et al., 2010). In animal models, activated brown adipose tissue has been shown to increase resting metabolic rate by 70% (Heim & Hull, 1966; Hayward & Davies, 1972). For several decades, it was thought that brown adipose tissue, capable of NST, was only present in humans for the first few years of life. Recent studies using PET scans have shown that adults preserve substantial amounts of brown adipose tissue which remains metabolically active into adulthood (Tan, Manchester, Fuentes-Broto, Paredes, & Reiter, 2011). The aforementioned studies suggest that sleep timing may alter nocturnal energy expenditure via melatonin suppression with potential downstream consequences for insulin functioning and body weight.

Melatonin suppression may be more pronounced when light exposure occurs after one's normal bedtime. In a study of healthy young adults, exposure to room light before bedtime resulted in a later melatonin onset in 99% of participants and a shortened duration of melatonin secretion by an average of 90 minutes (Gooley et al., 2011). The effect of light on melatonin was

more pronounced when exposure to light coincided with a participant's self-reported usual sleep time. In another study, exposure to incandescent lighting for less than 1 hour during one's normal sleep time was shown to reduce circulating melatonin levels by 50% (Pauley, 2004). These studies suggest that intra-week bedtime delay may be an additional indicator of sleep timing relevant for metabolic health.

1.3 SLEEP TIMING AND METABOLIC HEALTH IN MIDLIFE WOMEN

Midlife is an optimal time to study the association between sleep timing and metabolic health in women, given the accelerated risk for metabolic disturbances, changes in sleep, and circadian dysfunction accompanying the menopausal transition. Converging evidence suggests that physiological changes during menopause may cause midlife women to be more vulnerable to changes in sleep. For instance, the Study of Women's Health Across the Nation (SWAN) has reported that risk for the metabolic syndrome as well as other metabolic risk factors, including low-density lipoprotein cholesterol, increase with the menopausal transition (Janssen, Powell, Crawford, Lasley, & Sutton-Tyrrell, 2008; Matthews et al., 2009). SWAN investigators have also shown that difficulties with sleep latency and sleep maintenance increase across the menopausal transition (Kravitz et al., 2008), mediated in part by vasomotor symptoms, changing hormone profiles, and waking health behaviors (Sowers et al., 2008; Kravitz et al., 2003; Polo-Kantola & Erkkola, 2004; Thurston, Santoro, & Matthews, 2012; Kline et al., 2013; Irish, Dougall, Delahanty, & Hall, 2013). No study to date has evaluated the influence of sleep timing on metabolic health in midlife women.

Women in mid-life may also be more sensitive to changes in sleep timing due to changes in melatonin synthesis by estrogen and progesterone (Toffol et al., 2013). Melatonin levels are known to diminish with age and demonstrate a sharp decline following menopausal onset (Walters, Hampton, Ferns, & Skene, 2005). Moreover, melatonin may be less effective in midlife due to age-related changes in photosensitivity (Herljevic, Middleton, Thapan, & Skene, 2005). Collectively, these studies suggest that sleep timing may be particularly important and modifiable health behavior for midlife women.

1.4 THE PRESENT STUDY

The sleep and circadian literature provide compelling support for an investigation of day-to-day sleep timing and metabolic health. The health consequences of permanent and rotating shift work have been well documented. Moreover, the emerging literature on sleep timing and health in the general population suggests that further inquiries into this relationship are warranted and that longitudinal assessment of this relationship is needed. The present study assessed indices of sleep timing, namely average bed time, variability in bed time, bedtime delay and social jetlag in relation to metabolic health in midlife women.

The aim of the present study was to characterize sleep timing in midlife women and to evaluate its cross-sectional and prospective associations with indices of metabolic functioning in the multi-ethnic cohort of midlife women who participated in the SWAN Sleep Study. Cross-sectional analyses were used to assess sleep timing in relation to BMI and HOMA-IR measures obtained during the core SWAN assessment closest to the SWAN Sleep Study (Time 1). Prospective analyses examined indices of sleep timing in relation to BMI and HOMA-IR measured at the most recent core SWAN visit (Time 2). Understanding how sleep timing is associated with cross-sectional and prospective metabolic outcomes may be used to inform behavioral lifestyle interventions and sleep hygiene recommendations.

2.0 RESEARCH DESIGN AND METHODS

2.1 PARTICIPANTS AND PROTOCOL

Participants were drawn from the SWAN Sleep Study, an ancillary project to SWAN, a project that enrolled a multi-ethnic cohort of midlife women from 7 different sites across the United States. Four sites (Pittsburgh, PA; Detroit, MI; Oakland, CA; & Chicago, IL) participated in the ancillary Sleep Study, yielding 370 Caucasian, African American and Chinese women. All women in the SWAN Sleep Study were either pre-, peri-, or post-menopausal and were between the ages of 48-58. Participants provided written informed consent in accordance with guidelines put forth by the Institutional Review Boards at each participating institution.

Women enrolled in the SWAN Sleep Study completed three nights of in-home overnight polysomnography and questionnaire data. Concurrent wrist actigraphy and the Pittsburgh Sleep Diary were collected for the duration of the protocol (up to 35 days). Metabolic health data were collected during annual core SWAN assessments. Data used in the current analyses were drawn from assessments closest to the SWAN Sleep Study (Time 1) and from the most recent and available assessment (visit 12; Time 2).

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. Participants were excluded from the present analysis if they provided less than 11 days of SWAN Sleep Dairy data (n = 10) and were excluded from HOMA-IR analyses if they were missing blood data at Time 1 (n = 3). Participants were excluded from prospective BMI analyses if they were missing BMI from either Time 1 or Time 2 (n = 10) and were excluded from prospective HOMA-IR analyses if they were missing blood data from either Time 1 or Time 2 (n = 65). Additionally, participants were excluded from any analysis for taking

insulin or insulin-related medications (n = 22 and 44 for Time 1 and Time 2, respectively). Accordingly, sample sizes were 338 and 335 for BMI and HOMA-IR in cross-sectional analyses, respectively, and were 306 and 241 for BMI and HOMA-IR in prospective analyses, respectively.

2.2. SLEEP TIMING

Clock times for turning out bedroom lights before bed were recorded in Pittsburgh Sleep Diaries. Clock times were converted into minutes elapsed from the previous midnight. *Average bedtime* was calculated across the first 14 nights of data collection (11, 12 or 13 days was used for n = 10 participants). *Variability in bedtime* was quantified as the standard deviation from an individual's average sleep time, such that, high variability in bedtime was indicated by high standard deviations. *Social jetlag* was calculated as the difference between mid-sleep point on free-days and mid-sleep point on non-free days. Consistent with the social jetlag literature, we based non-free days on the standard Monday through Friday work week. A fourth index of sleep timing was calculated to quantify *bedtime delay*, a proxy for exposure to light following one's typical bedtime. Bedtime delay was calculated as the sum of minutes past average bedtime in a given week. Since two weeks of diary data were used to calculate sleep timing variables, we calculated bedtime delay for each week and took the average of the two bedtime delay values.

2.3 BODY MASS INDEX

Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Body mass index was measured at Time 1 and Time 2 and was used in both cross sectional and prospective analyses. Although it is suggested that waist circumference is a better predictor of adiposity than BMI (Janssen, Katzmarzyk, & Ross, 2004), we chose to evaluate BMI in order to compare and contrast our results with those in the extant literature.

2.4 INSULIN RESISTANCE

Homeostasis Model Assessment (HOMA) was used to estimate insulin resistance (Matthews et al., 1985). The HOMA method apportions insulin and glucose in terms of sensitivity (resistance is the inverse of sensitivity) and yields percentages based on a normal reference population. For instance, a HOMA-insulin sensitivity value of .50 would suggest that insulin sensitivity is operating at about 50%, which is considered to be relatively low. Subsequently, insulin resistance (the inverse of insulin sensitivity) is then estimated to be at about 200%, resulting in a HOMA-IR value of 2, which considered relatively high.

The most recent method (HOMA2) was used for assessing HOMA-IR. HOMA2 was developed by Jonathan Levy in 1998 and adapts the original model (fasting plasma glucose (mmol/L) x fasting insulin (mIU/L)/22.5); Matthews et al., 1985) to account for variations in hepatic and peripheral glucose resistance, circulating pro-insulin and allows for an insulin secretion curve for glucose concentrations above 180 mg/dL (Kong, Chua, & Tow, 1998). The HOMA model is comparable to euglycemic-hyperinsulinemic clamp (r = 0.88) for both diabetic and non-diabetic individuals (Matthews et al., 1985).

2.5 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. These include socio-demographics, such as age, race, and education. Candidate covariates were variables known to affect indices of metabolic health. Socio-demographic data, medical diagnoses and medication usage were assessed by self-report. Menopausal status was based on menstrual bleeding patterns outlined by WHO criteria (World Health Organization, 1996). Sleep and nocturnal physiology variables included apnea hypopnea index (AHI), total sleep time, sleep latency, and wakefulness after sleep onset. Study site, season and years elapsed between Time 1 and Time 2 were also evaluated as additional covariates.

2.6 STATISTICAL ANALYSIS

2.6.1 Descriptive Statistics and Covariate Evaluation

Descriptive statistics were used to characterize the study sample according to Aim 1. The distributions of sleep timing variables were partitioned into tertiles and participants were characterized by early, moderate, or late bedtime groups; low, medium, or high variability, social jetlag, and bedtime delay groups. Chi-square statistics and one-way ANOVAs were used to characterize the sample across each set of sleep timing groups. Pearson correlations were used to identify significant bivariate associations between candidate covariates and both predictor and outcome variables. In order to reduce the number of statistical comparisons, only variables with significant bivariate associations ($p < 0.1$) with the primary outcome variables were included as covariates in the final statistical models.

2.6.2 Cross-Sectional Analyses

Hierarchical linear regressions were used to test the hypothesis that later sleep time and greater variability in sleep time were cross-sectionally associated with sub-optimal metabolic health. Relevant covariates were entered into step one for each model. Due to high correlations among sleep timing variables (see Appendix Table A1), separate regression models were used for each independent predictor. Regression analyses assessed the variance in BMI and HOMA-IR explained by each sleep timing variable.

