Phase Relationship between DLMO and Sleep Onset and the Risk of Metabolic Disease among Normal Weight and Overweight/Obese Adults

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Abstract Circadian misalignment is hypothesized to contribute to increased diabetes and obesity among shift workers and individuals with late sleep timing. Accordingly, the goal of our study was to identify—among normal and overweight/obese adults—associations between circadian timing (dim light melatonin onset; DLMO) and circadian misalignment (the interval between DLMO and sleep onset) with metabolic disease risk. This was a secondary analysis of data from a larger study. Participants ages 18 to 50 years without depression, diabetes, or shift work, with sleep duration 6.5 h or more, completed the following evaluations: 7 days of wrist actigraphy, circadian timing assessment (DLMO), and a fasting blood draw to measure glucose and insulin and calculate the Homeostatic Model of Assessment–Insulin Resistance (HOMA-IR). Data were analyzed using correlation and regression analyses controlling for age, sex, DLMO, and sleep duration. Analyses were conducted for the entire sample (n = 54) and stratified by normal weight (n = 36) and overweight/obese groups (n = 18). Mean age was 26.4 years (SD = 7.1 years). Average sleep duration was 436.2 min (SD = 55.1 min), DLMO was 2250h (SD = 01:31), and interval between DLMO and sleep onset was 2 h 18 min (SD = 53 min). Average BMI was 24.3 kg/m^2 (SD = 4.5 kg/m^2). Circadian timing and interval between DLMO and sleep onset were not associated with glucose, insulin, or HOMA-IR in the main analyses. Among overweight/obese participants, a shorter interval between DLMO and sleep onset was associated with higher insulin (B[SE] = −5.12 [2.24], p = 0.04) and HOMA-IR (B[SE] = −1.32 [0.57], p = 0.04). Results of our multivariable model indicated that among overweight/obese participants, insulin was 5.1 pmol/L higher and HOMA was 1.3 µU/mL higher for every hour closer that sleep onset was to DLMO. The strengths of this study include the use of objective measures of circadian timing, but results should be considered hypothesis generating due to the small sample size and use of subgroup analyses.

Keywords circadian misalignment, sleep, melatonin, insulin, HOMA

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Circadian misalignment, defined as alterations of the sleep period relative to the internal biological rhythm, is hypothesized to contribute to increased risk for cardiometabolic disease among shift workers, but less is known about circadian disruption in non–shift workers (Qian and Scheer, 2016). Circadian misalignment is typically considered to occur when there is a mismatch between sleep-wake timing and the endogenous circadian rhythm generated by the suprachiasmatic nucleus. However, when the sleep-wake rhythm is shifted, other behaviors and physiological processes such as feeding, blood pressure maintenance, and measures of metabolic function are often shifted as well. Laboratory studies have demonstrated that circadian misalignment is associated with insulin resistance and altered levels of appetite-regulating hormones above and beyond changes in sleep duration and sleep quality (Scheer et al., 2009; Buxton et al., 2012; Leproult et al., 2014). The mismatch between endogenous circadian rhythms and sleep-wake schedule may be more common among individuals with late sleep timing due to differences between sleep preference and social and occupational demands (Baron et al., 2011; Roenneberg et al., 2012; Yu et al., 2015).