2.6.3 Prospective Analyses

Hierarchical linear regressions were used to test the hypothesis that later bedtime, greater variability in bedtime, more social jetlag, and more bedtime delay were prospectively associated with sub-optimal metabolic health. 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. Again, separate regression models were used for each independent predictor.

Regression analyses assessed the variance in BMI and HOMA-IR accounted for by each sleep timing variable while controlling for covariates and measures of metabolic health at Time 1.

2.6.4 Exploratory Analyses

The chronobiological model suggests that the timing of light exposure may be the mechanism through which sleep timing influences metabolic health. The current study included data from four sites across the country, all of which receive varying degrees of light exposure. Moreover, seasonal changes are also associated with varying degrees of light exposure. Therefore, moderation analyses were conducted to assess whether cross-sectional or prospective relationships between indices of sleep timing and metabolic health varied as a function of study site or season during which sleep was measured. Geographical and seasonal differences were taken into account to determine whether these factors moderated the sleep timing-metabolic health relationship. Additionally, a limited but compelling body of research suggests that endogenous circadian rhythms may vary across race and that African Americans may be more vulnerable to circadian dysregulation (Lieu, Curhan, Schernhammer, & Forman, 2012; Profant & Dimsdale, 1999; Smith, Burgess, Fogg, & Eastman, 2009). Moderation analyses were conducted to determine whether the sleep timing-metabolic health relationship varies as a function of race in this sample. Finally, given the small number of Chinese women in the sample, sensitivity analyses were conducted to assess whether results were independent of their inclusion.

3.0 RESULTS

We evaluated associations between measures of sleep timing and indices of metabolic health in order to assess the importance of sleep timing to metabolic health in midlife women. Four measurements of sleep timing were calculated for the current study: average bedtime, variability in bedtime, bedtime delay, and social jetlag. The primary aims of the study were: 1) to characterize sleep timing in midlife women across socio-demographic characteristics, measures of mental and physical health, and other domains of sleep; 2) to evaluate cross-sectional relationships between measures of sleep timing and metabolic health in midlife women; and 3) to evaluate prospective relationships between measures of sleep timing at Time 1 and metabolic health at Time 2 (average years between time points = 5.39 ± 0.71). We expected later average bedtime, greater variability in bedtime, more bedtime delay, and more social jetlag to be associated with higher BMI and higher levels of HOMA-IR at Time 1 and Time 2. Several exploratory aims were included to evaluate potential modifiers of the sleep timing-metabolic health relationship. Specifically, the exploratory aims evaluated whether associations were moderated by race, study site, and season.

A total of 370 women participated in the SWAN Sleep Study. Among them, all had complete BMI data and 367 women had complete HOMA-IR data from one of four possible annual visits that overlapped with the SWAN Sleep Study. Ten women were excluded from analysis due to missing or insufficient Sleep Diary data (less than 11 days; $n = 10$). Finally, participants were excluded if they were taking insulin or medications for type 2 diabetes ($n = 22$). Therefore, cross-sectional analyses were performed using a total sample size of 338 for and 335 for analyses assessing BMI and HOMA-IR, respectively.

Participants who were excluded from analyses were more likely to be employed for at least 20 hrs/week ($\chi^2 = 5.212$; $p = .022$), report less time engaging in moderate to vigorous exercise ($F(1, 363) = 7.959$; $p = .009$), have higher self-reported symptoms of depression ($F(1, 367) = 7.614$; $p = .046$), fewer daily servings of alcohol ($F(1, 363) = 4.716$; $p = .028$) and have

more fragmented sleep $F(1, 366) = 2.787$; $p = .001$); see Appendix Table A19). Cross-sectional analyses were performed on a sample of 161 Caucasian, 121 African American, and 56 Chinese women (age 52.12 ± 2.10). Socio-demographic, health, and sleep characteristics are displayed in Table 1. A substantial portion of the sample was either married or living with a partner ($n = 219$; 65.75%), had a college degree ($n = 174$; 52.29%) or worked more than 20 hours per week ($n = 270$; 79.88%). Marital status ($\chi^2 = 26.186$; $p < .001$) and education ($\chi^2 = 21.860$; $p < .001$) tended to vary by race (see Table 1).

On average, the sample was overweight (BMI = 29.55 ± 7.57) with HOMA-IR values within the normal range (1.73 ± 1.29; see Table 1; Wahrenberg et al., 2005). About two thirds of the sample were peri- or early peri-menopausal ($n = 211$, 63%). On average, participants reported vasomotor symptoms, such as hot flashes or night sweats, on 32.84% (± 33.92) of study days and reported exercising on 20.84% (± 23.89) of study days. The sample contained few smokers ($n = 34$, 10.06%) and on average, participants consumed 0.29 (± 0.50) servings of alcohol and 1.6 (± 1.37) servings of caffeine per day while participating in the study. Average symptoms of depression were low (4.65 ± 2.78). Almost all health characteristics varied by race (see Table 1). Specifically, BMI and HOMA-IR values were significantly higher among African American women compared to Caucasian, ($t(335) = -5.141$; $p < .001$ and $t(332) = -4.665$; $p < .001$) or Chinese women ($t(335) = 9.150$; $p < .001$ and $t(332) = 3.577$; $p < .001$). African American women also reported more frequent vasomotor symptoms and were more likely to be a current smoker than Caucasian ($t(335) = -3.941$; $p < .001$and $t(280) = -2.970$; $p = .003$) or Chinese women ($t(335) = 3.135$; $p = .002$ and $t(175) = -5.307$; $p < .001$). Caucasian women reported higher alcohol and caffeine consumption compared to African American ($t(335) = 5.492$; $p < .001$ and $t(335) = 6.601$; $p < .001$) and Chinese women ($t(335) = 4.508$; $p < .001$ and $t(335) = 4.504$; $p < .001$). Caucasian women also reported more frequent moderate to vigorous exercise than African American women ($t(335) = 3.626$; $p < .001$). Finally, symptoms of depression varied by race ($F(2,220) = 7.99$; $p < .001$), with African American women reporting more depression than either Caucasian women ($t(335) = -2.657$; $p = .008$) or Chinese women ($t(335) = 2.378$; $p = .011$).

Average sleep duration in the current sample was a little over 6 hours (6.23 hrs ± 55.51 mins). Participants spent an average of 21.19 minutes ($SD = 20.51$) trying to fall asleep and 52.71 minutes ($SD = 30.87$) awake after sleep onset. Sleep complaints measured by the

Pittsburgh Sleep Quality Index (PSQI) were high (5.64 ± 3.06). Sleep disordered breathing, measured by apnea hypopnea index, was relatively low (8.05 ± 9.07), and women reported taking sleep medication on an average of 25.70% of study nights. Race differences were significant across several sleep measures, as previously reported (Hall et al., 2009). In general, African American women had shorter sleep duration, took longer to fall asleep, and spent more time awake after sleep onset (see Table 1).

Participants reported an average bedtime of 11:30 pm (*SD* = 59.27 mins), variability in bedtime of about 56 minutes (*SD* = 32.22 mins), bedtime delay of 138.27 minutes (*SD* = 56.48 mins) and social jetlag of about 42.71 minutes (*SD* = 43.11 mins; see Table 1). Sleep timing variables were partitioned into tertiles and rounded to the nearest half hour to create three groups per variable. Demographic, health, and sleep characteristics were examined across sleep timing groups. One-way ANOVAs and chi-square tests were used to assess significant differences across sleep timing categories. Follow-up t-tests were performed when omnibus tests were significant. Continuous sleep timing variables were used in follow-up t-tests to dissect significant chi-square results.

3.1 SOCIO-DEMOGRAPHIC CORRELATES OF SLEEP TIMING

Racial differences were found among average bedtime ($\chi^2 = 14.282$; $p = .006$), variability in bedtime ($\chi^2 = 31.049$; $p < .001$), and bedtime delay ($\chi^2 = 24.497$; $p < .001$) and are presented in Figure 2. Caucasian women were more likely to have an early bedtime compared to African American ($t(280) = -2.937$; $p = .004$) and Chinese women ($t(152) = -2.431$; $p=.016$). African American women were more likely to have higher variability in bedtime and greater bedtime delay compared to Caucasian women ($t(280) = -5.195$; $p < .001$ and $t(280) = -4.895$; $p < .001$, respectively) and compared to Chinese women ($t(175) = -3.263$; $p = .001$ and $t(175) = -4.384$; $p < .001$, respectively). Sleep timing also tended to vary by marital status and education. Women who were married or living with a partner had lower variability in bedtime and less bedtime delay than women who were single ($t(336) = -2.779$; $p = .006$ and $t(336) = -2.491$; $p = .013$, respectively). Similarly, women with a college degree had lower variability in bedtime and less bedtime delay than women without a college degree ($t(330) = -2.988$; $p = .003$ and $t(330) = -3.740$; $p < .001$, respectively). Finally, women who were employed for at least 20 hours/week

had significantly more social jetlag than women who were unemployed or underemployed had lower variability in bedtime and less bedtime delay than women who were single ($t(336) = -3.115$; $p = .002$). These associations were not moderated by race (p-values > .05).

3.2 HEALTH CORRELATES OF SLEEP TIMING

Health behaviors and measures of both mental and physical health varied by sleep timing groups. Women with the latest bedtimes reported significantly less time exercising compared to those in the early bedtime group ($t(335) = 2.460$; $p = .014$; see Table 2). Reported frequency of vasomotor symptoms was also highest among women with the latest bedtimes ($F(2,337) = 4.560$, $p = .011$) and the least amount of social jetlag ($F(2,337) = 4.124$, $p = .017$). Finally, depression scores were significantly higher among women with the latest bedtimes ($F(2,337) = 3.568$, $p = .029$), the highest variability in bedtime ($F(2,337) = 5.804$, $p = .003$) and the most bedtime delay ($F(2,337) = 6.025$, $p = .003$). No associations between sleep timing and health characteristics were moderated by race (p-values > .05).

3.3 SLEEP CORRELATES OF SLEEP TIMING

Sleep latency and sleep quality also differed by sleep timing groups. Specifically, early bedtime and moderate social jetlag were both associated with shorter sleep latency ($F(2,337) = 3.873$, $p = .022$ and $F(2,337) = 3.689$, $p = .026$, respectively; see Tables 2 and 5). Subjective sleep complaints were highest among those with the latest bedtimes, the greatest variability in bedtime and the most bedtime delay ($F(2,337) = 3.898$, $p = .021$; $F(2,337) = 4.260$, $p = .015$ and $F(2,337) = 5.869$, $p = .003$, respectively). Associations between sleep timing and sleep were independent of race effects (p-values > .05).

3.4 COVARIATE SELECTION

After assessing the relationships between relevant covariates and the outcome measures, 5 and 6 covariates were included in the final cross-sectional models predicting BMI and HOMA-IR, respectively. These covariates included race, menopausal status, exercise, depression and sleep

duration. Body mass index was also controlled for in models predicting HOMA-IR. In prospective analyses, metabolic health variables at Time 1 were also controlled for. Study site, season nor time elapsed between Time 1 and Time 2 were associated with metabolic health variables and were therefore not included in the models.

3.5 CROSS-SECTIONAL ASSOCIATIONS BETWEEN SLEEP TIMING AND BMI

As shown in Table 6, several unadjusted cross-sectional associations between sleep timing and BMI were significant. Specifically, greater variability in bedtime and more bedtime delay were associated with higher BMI (β = .188; p = .001 and β = .258; p < .001, respectively). After controlling for race, menopausal status, sleep duration, exercise and depression, the relationship between bedtime delay and BMI remained significant (β = .128; p = .010). Race, exercise, depression and sleep duration were also significant predictors of BMI (see Appendix Tables A2-A5).

3.6 CROSS-SECTIONAL ASSOCIATIONS BETWEEN SLEEP TIMING AND HOMA-IR

In unadjusted models presented in Table 7, variability in bedtime and bedtime delay were both associated with the HOMA-IR (β = .259; p <.001 and β = .258; p < .001, respectively). Variability in bedtime and bedtime delay remained statistically significant after adjusting for race, menopausal status, sleep duration, exercise, depression, and BMI (β = .132; p = .005 and β = .098; p = .038, respectively). Variability in bedtime and bedtime delay explained an additional 1.5% and 0.8% of the variance in HOMA-IR, respectively, above and beyond other variables in the model. Average bedtime and social jetlag were unrelated to HOMA-IR before and after adjustment (p > .05). Other significant predictors of HOMA-IR included race and BMI (see Appendix Tables, A6-A9)**.**

3.7 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 Time2, and 12 started taking insulin-related medication. Prospective analyses were run using 306 and 241participants for BMI and HOMA-IR outcomes, respectively. Means and correlations between BMI and HOMA-IR values at Time 1 and Time 2 are presented in Appendix Table A18. There was a significant increase in BMI between Time 1 and Time 2, $t(320)= -3.228$, $p = .001$. There was no significant change in HOMA-IR across time, $t(262)= .380$, $p = .704$. All covariates from cross-sectional analyses were carried over to prospective analyses with the addition of metabolic health measures at Time 1. Time between assessments was evaluated as a covariate for prospective relationships but was not included due to lack of association with outcome variables.

As seen in Table 8, unadjusted prospective associations were found between several measures of sleep timing and BMI at Time 2. However, after adjusting for race, menopausal status, sleep duration, exercise, depression, and BMI at Time 1, relationships between sleep timing and BMI at Time 2 were no longer present. Bedtime delay was associated with HOMA-IR at Time 2 in unadjusted models. However, no index of sleep timing predicted HOMA-IR at Time 2 after adjusting for covariates and HOMA-IR values at Time 1 (Table 9).

3.8 AD-HOC EXPLORATORY ANALYSES

3.8.1 Do associations between sleep timing and metabolic health vary by study site or season?

The current study used bedtime as a behavioral proxy for exposure to light at night. However, other factors can influence light exposure. For instance, in the current sample, light exposure would likely vary across study site and across season. Exploratory analyses were conducted to assess whether associations among sleep timing and metabolic health varied as a function of these two variables. Moderation analyses were conducted to evaluate whether results varied between participants in Oakland, California and participants studied at other locations. Results

revealed no significant interaction with study site (data not shown). Due to the ancillary nature of the sleep study, metabolic health data and sleep timing data were collected at different points in time, and it was not possible to assess moderation by season. For instance, metabolic health and sleep timing were measured during the same season in only 28.5% of the sample (n = 63). Among those participants, only 39.7% had concurrent measures during the same month (n = 25).

3.8.2 Do associations between sleep timing and metabolic health vary by race?

Given significant differences in sleep timing between race groups, additional analyses were conducted to assess whether relationships between sleep timing and metabolic health variables varied as a function of race. Moderation analyses were conducted by entering sleep-timing by race interaction terms into the regression models. No cross-sectional or prospective associations between sleep timing and metabolic health varied as a function of race (data not shown).

3.8.2.1 Sensitivity Analysis Given the small number of Chinese women in the sample, a sensitivity analysis was conducted to determine whether results remained significant after removing Chinese women. Sensitivity analysis preserved nearly all associations identified in the original model. However, the cross-sectional association between bedtime delay and insulin resistance was no longer significant after excluding Chinese women (β = .007; p = .081; See Table 10).

4.0 DISCUSSION AND CONCLUSIONS

Epidemiological studies of shift work and experimental circadian dysregulation protocols have demonstrated that highly irregular sleep timing has adverse consequences for metabolic health. However, this is the first study to assess whether moderate differences in sleep timing are associated with metabolic health in a normative population, using naturalistic parameters of sleep timing and both cross-sectional and longitudinal outcomes. We examined cross-sectional (N = 338) and prospective (N = 306) relationships between four measures of sleep timing and two indices of metabolic health in a multi-ethnic cohort of midlife 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, cross-sectional analyses also showed that bedtime delay was associated with both BMI and HOMA-IR, such that more bedtime delay was associated with higher BMI and greater HOMA-IR after controlling for race, menopausal status, sleep duration, exercise, depression, and BMI. Prospective analyses yielded no significant relationships between sleep timing and metabolic health after adjusting for covariates. These data indicate that individual differences in sleep timing are associated with metabolic health in a non-shift working population. The current findings provide partial support for a chronobiological model linking sleep timing with metabolic health.

Sleep timing acts as a behavioral marker for the extent to which people are exposed to light before sleep. We propose that sleep timing may act on health outcomes via a melatonergic-metabolic pathway by gating the effect of light on circadian signaling. Light at night is known to suppress melatonin. Converging evidence indicates that melatonin plays a vital role in regulating the daily rhythm in glucose tolerance and that melatonin suppression may have consequences for energy homeostasis (Picinato, Haber, Carpinelli, & Cipolla-Neto, 2002; Nishida, Sato, Murai, & Nakagawa, 2003; Pimenta, Kac, Souza, Ferreira, & Silqueira, 2012). In particular, melatonin is thought to bind with receptors on the pancreas and liver to inhibit the production of insulin and inhibit hepatic gluconeogenesis, thereby allowing stored glucose in liver and muscle tissues to

re-enter the blood stream for metabolic use, otherwise known as the catabolic or energy expenditure phase of digestion (Faria et al., 2013). Light at night is therefore thought to delay this catabolic phase of digestion and promote a prolonged anabolic phase of energy storage. As described earlier, rhythmic patterns of energy storage and energy usage are needed to maintain energy homeostasis. When the anabolic phase of digestion is prolonged, glycogen stores become full and extra glucose is stored in adipose tissue as fat or is maintained in the blood stream resulting in a hyperglycemic state. Chronic exposure to light at night could eventually result in weight gain and dysregulated glucose metabolism via insulin. We predicted that habitual sleep timing patterns would be associated with BMI and HOMA-IR.

Bedtime delay was associated with higher BMI and greater HOMA-IR in cross-sectional analyses. This finding is consistent with our model and with the literature. Bedtime delay may have direct effects on melatonin suppression through extended light exposure after when one would usually be asleep. For instance, melatonin suppression by light has been shown to be stronger when the light exposure occurs during usual sleeping hours (Gooley et al., 2011). Bedtime delay may even have consequences for melatonin after light is no longer directly inhibiting secretion. For instance, duration and intensity of light exposure at night has been shown to be inversely associated with nocturnal melatonin levels during sleep (Aoki, Yamada, Ozeki, Yamane, & Kato, 1998) and studies of permanent night work suggest that chronic melatonin suppression may have long term consequences for pineal functioning and melatonin production (Barbadoro et al., 2013). Findings from the animal literature also indicate that reduced melatonin levels may also impact BMI by limiting the efficacy of weight loss efforts. Specifically, low nocturnal melatonin has been shown to blunt adipose tissue response to aerobic exercise and fasting in rodent models (Borges-Silva et al., 2007; Borges-Silva et al., 2005; Alonso-Vale et al., 2004).

Variability in bedtime was significantly associated with increased HOMA-IR, cross-sectionally. This finding is consistent with the two other studies of sleep timing and health that have been conducted in non-shift workers that found that higher variability in bedtime was associated with greater risk for obesity (Logue et al., 2014b; Bailey et al., 2014b). Our finding is also consistent with our model and suggests that high variability in bedtime may be analogous to inconsistent circadian signaling. A review by Van Someren & Riemersma-Van Der Lek (2007) suggests that internal synchrony among peripheral clocks is achieved by sustained and regular

24-hour patterns of input from environmental zeitgebers (Van Someren & Riemersma-Van Der Lek, 2007). The authors of this review provide a metaphor of an adult pushing a child on a swing to illustrate the effect of time cues on peripheral pacemakers. Zeitgebers, or time cues, are represented by the adult in this metaphor, providing regular input to maintain oscillations in peripheral pacemakers. As the authors state, children can move the swing back and forth on their own by systematically raising and lowering their center of mass. However, their ability to maintain a robust rhythm depends on their mastery of swinging, or the endogenous strength of the peripheral oscillator.