Laboratory research has used forced desynchrony and simulated shift work to experimentally create circadian misalignment. However, individual differences in circadian alignment also exist in daily life. The interval between phase markers of the central circadian rhythm and the sleep period has been used to quantify circadian misalignment (Wright et al., 2005; Lewy, 2007). The average interval between dim light melatonin onset (DLMO) and sleep onset is approximately 2 h (Wright et al., 2005). Several studies have evaluated the roles of circadian misalignment and metabolic function (Eckel et al., 2015; Morris et al., 2015; Morris et al., 2016b), but most have been conducted in laboratory settings, where circadian misalignment was the result of shifting the sleep-wake cycle by 8 to 12 h relative to the circadian system. Therefore, we conducted a study of circadian timing and circadian misalignment in daily life. We found that a shorter interval between DLMO and sleep onset was associated with higher caloric intake and greater meal frequency among non-shift-working adults free from depression and diabetes with habitual sleep duration of 6.5 h or more (Baron et al., 2017). The purpose of the present study was to identify associations between this measure of circadian misalignment and metabolic disease risk among the subset of participants in this sample who completed fasting blood draws. We predicted that a shorter interval between DLMO and sleep onset would be associated with higher values on metabolic disease risk variables independent of circadian timing (DLMO). Given that overweight and obese individuals have increased risk of developing prediabetes and diabetes (Mokdad et al., 2003), in the present study we followed our main analyses with analyses stratified by body mass index (BMI) category (normal versus overweight/obese participants).

METHODS

Participants

This was a secondary analysis of a study that evaluated associations between circadian timing, misalignment, and obesity (Baron et al., 2017). Participants were recruited from the community through use of flyers, web advertisements, and participant registries with advertisements for healthy volunteers with "normal" or "late" sleep timing. Inclusion criteria were (1) age 18 to 50 years, (2) habitual sleep duration ≥6.5 h but ≤8.5 h, and (3) ability to read and write English. Exclusion criteria were (1) comorbid sleep, medical, or psychiatric disorders; (2) current use of psychiatric medications and medications that could affect sleep, melatonin production, or metabolism (e.g., antidepressants, decongestants, anti-inflammatory medications, cardiac medications); (3) use of illicit drugs or alcohol intake more than 2 drinks per day; (4) shift work or travel over 2 time zones in the past 6 months; (5) caffeine intake more than 300 mg per day; (6) current smoking; and (7) pregnancy or the desire to become pregnant during the study period.

Procedure

The protocol was approved by the Northwestern University Institutional Review Board, and all participants provided written informed consent.

Screening Procedures. Prospective participants first completed an initial web or telephone screening so we could screen for self-reported sleep duration, comorbid conditions, and health behaviors (smoking, alcohol, and substance use). Next, potential participants attended an in-person screening visit. During this visit, they completed questionnaires and then 1 night of home sleep apnea screening and 7 days of actigraphy to determine whether they met study criteria. After screening actigraphy and apnea screening data were reviewed, eligible participants were scheduled for 1 night in the Clinical Research Unit for DLMO assessment and dual-energy x-ray absorptiometry (DXA).

Laboratory Session. Participants completed 7 days of actigraphy prior to the laboratory session. The day of the laboratory visit, they arrived at approximately 1300 h. After admission, participants underwent a history and physical examination by a sleep medicine physician, and female participants underwent a urine pregnancy screening. Then, participants completed a DXA tissue measurement to assess body fat. Bedtime, wake time, and blood sampling times were determined based on habitual bedtime in the previous week as indicated by actigraphy and sleep logs. Experimental time 0 (ET 0) was determined by average habitual bedtime plus 8 h. On day 1, the lights were dimmed to less than 20 lux at ET 8. An IV was inserted by ET 10, and blood samples were taken every 30 min from ET 11 to ET 18. Lights out (<5 lux) was ET 16. Wake time was scheduled for 8 h after participants' habitual sleep onset time. Timing of meals was controlled, but the content was provided from the general hospital menu. Participants consumed a dinner provided by the hospital at 1800 to 1900 h and were also offered a snack at ET 14 from the clinical research unit kitchen, which included items such as fruit, a noncaffeinated drink, or a single serving bag of pretzels. Participants were not permitted to consume food from home or to eat between ET 14 and wake time. Participants were woken by the nursing staff at the scheduled wake time and were asked to void, and then their weight was measured without shoes in light clothing before eating or drinking. After weight measurements, participants were seated for 5 min and their vital signs were recorded by nursing staff. Between the vital sign assessment and blood draw, participants were seated in room light with window shades open. The fasting blood draw was taken 20 min after wake time. Participants completed self-report questionnaires, were offered breakfast, and were discharged after breakfast.