Light is the most salient zeitgeber that entrains the circadian system by directly regulating melatonin, the most robust neuroendocrine signal of the circadian timing system or the "arm" of the biological clock (Mirick & Davis, 2008). From tightly controlled animal studies, we know that the absence of a zeitgeber, such as light, can lead to dampening and eventually halting oscillations in peripheral tissues. Moreover, abrupt shifts in light exposure can result in desynchrony between pacemakers, such as those in the liver and adipose tissue (Young, 2006; Yamazaki et al., 2000). Clock genes in the liver and adipose tissue rely on external cues to maintain the translational and transactional negative feedback loops that regulate glucose homeostasis and processes of energy mobilization (la Fleur, Kalsbeek, Wortel, Fekkes, & Buijs, 2001; Alonso-Vale et al., 2004). Therefore, variability in bedtime may impair metabolic health via irregular circadian input.

The association between variability in bedtime and insulin resistance is also consistent with the shift work literature. Although permanent night-shift work and rotating night-shift work have both been associated with adverse health outcomes, several studies have reported that rotating shift work is associated with worse subjective well-being (Alward & Monk, 1990), a higher prevalence of cardiovascular risk factors (Moore-Ede & Richardson, 1985; Knutsson, Akerstedt, & Jonsson, 1988; Thelle, Foorde, Try, & Lehmann, 1976; Theorell & Akerstedt, 1976), and greater risk for certain types of cancer (Papantoniou et al., 2014). Variability in the timing of behaviors such as sleep may help to explain increased relative risk among rotating shift workers compared to permanent night shift workers.

Alternative explanations for the significant associations between indices of sleep timing and metabolic health should also be considered. For instance, bedtime delay could be associated with eating later at night while variability in bedtime could be associated with variability in

eating time (Spaeth, Dinges, & Goel, 2013). In the absence of one zeitgeber, such as light, the circadian system has been known to rely on other time cues to maintain regular oscillation. For instance, in the absence of a light/dark cycle, rodents will entrain to food availability (Holmes & Mistlberger, 2000; Yokoi et al., 2002). The significance of food-entrained oscillation may be particularly important for peripheral clocks of those organs involved in glucose metabolism and insulin production such as the liver and the pancreas (Damiola et al., 2000; Stokkan, Yamazaki, Tei, Sakaki, & Menaker, 2001; Ekmekcioglu & Touitou, 2011). For instance, circadian genes such as *BMAL* and *PER2*, appear to be preferentially sensitive to different circadian time cues (Saini et al., 2013). *BMAL* and *PER2* are both entrained by light; however, *PER2* is highly sensitive to food intake and macronutrient content (Sherman et al., 2012).

Follow-up analyses were conducted to assess whether indices of meal timing explained significant associations between sleep timing and metabolic health. Dinner time was not associated with cross-sectional measures of BMI after controlling for covariates (ΔR^2= .004; β = .061; p = .216) and did not attenuate significant associations between bedtime delay and BMI. Similarly, variability in bedtime was robust to adjustment for variability in dinner time, which did not account for a significant proportion of the variance after adjustment for covariates (ΔR^2 = .003; β = .056; p = .251). In our sample, measures of meal timing did not explain associations between sleep timing and metabolic health. However, future studies should employ tightly controlled methods to parse out the relative influence of sleep timing and meal timing and how they might interact with one another. It should also be noted that indices of sleep timing could also reflect employment and lifestyle characteristics. Future studies should examine predictors of sleep timing such as elective work hours, domestic and familial responsibilities, features of chaotic lifestyles (Patel et al., 2014) and mood disorder symptomatology (Harvey, 2009).

Contrary to expectations, later average bedtime was not associated with higher BMI or greater HOMA-IR in either cross-sectional or prospective analyses. This may be considered inconsistent with our model of melatonin suppression. However, this null finding may also suggest that later average bedtime may reflect a later endogenous circadian rhythm and later melatonin onset. Therefore, light exposure during the time before one would normally go to bed would not act on the circadian system to suppress melatonin in the same way that light exposure past one's average bedtime would. Future studies should examine the congruence between

endogenous circadian rhythms and behavioral rhythms and examine the downstream effects on metabolic physiology.

Social Jetlag was also unrelated to either HOMA-IR or BMI at either time point. However, this null finding was likely due to the limited amount of social jetlag in the sample. Participants demonstrated an average social jetlag of 42.71 minutes (*SD* = 43.11 minutes). Previous studies of social jetlag have identified increased risk for metabolic health problems with greater than or equal to 2 hours of social jetlag (Roenneberg et al., 2012). In the current sample, only 5.33% (*n* = 18) had a social jetlag of 2 hours or more at Time 1. Moreover, social jetlag in this sample ranged from -115.08 to 162.05 minutes. This range indicates that 13.90% of the sample had a later mid-sleep point on week days compared to weekends, suggesting that some participants may not have worked a Monday-Friday schedule. Consistent with previous social jetlag studies, we based free days and non-free days on the standard five-day work week. Future studies should directly assess participants' schedules.

In light of the current findings, we might consider revising the model to differentiate between sleep timing variables that measure extent of exposure to light at night and inconsistent exposure to light at night. For instance, bedtime delay may be more appropriate measures to test a melatonin suppression model which may be adequate to assess risk for weight gain, given the strong research linking adipose accumulation and adipose dysfunction in the absence of melatonin described above. Conversely, variability in bedtime may be associated with desynchrony between multiple peripheral pacemakers located in different physiological systems. Intermittent or unpredictable zeitgeber exposure may prevent entrainment and interrupt signaling cascades that are needed to maintain synchrony across peripheral clocks (Van Someren & Riemersma-Van Der Lek, 2007).

The effect sizes for significant associations between sleep timing and metabolic health were all quite small. Specifically, bedtime delay explained 1.4% of the variance in BMI at Time 1 which is comparable to or greater than other correlates of BMI identified in the extent literature such as age, menopausal status, education, number of children and smoking (Matthews et al., 2001). However, the effect size for bedtime delay is considerably lower than other correlates of BMI such as race, physical activity and indices of sleep (Matthews et al., 2001; Mezick, Matthews, Hall, Richard, & Kamarck, 2014). Similarly, variability in bedtime and bedtime delay explained 1.5% and 0.8% of the variance in HOMA-IR, respectively. These effect sizes are

significantly lower than those for correlates of HOMA-IR such as physical activity, smoking or depression (Jeffery, Babeu, Nelson, Kloc, & Klette, 2013; Slagter et al., 2013; Kan et al., 2013). The small effect sizes found within the current set of results indicate that although sleep timing is significantly associated with metabolic health, the clinical relevance of sleep timing for these measures may be limited. Additional testing is needed to understand the importance of sleep timing within the context of other health behaviors.

Several limitations of the current study are worth addressing. Within this study, sleep timing variables were used as a behavioral marker to approximate exposure to light at night; however, direct measurement of light exposure was not conducted within this study. Therefore, we were unable to determine whether light exposure mediated associations among sleep timing and metabolic health. Direct measurement of light is needed in order to fully understand its effects on melatonin suppression and subsequent metabolic processes. For instance, in addition to simply exposure, studies have shown that there is a dose-response relationship between the intensity of light at night and melatonin suppression (Boivin, Duffy, Kronauer, & Czeisler, 1996; McIntyre, Norman, Burrows, & Armstrong, 1989). Measurements of ambient light intensity may therefore provide vital information for understanding the role of sleep timing in metabolic health. Additionally, individual differences in melatonin secretion and sensitivity to light at night should also be taken into consideration (Lindsay et al., 2002). Objective measurement of melatonin is needed to more accurately test the proposed melatonergic-metabolic model. Dim-light melatonin onset values should be measured among participants in order to understand when melatonin suppression by light would/could take place.

Measurements of metabolic health and sleep data were not concurrent. Because the SWAN Sleep Study was ancillary to SWAN, measurements of metabolic health and sleep were often taken at different time points. This limits our ability to draw conclusions from these analyses. Sleep timing is likely variable across many circumstances including changing seasons. Seasonal differences alter exposure to light via length of day which may have implications for sleep timing, as well as other behaviors relevant to metabolic health. Concurrent measures at multiple time points are needed to better understand the acute effects of sleep timing on metabolic health as well as how relationships between sleep timing and health influence each other over time.

Prospective analyses did not take into account changes in sleep timing from Time 1 to Time 2. We conducted reliability tests to assess the stability of our sleep timing measures. Several sleep timing variables demonstrated excellent reliability between Time 1 and Time 2. Specifically, average bedtime and variability in bedtime remained very stable among participants across time points, intra-class correlation coefficients were .900 (95% CI: .876 - .919) and .939 (95% CI: .925 - .951), respectively. Bedtime delay demonstrated acceptable reliability while social jetlag demonstrated poor reliability with intra-class correlation coefficients of .606 (95% CI: .506 - .685) and .096 (95% CI: -.122 - .271), respectively (Streiner, 1995). Therefore, it is possible that bedtime delay and social jetlag are not stable over time in midlife women. Short-term reliability was also assessed to determine how stable sleep timing variables were between weeks 1 and 2 of diary data collection. Average bedtime demonstrated strong short-term reliability with an intra-class correlation coefficient of .888 (95% CI: .863 - .909). Variability in bedtime and bedtime delay demonstrated reliability within the acceptable range with intra-class correlation coefficients of .569 (95% CI: .470 - .649) and .578 (95% CI: .481 - .656), respectively. Measures of social jetlag demonstrated poor short-term reliability between weeks 1 and 2 with an intra-class correlation coefficient of .391(95% CI: .252 - .505). Due to the low short-term reliability demonstrated here, the current results must be interpreted with caution. These reliability statistics demonstrate that a longer window of observation is needed to understand habitual sleep timing variables and assess whether people demonstrate stable sleep timing profiles across periods of time.

The limitations of the current study are offset by several notable strengths. Both SWAN and the SWAN Sleep Study sampled from a diverse population of multi-ethnic women, allowing us to look at race differences among the associations between sleep timing and metabolic health. Given the race disparities seen across metabolic health outcomes, race moderation analyses are warranted to gain a better understanding of the bio-behavioral pathways through which disparities might arise. Moreover, sleep timing was measured over the course of at least 11 full days (14 full days in 94.08% of subjects). Studies of habitual sleep timing have largely used single item questionnaires to probe typical bed and wake times on work and non-work days. The use of the Pittsburgh Sleep Diary allowed us to track sleep timing without the limitation of recall bias. Lastly, we used objective measures of metabolic health at multiple time points. The

homeostasis model assessment of insulin resistance and BMI allowed us to look at sleep timing in relation to a continuous gradient of risk for metabolic health problems.

In summary, the current study provided preliminary support for a melatonergic-metabolic pathway linking sleep timing with metabolic health. As indicated above, future studies would benefit from measuring ambient light exposure using objective means. Many actigraph devices are now equipped with light-sensing capability. Enhanced devices such as the Actiwatch Spectrum are able to collect light data from multiple channels such as photopic white light illuminance and red, green and blue light irradiance. Detailed information regarding ambient light exposure would inform our understanding of how sleep timing and other pre-sleep behavior (e.g., reading, watching TV) contributes to circadian functioning. Moreover, an objective measure of melatonin secretion is needed in future studies of habitual sleep timing. Dim-light melatonin onset provides a measure of the endogenous circadian rhythm of melatonin in the absence of time cues such as light. The timing of endogenous melatonin secretion is needed to understand when the production of melatonin would be interrupted by light exposure. Finally, experimental manipulations of sleep timing are needed to evaluate observed associations under controlled circumstances and assess the impact of melatonin suppression on downstream metabolic physiology. The current study warrants a systematic evaluation of light exposure and melatonin suppression as a mechanistic pathway through which sleep timing may influence metabolic health.

Table 1

Sample characteristics by race

	Total (n = 338)	Race: Caucasian (n = 161)	African American (n = 121)	Chinese (n = 56)	Sig
Demographic Characteristics					
Age mean(sd)	52.12±2.10	52.17±2.11	51.83±2.07	52.57±2.12	.083
Marital Status					
Married/living w/ partner N(%)	219(65.75)	122(75.78)	57(47.11)	40(71.43)	<.001***
Education					
≥ college degree N(%)	174(52.29)	98(60.87)	41(33.88)	35(62.50)	<.001***
Employment					
Unemployed or <20 hrs/wk N(%)	68(18.96)	29(18.01)	28(23.14)	11(19.64)	.566
Menopausal Status					
Peri/early peri-menopausal N(%)	211(63.00)	105(65.22)	71(58.68)	35(62.50)	.512
Health Characteristics					
BMI mean(sd)	29.55±7.57	29.01±6.82	33.20±7.91	23.19±2.74	<.001***
HOMA-IR (N=335) mean(sd)	1.73±1.29	1.47±0.82	2.23±1.81	1.37±0.51	<.001***
Current smoker N(%)	34(10.06)	11(6.83)	23(19.01)	0(0.00)	<.001***
Caffeine consumption mean(sd)	1.57±1.37	2.08±1.49	1.07±0.95	1.19±1.25	<.001***
Alcohol consumption mean(sd)	0.29±0.50	0.46±0.61	0.14±0.33	0.12±0.28	<.001***
% days mod/vig exercise mean(sd)	20.84±23.89	25.60±24.22	15.35±21.76	18.98±24.91	.001**
% days vms mean(sd)	32.84±33.92	27.40±29.86	43.11±36.48	26.32±34.50	<.001***
IDS mean(sd)	4.65±2.78	4.37±2.30	5.25±3.23	4.11±2.84	.009**
STAI mean(sd)	15.28±4.45	15.16±4.13	15.43±4.71	15.27±4.79	.878
Sleep Characteristics					
Duration mean(sd)	373.86±55.51	385.96±48.95	352.91±62.85	384.18±42.46	<.001***
Wakefulness after sleep onset(sd)	52.71±30.87	49.93±26.11	60.20±37.58	44.60±23.75	.002**
Latency	21.19±20.51	18.98±16.57	26.98±26.75	15.09±9.80	<.001***
PSQI	5.64±3.06	5.04±2.61	6.63±3.51	5.18±2.72	<.001***
AHI	8.05±9.07	8.56±9.80	7.73±8.58	7.27±7.84	.599
% days sleep meds	25.70±42.58	27.88±43.71	23.66±41.39	23.88±42.30	.671
Average Bedtime	11:30pm±59.27mins	11:19pm±56.06mins	11:40pm±66.08mins	11:39pm±48.58mins	.005**
Variability in Bedtime	56.34±32.22	48.49±24.85	70.44±38.94	50.89±27.04	<.001***
Bedtime Delay	138.27±56.48	127.47±53.43	160.37±58.97	121.57±44.18	<.001***
Social Jetlag	42.71±43.11	45.84±43.11	40.04±44.50	39.47±40.07	.443

*p < .05. **p < .01. ***p < .001.

Table 2

Demographic, health and sleep characteristics across early, moderate and late bedtime categories

	Average Bedtime			
	Early (n=100)	Moderate (n=155)	Late (n=83)	Sig
Demographic Characteristics				
Age mean(sd)	52.15±2.05	52.11±2.10	52.09±2.19	.978
Race				
White N(%)	58(58.00)	77(49.68)	26(31.32)	.006**
Black N(%)	28(28.00)	56(36.13)	37(44.58)	
Chinese N(%)	14(14.00)	22(14.19)	20(24.10)	
Marital Status				
Married/living w partner N(%)	68(68.00)	97(62.58)	54(65.06)	.675
Education				
≥ college degree N(%)	52(52.00)	86(55.48)	36(43.37)	.190
Employment				
Unemployed or <20 hrs/wk N(%)	13(13.00)	34(21.94)	21(25.30)	.088
Menopausal Status				
Peri/early peri-menopausal N(%)	61(61.00)	102(65.81)	48(57.83)	.319
Health Characteristics				
BMI mean(sd)	28.59±6.52	29.83±7.54	30.18±8.69	.302
HOMA-IR (N=335) mean(sd)	1.64±1.20	1.65±1.23	1.98±1.49	.164
Current smoker N(%)	7(7.00)	17(10.97)	10(12.04)	.463
Caffeine consumption mean(sd)	1.39±1.24	1.68±1.41	1.57±1.42	.260
Alcohol consumption mean(sd)	0.31±0.59	0.32±0.48	0.20±0.42	.165
% days mod/vig exercise mean(sd)	24.25±26.40	21.41±23.20	15.65±21.24	.048*
% days vms mean(sd)	31.99±33.53	28.42±32.36	42.14±35.77	.011*
IDS mean(sd)	4.19±2.27	4.60±2.95	5.28±2.93	.029*
STAI mean(sd)	15.01±4.07	15.09±4.51	15.94±4.73	.287
Sleep Characteristics				
Duration mean(sd)	377.30±54.70	377.83±50.56	362.20±63.89	.091
Wakefulness after sleep onset(sd)	52.27±31.54	51.57±29.24	55.38±33.19	.657
Latency	17.02±11.07	21.62±20.22	25.40±27.85	.022*
PSQI	5.39±2.64	5.36±3.12	6.45±3.31	.021*
AHI	7.17±6.91	8.27±9.40	8.75±10.66	.479
% days sleep meds	19.35±38.20	26.59±42.85	31.70±46.44	.140

*p < .05. **p < .01. ***p < .001.

Table 3

Demographic, health and sleep characteristics across high, moderate and low bedtime variability categories

	Variability in Bedtime			
	Low (n=104)	Moderate (n=119)	High (n=115)	Sig
Demographic Characteristics				
Age mean(sd)	52.27±1.90	52.09±2.03	51.97±2.11	.557
Race				
White N(%)	65(62.50)	57(47.90)	39(33.91)	<.001***
Black N(%)	19(18.27)	40(33.61)	62(53.91)	
Chinese N(%)	20(19.23)	22(18.49)	14(12.17)	
Marital Status				
Married/living w partner N(%)	74(71.15)	81(68.07)	64(55.65)	.037*
Education				
≥ college degree N(%)	65(62.50)	63(52.94)	46(40.00)	.004**
Employment				
Unemployed or <20 hrs/wk N(%)	17(16.35)	25(21.01)	26(22.61)	.491
Menopausal Status				
Peri/early peri-menopausal N(%)	65(62.50)	76(63.87)	70(60.87)	.717
Health Characteristics				
BMI mean(sd)	28.19±6.63	29.07±7.14	31.27±8.47	.007**
HOMA-IR mean(sd)	1.39±0.85	1.64±0.96	2.10±1.72	.001**
Current smoker N(%)	7(6.73)	10(8.40)	17(14.78)	.107
Caffeine consumption mean(sd)	1.70±1.36	1.53±1.35	1.49±1.39	.481
Alcohol consumption mean(sd)	0.39±0.59	0.24±0.42	0.26±0.48	.059
% days mod/vig exercise mean(sd)	22.54±23.78	21.75±26.11	18.34±21.46	.377
% days vms mean(sd)	31.55±34.80	30.29±32.71	36.66±34.30	.321
IDS mean(sd)	4.13±2.58	4.44±2.71	5.33±2.92	.003**
STAI mean(sd)	14.63±3.66	15.29±4.82	15.84±4.64	.135
Sleep Characteristics				
Duration mean(sd)	380.81±46.74	374.13±59.22	367.25±58.51	.197
Wakefulness after sleep onset(sd)	52.30±27.86	51.06±30.05	54.79±34.28	.648
Latency	17.41±13.76	22.72±24.05	23.05±21.38	.077
PSQI	5.38±2.97	5.21±2.94	6.30±3.18	.015*
AHI	7.67±7.25	7.33±9.17	9.13±10.31	.293
% days sleep meds	31.50±45.15	16.08±35.71	30.42±45.27	.009**

*p < .05. **p < .01. ***p < .001.