Measures

Sleep. Participants wore the Actiwatch Spectrum (Philips/Respironics, Bend, OR) on the nondominant wrist for 7 days at screening and 7 days before their stay in the Clinical Research Unit. Actiwatches were set with 30-sec epoch length and medium sensitivity. Actigraphic sleep parameters were calculated using Actiware-Sleep 6.0 software with default settings and included the following variables: sleep onset time, sleep offset time, and sleep duration.

Circadian Timing (DLMO). Plasma melatonin levels were assayed with a commercially available radioimmunoassay (IBL International GmbH, Hamburg, Germany). DLMO was calculated as the time point when melatonin levels were 2 SD above the baseline plus 15% of the 3 highest values (Voultsios et al., 1997). We also calculated the interval between DLMO and average sleep onset time during the prior week.

Metabolic Disease Risk. Participants' BMI (kg/m^2) was calculated by use of height and weight measurements taken in the morning at the Clinical Research Unit. DXA scans were conducted to calculate total body fat percentage (Hologic, Bedford, MA; Version 13.1). Glucose and insulin were measured in a fasting blood sample. The Homeostatic Model of Assessment–Insulin Resistance (HOMA-IR) was calculated as [glucose (mmol/L) × insulin (μU/mL)]/22.5 (Matthews et al., 1985).

Statistical Analyses

Data were analyzed with SPSS (Version 22; IBM, Chicago, IL), descriptive statistics, Pearson correlations, and multivariable regression models. To control for potential confounds, hierarchical multivariable regression models were constructed to test circadian timing, interval between DLMO and sleep onset, and sleep timing as predictors of fasting glucose, insulin, and HOMA-IR, controlling for age, gender, and sleep duration (Pedhazur and Shmelkin, 1991). Control variables for the regression models were determined on a theoretical basis, according to the literature, which has reported differences in circadian timing and interval between DLMO and sleep onset with age, sex, and sleep duration (Wright et al., 2005; Roenneberg et al., 2007; Cain et al., 2010). We conducted analyses using the entire sample and then stratified the normal and overweight/obese participants for subgroup analyses. We did this to identify relationships between our variables of interest within a sample who were at increased risk for metabolic disorders. Data from 1 normal weight participant were removed because insulin and HOMA readings were more than 2 SD above the mean for the entire sample, which is considered a statistical outlier (Pedhazur and Shmelkin, 1991). Results from analyses conducted with and without data from this participant were similar. Given the small sample size for stratified analyses, we conducted a post hoc power analysis and nonparametric tests. The power analysis demonstrated moderate power ($f = 0.57$ for the univariate analyses and 0.84 for the multivariate analysis of HOMA.). The nonparametric analyses using Spearman's rho demonstrated a moderate but nonsignificant association between the DLMO–sleep onset interval and HOMA ($r = -0.41$, $p = 0.09$). In light

Table 1. Participant characteristics.