Table 4

Demographic, health and sleep characteristics across low, moderate and high bedtime delay categories

	Bedtime Delay			
	Low (n=105)	Moderate (n=118)	High (n=115)	Sig
Demographic Characteristics				
Age mean(sd)	52.30±2.14	51.97±2.03	52.06±1.90	.446
Race				
White N(%)	60(57.14)	60(50.85)	41(35.65)	<.001***
Black N(%)	21(20.00)	41(34.75)	59(51.30)	
Chinese N(%)	24(22.86)	17(14.41)	15(13.04)	
Marital Status				
Married/living w partner N(%)	74(70.48)	80(67.80)	65(56.52)	.067
Education				
≥ college degree N(%)	68(64.76)	59(50.00)	47(40.87)	.001**
Employment				
Unemployed or <20 hrs/wk N(%)	25(23.81)	17(14.41)	26(22.61)	.155
Menopausal Status				
Peri/early peri-menopausal N(%)	69(65.71)	74(62.71)	68(59.13)	.600
Health Characteristics				
BMI mean(sd)	27.16±6.39	29.75±7.18	31.52±8.36	<.001***
HOMA-IR mean(sd)	1.40±0.76	1.71±0.99	2.03±1.77	.004**
Current smoker N(%)	6(5.71)	13(11.02)	15(13.04)	.179
Caffeine consumption mean(sd)	1.65±1.31	1.56±1.37	1.51±1.42	.748
Alcohol consumption mean(sd)	0.33±0.50	0.34±0.58	0.20±0.40	.079
% days mod/vig exercise mean(sd)	22.63±24.47	21.85±24.95	18.15±22.14	.325
% days vms mean(sd)	26.89±32.64	35.51±33.97	35.55±34.61	.095
IDS mean(sd)	3.87±2.27	4.97±3.01	5.02±2.85	.003**
STAI mean(sd)	14.84±4.02	15.95±5.07	14.98±4.07	.122
Sleep Characteristics				
Duration mean(sd)	381.26±47.35	374.96±54.69	365.93±55.51	.120
Wakefulness after sleep onset(sd)	49.71±28.42	52.26±28.93	55.92±34.69	.326
Latency	17.80±15.16	22.00±24.09	23.48±20.58	.106
PSQI	4.79±2.29	5.95±3.42	6.07±3.15	.003**
AHI	7.36±7.51	7.23±6.30	9.49±12.07	.116
% days sleep meds	21.93±40.50	27.51±42.76	27.30±44.38	.551

*p < .05. **p < .01. ***p < .001.

Table 5

Demographic, health and sleep characteristics across low, moderate and high social jetlag categories

	Social Jetlag			
	Low (n=112)	Moderate (n=114)	High (n=112)	Sig
Demographic Characteristics				
Age mean(sd)	52.21±2.04	52.19±2.19	51.91±1.82	.472
Race				
White N(%)	47(41.96)	55(48.25)	59(52.68)	.590
Black N(%)	45(40.18)	39(34.21)	37(33.04)	
Chinese N(%)	20(17.86)	20(17.54)	16(14.29)	
Marital Status				
Married/living w partner N(%)	63(56.25)	83(72.81)	73(65.18)	.033*
Education				
≥ college degree N(%)	55(49.11)	62(54.39)	57(50.89)	.767
Employment				
Unemployed or <20 hrs/wk N(%)	32(28.57)	19(16.67)	17(15.18)	.023*
Menopausal Status				
Peri/early peri-menopausal N(%)	72(64.29)	72(63.16)	67(59.82)	.899
Health Characteristics				
BMI mean(sd)	30.04±7.68	29.37±8.32	29.24±6.64	.694
HOMA-IR mean(sd)	1.58±0.84	1.80±1.57	1.80±1.35	.395
Current smoker N(%)	12(10.71)	6(5.26)	16(14.29)	.076
Caffeine consumption mean(sd)	1.42±1.49	1.63±1.28	1.65±1.32	.389
Alcohol consumption mean(sd)	0.24±0.42	0.31±0.60	0.32±0.47	.381
% days mod/vig exercise mean(sd)	25.20±26.97	18.07±21.46	19.28±22.52	.057
% days vms mean(sd)	40.10±37.06	27.76±31.98	30.76±31.54	.017*
IDS mean(sd)	4.96±2.74	4.33±2.62	4.65±2.97	.228
STAI mean(sd)	15.49±4.40	15.54±5.03	14.80±3.81	.383
Sleep Characteristics				
Duration mean(sd)	372.49±62.02	374.36±54.75	374.71±49.68	.951
Wakefulness after sleep onset(sd)	56.30±32.02	54.36±33.32	47.49±26.37	.081
Latency	24.99±26.51	17.60±12.93	21.11±19.55	.026*
PSQI	6.01±3.21	5.50±3.15	5.40±2.81	.286
AHI	8.04±10.08	7.90±7.88	8.23±9.23	.964
% days sleep meds	28.02±43.96	24.38±41.62	24.73±42.45	.780

*p < .05. **p < .01. ***p < .001.

Table 6

Summary of regression analyses examining cross-sectional associations between sleep-timing variables and BMI (N=338)

	Unadjusted		Model 1[a]	
	ΔR2	β	ΔR2	β
Average Bedtime	.010	.099	.002	.046
Variability in Bedtime	.036	.190***	.003	.055
Social Jetlag	.003	-.052	.004	-.067
Bedtime Delay	.067	.258***	.014	.128**

[a] Adjusted for race, menopausal status, exercise, depression and sleep duration; *p < .05. **p < .01. ***p < .001.

Table 7

Summary of regression analyses examining cross-sectional associations between sleep-timing variables and HOMA-IR (N=335)

	Unadjusted		Model 1[a]		Model 2[b]	
	ΔR2	β	ΔR2	β	ΔR2	β
Average Bedtime	.006	.079	.000	-.002	.001	-.025
Variability in Bedtime	.071	.266***	.023	.164**	.015	.13**
Social Jetlag	.000	.021	.001	.027	.004	.064
Bedtime Delay	.067	.258***	.026	.171**	.008	.098*

[a] Adjusted for race, menopausal status, exercise, depression and sleep duration; [b]Adjusted for race, menopausal status, exercise, depression, sleep duration and BMI; [t]p<.1.*p<.05. **p<.01. ***p<.001.

Table 8

Summary of regression analyses examining prospective associations between sleep-timing variables and BMI (N=306)

	Unadjusted		Model1[a]		Model2[b]	
	ΔR2	β	ΔR2	β	ΔR2	β
Average Bedtime	.018	.136*	.007	.085	.000	.014
Variability in Bedtime	.022	.148**	.001	.031	.000	.001
Social Jetlag	.001	-.025	.001	-.036	.001	.028
Bedtime Delay	.046	.213***	.007	.091	.001	.025

[a]Adjusted for race, menopausal status, exercise, depression and sleep duration; [b]further adjusted for BMI at Time 1; *p<.05. **p<.01. ***p<.001.

Table 9

Summary of regression analyses examining prospective associations between sleep-timing variables and HOMA-IR (N=241)

	Unadjusted		Model1[a]		Model2[b]	
	ΔR2	β	ΔR2	β	ΔR2	β
Average Bedtime	.001	-.025	.009	-.095	.008	-.090
Variability in Bedtime	.003	.058	.000	-.023	.001	-.033
Social Jetlag	.002	.045	.001	.028	.000	.004
Bedtime Delay	.019	.139*	.000	.005	.000	-.001

[a]Adjusted for race, menopausal status, exercise, depression, sleep duration and BMI; [b]further adjusted for HOMA-IR at Time 1; *p<.05. **p<.01. ***p<.001.

Table 10

Sensitivity analysis examining cross-sectional associations between sleep-timing variables and HOMA-IR excluding Chinese women (N=279)

	Unadjusted		Model 1[a]		Model 2[b]	
	ΔR2	β	ΔR2	β	ΔR2	β
Average Bedtime	.065	.254***	.025	.170**	.007	.090[t]
Variability in Bedtime	.000	.021	.001	.032	.005	.071
Social Jetlag	.007	.086	.000	.005	.000	-.022
Bedtime Delay	.072	.269***	.027	.181**	.017	.143**

[a] Adjusted for race, menopausal status, exercise, depression and sleep duration; [b]Adjusted for race, menopausal status, exercise, depression, sleep duration and BMI; [t]p<.1.*p<.05. **p<.01. ***p<.001.

Figure 1

Nocturnal Energy Expenditure and Light at Night

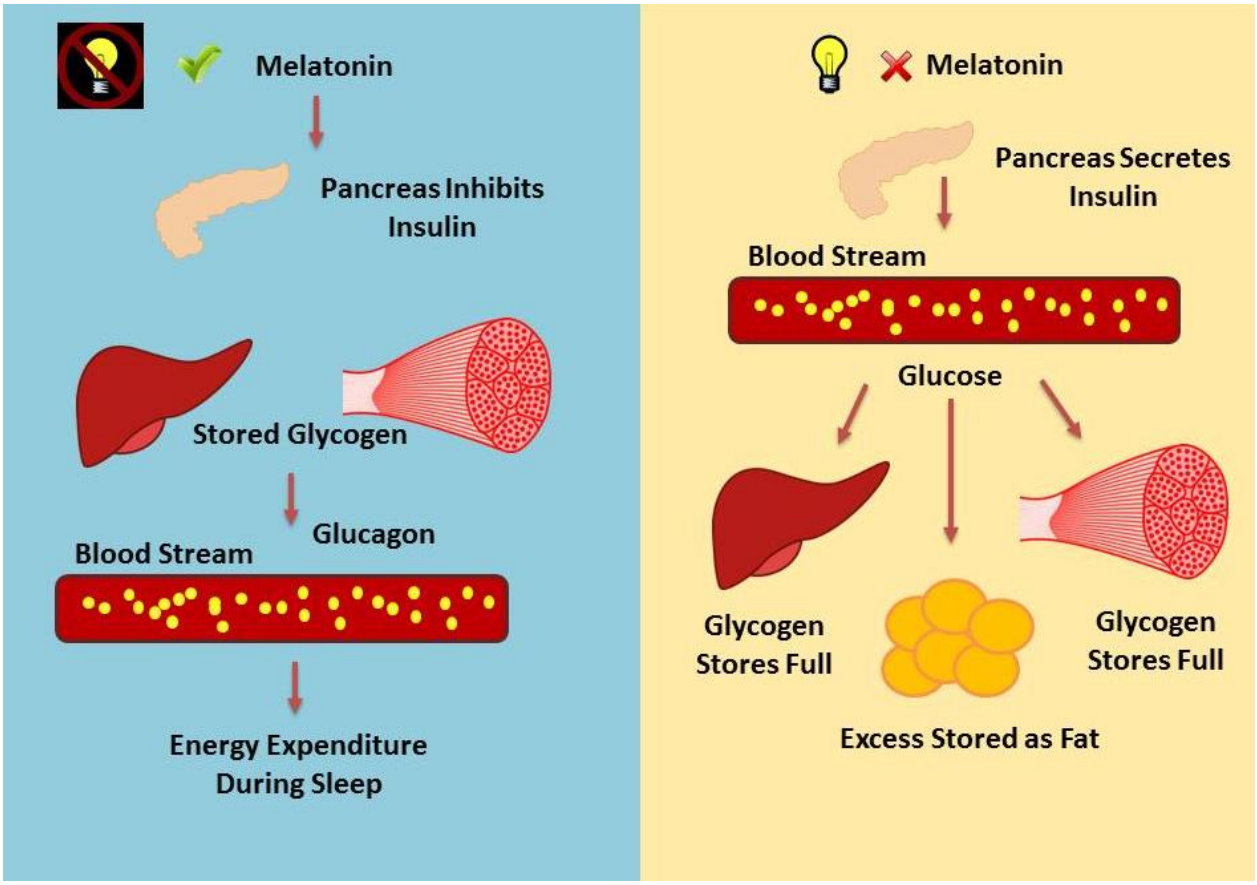


Figure 2

Mean Sleep Timing Values among Caucasian, African American and Chinese Women

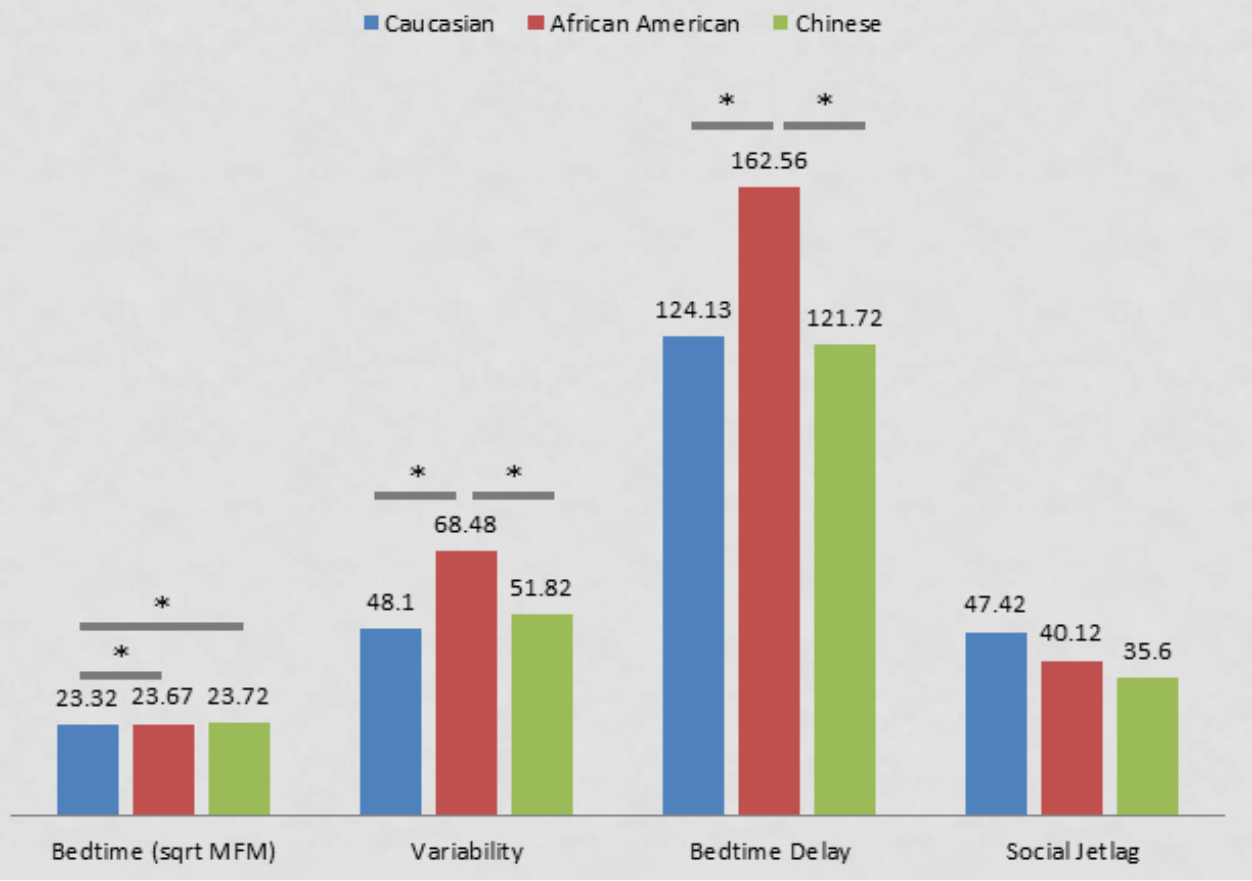
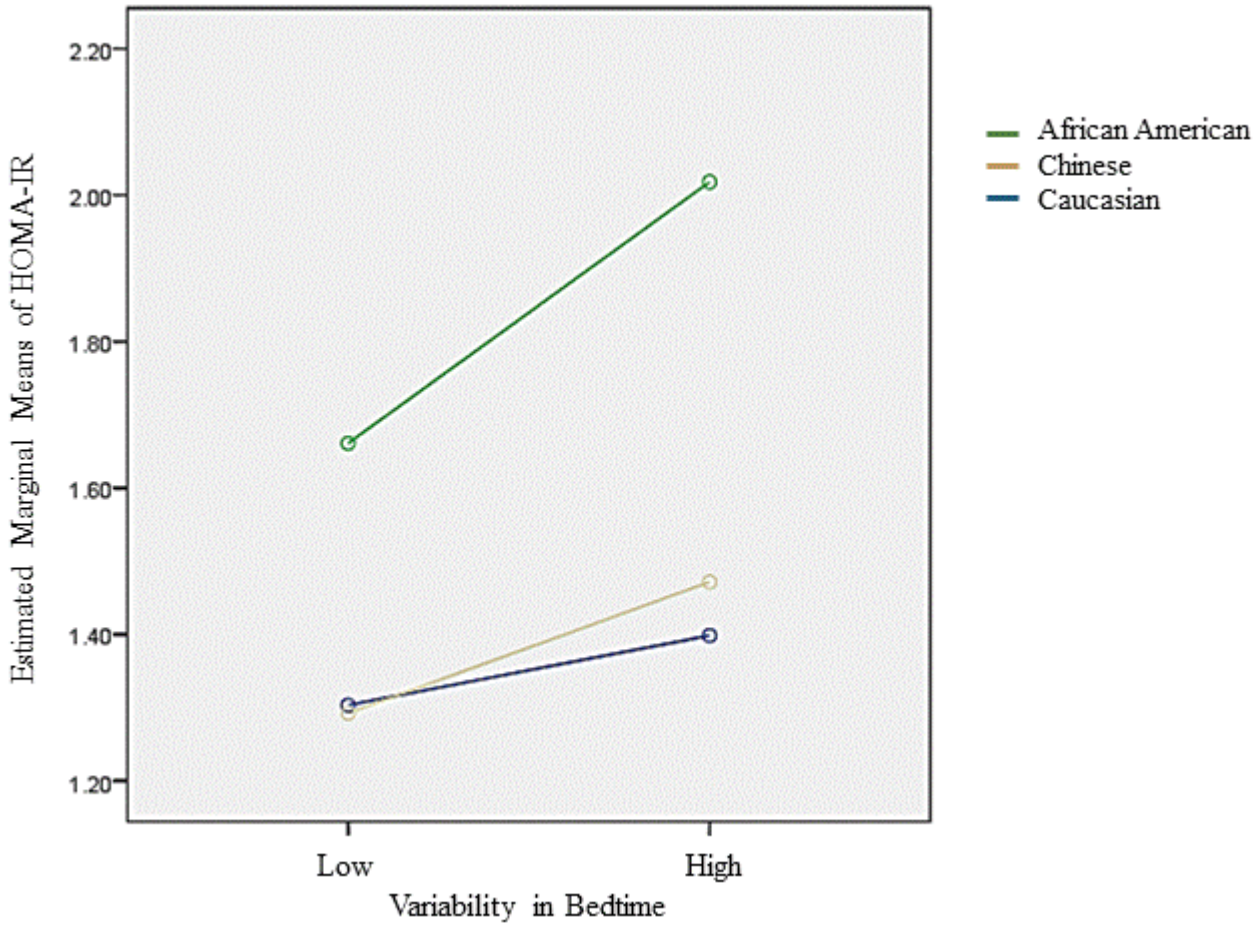


Figure 3

Interaction between race and variability in bedtime predicting HOMA-IR



APPENDIX TABLES

Table A1

Correlation matrix among sleep timing variables

	AB T1	BV T1	BD T1	SJ T1
Avg Bedtime T1	--	.284***	.207***	.027
Bedtime Var T1		--	.409***	.019
Bedtime Delay T1			--	.195***
Social Jetlag T1				--

*p<.05. **p<.01. ***p<.001.