Demographics	Total (*n* = 54)	Normal Weight (*n* = 36)	Overweight/Obese (*n* = 18)
Age, years, M (SD)	26.4 (7.1)	24.9 (6.9)	29.3 (6.9)
Sex, *n*			
Female	32	20	11
Male	22	15	7
Ethnicity, *n* (%)			
Hispanic/Latino	5 (9)	4 (11)	1 (5.6)
Non-Hispanic/Latino	49 (91)	32 (89)	17 (94)
Race, *n* (%)			
Asian	16 (29)	13 (36)	3 (16)
Black/African American	4 (7)	2 (5.6)	2 (11)
White	29 (55)	17 (50)	11 (61)
More than one race	5 (9)	2 (11)	2 (11)
Employment, *n* (%)			
Full time	14 (27.3)	6 (19)	7 (38)
Part time	11 (20.0)	7 (19)	4 (22)
Unemployed	3 (5.5)	1 (3)	2 (11)
Student	26 (47.3)	21 (58)	5 (27.8)
Metabolic risk factors, M (SD)			
Glucose, mg/dL	88.8 (7.2)	87.4 (6.4)	91.5 (8.1)
Insulin, μU/mL	14.8 (9.3)	14.5 (10.6)	15.6 (6.4)
HOMA-IR	3.3 (2.1)	3.1 (2.3)	3.5 (1.5)
Body mass index, kg/m^2	24.3 (4.5)	21.8 (2.1)	29.3 (3.5)
Body fat, %	30.4 (9.0)	27.7 (7.7)	35.7 (9.3)
Sleep, M (SD)			
Sleep onset time, h	0106 (0128)	0134 (0125)	0013 (0111)
Sleep offset time, h	0819 (0113)	0838 (0107)	0742 (0109)
Sleep duration, min	436.2 (55.1)	432.0 (59.3)	444.6 (45.8)
DLMO, h	2250 (0131)	2318 (0130)	2203 (0119)
DLMO–sleep onset, h	0218 (0053)	0220 (0034)	0212 (0046)

DLMO = dim light melatonin onset; HOMA-IR = Homeostatic Model of Assessment–Insulin Resistance.

of these results, we present the parametric statistics. Statistical significance was defined as $p < 0.05$ on 2-tailed tests.

RESULTS

Participant Characteristics

This study is a secondary analysis of a larger study of circadian timing, misalignment, and health (Baron et al., 2017). Only participants with complete glucose and insulin data were included in the present analysis, representing 54 of the 97 participants in the main study. The primary reason for excluding participants because of missing data was because the blood draw was added to the protocol after the study began (n = 42). Only 1 participant was excluded because of refusing the blood draw. Table 1 lists participant characteristics for the total participants (n = 54), normal weight participants (n = 36), and overweight/obese participants (n = 18). Participants for the total sample included 32 women and 22 men, age 26.4 ± 7.1 years (mean ± SD). Four participants had fasting glucose levels 100 mg/dL or higher (range, 100-102 mg/dL).

Univariate Analyses

Circadian timing, sleep timing, and interval between DLMO and sleep onset were not associated with fasting glucose, insulin, or HOMA-IR in the main analyses. In the stratified analyses conducted among overweight/obese participants, a shorter interval between DLMO and sleep onset was associated with higher fasting insulin ($r = -0.49$, $p < 0.05$) and HOMA-IR ($r = -0.54$, $p < 0.05$) and was unrelated to BMI and body fat.

Multivariable Analyses

In multivariable models conducted among overweight/obese participants, and controlling for age, sex, sleep duration, and circadian timing, a shorter interval between DLMO and sleep onset was associated with