Table A2

Cross-sectional regression results predicting BMI with average bedtime (N=338)

	B	SE	p
Step 1			
Race			
African American	2.426	.837	.004**
Chinese	-6.177	1.016	<.001***
Menopausal Status	1.146	.731	.118
Exercise	-.042	.015	.006**
Depression	.536	.129	<.001***
Sleep Duration	-.016	.007	.016*
Step 2			
Average Bedtime	.006	.006	.345

*p<.05. **p<.01. ***p<.001.

Table A3

Cross-sectional regression results predicting BMI with variability in bedtime (N=338)

	B	SE	p
Step 1			
Race			
African American	2.250	.866	.010**
Chinese	-6.104	1.009	<.000***
Menopausal Status	1.149	.731	.117
Exercise	-.043	.015	.004**
Depression	.526	.130	<.001***
Sleep Duration	-.017	.007	.012*
Step 2			
Variability in Bedtime	.223	.205	.277

*p<.05. **p<.01. ***p<.001.

Table A4

Cross-sectional regression results predicting BMI with bedtime delay (N=338)

	B	SE	p
Step 1			
Race			
African American	1.989	.848	.020*
Chinese	-5.970	1.00	<.000***
Menopausal Status	1.040	.725	.153
Exercise	-.042	.015	.005**
Depression	.498	.129	<.001***
Sleep Duration	-.017	.007	.153
Step 2			
Bedtime Delay	.017	.007	.010**

*p<.05. **p<.01. ***p<.001.

Table A5

Cross-sectional regression results predicting BMI with social jetlag

	B	SE	p
Step 1			
Race			
African American	2.412	.833	.004
Chinese	-6.157	1.009	<.000***
Menopausal Status	1.218	.732	.097
Exercise	-.045	.015	.003**
Depression	.544	.128	<.001***
Sleep Duration	-.017	.007	.010**
Step 2			
Social Jetlag	-.012	.008	.159

*p<.05. **p<.01. ***p<.001.

Table A6

Cross-sectional regression results predicting HOMA-IR with average bedtime (N=335)

	B	SE	p
Step 1			
Race			
African American	.091	.057	.110
Chinese	.242	.072	.001***
Menopausal Status	.020	.049	.688
Exercise	-.001	.001	.466
Depression	.016	.009	.070
Sleep Duration	.000	.000	.438
Step 2			
BMI	.041	.004	<.000***
Step 3			
Average Bedtime	.000	.000	.577

*p<.05. **p<.01. ***p<.001.

Table A7

Cross-sectional regression results predicting HOMA-IR with variability in bedtime (N=335)

	B	SE	p
Step 1			
Race			
African American	.043	.058	.462
Chinese	.224	.070	.002**
Menopausal Status	.025	.049	.613
Exercise	-.001	.001	.444
Depression	.011	.009	.197
Sleep Duration	.000	.000	.446
Step 2			
BMI	.040	.004	<.000***
Step 3			
Variability in Bedtime	.038	.014	.005**

*p<.05. **p<.01. ***p<.001.

Table A8

Cross-sectional regression results predicting HOMA-IR with bedtime delay (N=335)

	B	SE	p
Step 1			
Race			
African American	.061	.057	.285
Chinese	.235	.071	.001***
Menopausal Status	.017	.049	.732
Exercise	-.001	.001	.482
Depression	.013	.009	.136
Sleep Duration	.000	.000	.395
Step 2			
BMI	.040	.004	<.001***
Step 3			
Bedtime Delay	.001	.000	.038*

*p<.05. **p<.01. ***p<.001.

Table A9

Cross-sectional regression results predicting HOMA-IR with social jetlag (N=335)

	B	SE	p
Step 1			
Race			
African American	.092	.056	.102
Chinese	.245	.071	.001***
Menopausal Status	.015	.049	.767
Exercise	-.001	.001	.576
Depression	.016	.009	.072
Sleep Duration	.000	.000	.503
Step 2			
BMI	.041	.004	<.001***
Step 3			
Social Jetlag	.001	.001	.152

*p<.05. **p<.01. ***p<.001.

Table A10

Prospective regression results predicting BMI with average bedtime (N=306)

	B	SE	p
Step 1			
Race			
African American	-.657	.319	.041*
Chinese	-1.066	.383	.006**
Menopausal Status	-.026	.270	.924
Exercise	-.015	.006	.010**
Depression	.016	.048	.746
Sleep Duration	-.001	.002	.731
Step 2			
BMI at Time 1	.942	.021	<.001***
Step 3			
Average Bedtime	.002	.002	.453

*p<.05. **p<.01. ***p<.001.

Table A11

Prospective regression results predicting BMI with variability in bedtime (N=306)

	B	SE	p
Step 1			
Race			
African American	-.632	.331	.057
Chinese	-1.028	.381	.007**
Menopausal Status	-.036	.271	.896
Exercise	-.015	.006	.009**
Depression	.019	.049	.698
Sleep Duration	-.001	.002	.679
Step 2			
BMI at Time 1	.943	.021	<.001***
Step 3			
Variability in Bedtime	.002	.074	.976

*p<.05. **p<.01. ***p<.001.

Table A12

Prospective regression results predicting BMI with bedtime delay (N=306)

	B	SE	p
Step 1			
Race			
African American	-.722	.324	.027*
Chinese	-1.025	.379	.007**
Menopausal Status	-.054	.270	.842
Exercise	-.015	.006	.011*
Depression	.013	.048	.785
Sleep Duration	-.001	.002	.626
Step 2			
BMI at Time 1	.941	.021	<.001***
Step 3			
Bedtime Delay	.003	.003	.184

*p<.05. **p<.01. ***p<.001.

Table A13

Prospective regression results predicting BMI with social jetlag (N=306)

	B	SE	p
Step 1			
Race			
African American	-.581	.318	.068
Chinese	-.969	.381	.011*
Menopausal Status	-.076	.270	.778
Exercise	-.014	.006	.014*
Depression	.021	.048	.666
Sleep Duration	-.001	.002	.749
Step 2			
BMI at Time 1	.946	.021	<.001***
Step 3			
Social Jetlag	.005	.003	.119

*p<.05. **p<.01. ***p<.001.

Table A14

Prospective regression results predicting HOMA-IR with average bedtime (N=241)

	B	SE	p
Step 1			
Race			
African American	.158	.053	.003**
Chinese	.006	.062	.925
Menopausal Status	.087	.045	.054
Exercise	-.001	.001	.416
Depression	-.028	.008	.001***
Sleep Duration	.000	.000	.285
BMI	.020	.004	<.001***
Step 2			
HOMA-IR at Time 1	.426	.080	<.001***
Step 3			
Average Bedtime	-.001	.000	.088

*p<.05. **p<.01. ***p<.001.

Table A15

Prospective regression results predicting HOMA-IR with variability in bedtime (N=241)

	B	SE	p
Step 1			
Race			
African American	.159	.055	.004**
Chinese	-.007	.062	.904
Menopausal Status	.088	.046	.054
Exercise	-.001	.001	.491
Depression	-.029	.008	<.001***
Sleep Duration	.001	.000	.216
BMI	.019	.004	<.001***
Step 2			
HOMA-IR at Time 1	.431	.081	<.001***
Step 3			
Variability in Bedtime	-.008	.013	.549

*p<.05. **p<.01. ***p<.001.

Table A16

Prospective regression results predicting HOMA-IR with bedtime delay (N=241)

	B	SE	p
Step 1			
Race			
African American	.150	.054	.006**
Chinese	-.010	.062	.868
Menopausal Status	.092	.045	.044*
Exercise	-.001	.001	.485
Depression	-.029	.008	<.001***
Sleep Duration	.000	.000	.226
BMI	.019	.004	<.001***
Step 2			
HOMA-IR at Time 1	.428	.081	<.001***
Step 3			
Bedtime Delay	.000	.000	.989

*p<.05. **p<.01. ***p<.001.

Table A17

Prospective regression results predicting HOMA-IR with social jetlag (N=241)

	B	SE	p
Step 1			
Race			
African American	.151	.054	.005**
Chinese	-.010	.062	.872
Menopausal Status	.091	.046	.046*
Exercise	-.001	.001	.492
Depression	-.029	.008	<.001***
Sleep Duration	.000	.000	.224
BMI	.019	.004	<.001***
Step 2			
HOMA-IR at Time 1	.427	.081	<.001***
Step 3			
Social Jetlag	.000	.000	.935

*p<.05. **p<.01. ***p<.001.

Table A18

Body mass index and HOMA-IR Time 1 and Time 2 correlations

	Time 1	Time 2	R^2	t-statistic	p
HOMA-IR	1.51 ± .93	1.49 ± 1.41	.429	.288	.773
BMI	28.95 ± 7.22	29.40 ± 7.29	.950	-3.414	.001***

*p<.05. **p<.01. ***p<.001.

Table A19
Significant differences between participants included and excluded from primary analyses

	Included (n=338)	Excluded (n=32)	Statistic (Chi^2 or t)
Age	52.10±2.02	52.54±1.97	1.159
Race	161(47.63)	12(37.50)	3.943
N(%) Caucasian	121(35.80)	17(53.13)	
N(%) African American	56(16.57)	3(9.37)	
N(%) Chinese			
Menopausal Status			
N(%) Pre- or Early Peri-	211(62.43)	17(53.13)	1.069
N(%) Late Per- or Post	127(37.57)	15(46.87)	
Employment			
N(%) Unemployed or <20 hrs/week	68(20.12)	12(37.50)	5.212*
N(%) Employed or ≥20 hrs/week	270(79.88)	20(62.50)	
Marital Status			
N(%) Married or living as married	219(64.79)	16(50.00)	2.760
N(%) Single, widowed or divorced	119(35.21)	16(50.00)	
BMI	29.55±7.57	35.64±8.65	3.846***
HOMA-IR	1.68±1.28	3.47±3.31	3.042**
Exercise (% days ± SD)	20.84±23.89	11.28±16.75	-2.749**
Alcohol (mean daily serving ± SD)	0.29±0.50	0.14±0.31	-2.285*
Depression	4.65±2.78	6.16±3.98	2.073*
Wakefulness after Sleep Onset	52.71±30.87	71.83±40.21	3.254***

*p<.05. **p<.01. ***p<.001.

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