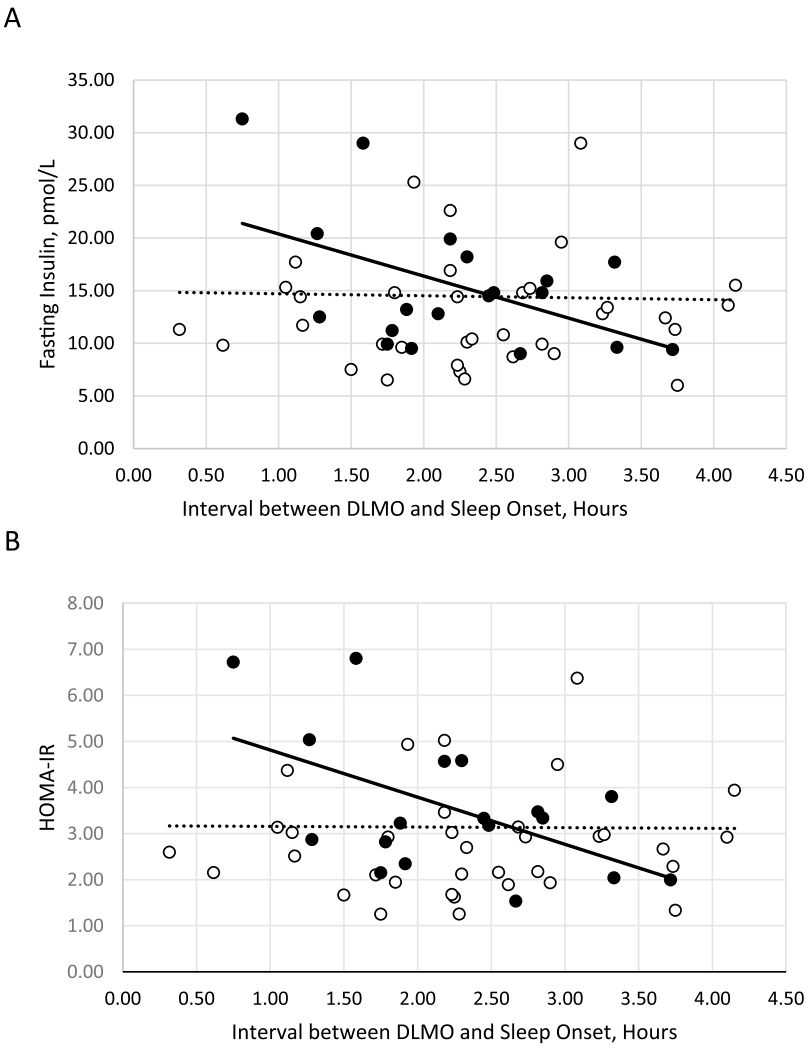

Figure 1. (A) Relationship of the interval between dim light melatonin onset (DLMO) and sleep onset with fasting insulin among normal weight and overweight/obese participants. Normal weight participants are depicted with open markers and a dotted trend line. Overweight/obese participants are depicted with closed markers and a solid trend line. (B) Relationship of the interval between DLMO and sleep onset with the Homeostatic Model of Assessment–Insulin Resistance (HOMA-IR) among normal weight and overweight/obese participants. Normal weight participants are depicted with open markers and a dotted trend line. Overweight/obese participants are depicted with closed markers and a solid trend line.

higher insulin (B(SE) =–5.12 (2.24), p = 0.04) and HOMA-IR (B(SE) = −1.32 (0.57), p = 0.04). Figure 1 depicts the unadjusted relationships among normal weight and overweight/obese participants in the interval between DLMO and sleep onset with fasting insulin and HOMA-IR.

DISCUSSION

The goal of this study was to identify associations between circadian misalignment (i.e., the interval between DLMO and sleep onset) and measures of metabolic disease risk among a sample of healthy adults with at least 6.5 h of habitual sleep duration. Our results demonstrated that circadian timing, sleep timing, and the interval between DLMO and sleep onset were not associated with metabolic disease risk variables among the entire sample, and only the interval between DLMO and sleep onset was associated with higher insulin and HOMA-IR among overweight/obese adults. Results of our multivariable model indicated that among overweight/obese participants, insulin was 5.1 pmol/L higher and HOMA was 1.3 µU/mL higher for every hour closer that sleep onset was to DLMO.

Our results are partly consistent with the literature which shows a relationship between circadian misalignment and insulin resistance, which may

explain the increased risk for diabetes and weight gain among both shift workers and individuals with late sleep-wake timing. Although we did not set a quantitative cutoff for aligned versus misaligned individuals, we observed a linear association between a shorter interval between DLMO and sleep onset with higher HOMA-IR among the overweight/obese participants. Laboratory studies of circadian misalignment have demonstrated insulin resistance as well as changes in appetite-regulating hormones (lower leptin and higher peptide YY levels) and inflammatory markers in simulated shift work and forced desynchrony protocols (Scheer et al., 2009; Buxton et al., 2012; Leproult et al., 2014; McHill et al., 2014; Wright et al., 2015; Morris et al., 2016a). Research using animal models suggests that shifting the rest-activity rhythm relative to the central circadian rhythm may contribute to insulin resistance through disruption of cellular and molecular rhythms and through relationships between central and peripheral rhythms (Bass, 2012). Our data demonstrate that a similar relationship between circadian misalignment and metabolic factors may exist under real-world conditions in overweight/obese individuals. Our sample and other studies have shown that individuals with late sleep timing show a sleep onset closer to DLMO (Duffy et al., 1999; Baron et al., 2017), which may reflect a persistent individual difference in the phase relationship between melatonin and sleep that potentially increases risk for sleep, mood, and metabolic disorders. The causes of these differences in circadian misalignment are not known but may be due to both biological factors (e.g., circadian period length) and environmental factors such as light exposure and behavior (Wright et al., 2005).

In our previous article regarding this sample (Baron et al., 2017), a shorter interval between DLMO and sleep onset was associated with higher caloric intake and greater meal frequency but not with BMI, body fat, or physical activity. It was not clear why the higher caloric intake did not translate to higher BMI, but in this sample of young, healthy, and primarily lean individuals, there may be compensation in energy expenditure that was not measured by our monitors. The present report showed greater insulin resistance in individuals with sleep onset closer to DLMO only among overweight/obese participants. This may mean that for normal weight individuals, perhaps a little "misalignment" does not affect metabolic health. However, in those who already have a risk factor (overweight/obese), such misalignment can tip them over the edge to poorer metabolic health. Given the use of a subgroup analysis and small sample size, these findings should be considered hypothesis generating, and this hypothesis will need to be examined in future studies of metabolic mechanisms.

One possible mechanism that may explain the higher insulin and HOMA-IR levels observed in overweight/obese individuals with a shorter interval between DLMO and sleep onset is higher morning melatonin levels. A previous study of sleep restriction (5 days of 5 h of time in bed, due to typical sleep time delayed by 2 h and wake time advanced by 2 h, in room and sunlight) demonstrated delayed DLMO as well as higher morning melatonin levels (Eckel et al., 2015). In that study, longer duration of melatonin elevation after the scheduled morning wake time was associated with lower sensitivity to insulin and higher insulin levels. We did not measure morning melatonin in our study and our participants were not exposed to experimental sleep loss, but it is possible that individuals with sleep onset closer to DLMO are likely to have higher circulating melatonin at wake time, due to waking at an earlier circadian phase.

The limitations of this study include use of a small, healthy sample of young adults, which may underestimate associations of our variables of interest with metabolic disease risk among participants with greater metabolic vulnerability (e.g., those with prediabetes). The use of more in-depth metabolic measures such as postprandial glucose or the oral glucose tolerance test and euglycemic/hyperinsulinemic clamp techniques could yield more information regarding the underlying metabolic mechanism by comparing changes in insulin sensitivity versus β-cell function (Wallace et al., 2004). This study was not powered to test potential mediation pathways such as whether the associations between the DLMO–sleep onset interval and insulin and HOMA-IR are due to differences in body fat, caloric intake, or meal pattern. Another factor to consider is that by design, we limited the range of sleep duration by selecting participants with at least 6.5 h of habitual sleep duration and we also statistically controlled for sleep duration. However, it should be noted that 6.5 h of sleep duration may still be insufficient sleep for some individuals, particularly young adults (Watson et al., 2015). A strength of our study is that our results demonstrate translation of laboratory research to real-world settings and suggest the potential importance of the relationship between DLMO and sleep for insulin resistance independent of sleep duration among overweight/obese individuals.

In conclusion, our results suggest that the interval between DLMO and sleep onset in non–shift workers was associated with higher insulin and HOMA-IR only among overweight/obese adults and was unrelated in normal weight adults. Future research is needed to determine the role of circadian misalignment among individuals at risk for cardiometabolic disease and to examine whether strategies aimed at

improving circadian misalignment can alter metabolic disease risk.

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CONFLICT OF INTEREST STATEMENT

The author(s) have no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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