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Clinical Research Article

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Variations in Sleep Characteristics and Glucose Regulation in Young Adults With Type 1 Diabetes

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Abbreviations: CGM, continuous glucose monitoring; CV, coefficient of variation;EMR, electronic medical record;HbA1c, glycosylated hemoglobin A1c; MSSD, mean of squared successive daily differences;OSA, obstructive sleep apnea;T1D, type 1 diabetes.

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Abstract

Context: Short sleep duration and sleep disruptions are associated with impaired glucoregulation in type 1 diabetes (T1D). However, the mechanistic pathways between sleep and glucose variability remain unclear.

Objective: To determine within- and between-person associations between objective sleep-wake characteristics and glucose variability indices.

Methods: Multilevel models were used to analyze concurrent sleep and glucose patterns over 7 days in 42 young adults with T1D in their natural home environment. Young adults with T1D (mean age 22.2 ± 3.0 years, HbA1c 7.2%, 32.6% male) for at least 6 months

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with no other medical or major psychiatric comorbidity were included. Sleep-wake characteristics were measured via wrist actigraphy and glucose variability indices via a continuous glucose monitor (CGM).

Results: Lower sleep efficiency predicted higher glucose variability (less time in range $\beta = 0.011$ and more time in hyperglycemia $\beta = -0.011$) within-person. A longer wake after sleep onset and more sleep disruptions were associated with higher glucose variability between persons ($\beta = 0.28$ and 0.31). Higher glucose variability predicted poorer sleep within-person (delayed bedtime, waketime, mid-sleep time, and lower sleep efficiency), while higher glucose variability was associated with poorer sleep and more sleep disruptions between persons (lower sleep efficiency, longer wake after sleep onset, and a higher sleep fragmentation index).

Conclusion: Clinicians can address the reciprocal nature of the sleep-glucose relationship by optimizing sleep and targeting efforts toward a euglycemic range overnight. Sleep habits are a modifiable personal target in diabetes care.

Key Words: sleep, actigraphy, young adult, type 1 diabetes, glucose variability, multilevel model

Sleep is a multidimensional facet of health, but one component, sleep duration, is decreasing in the United States, with a majority of young adults ages 18 to 30 years not meeting the recommended sleep duration of 7 to 9 hours per night (1-3). Environmental, social, and biological factors (eg, blue light, social interactions, the stress of academics or work, and delayed melatonin onset, later chronotype) contribute to young adults' short sleep. These influencing factors are also juxtaposed with a competing need to maintain early wake times during the school or work week (2). Young adults with type 1 diabetes (T1D) have additional barriers to achieving adequate sleep, with more variability in their sleep duration than the general population (4-6). These barriers may include a need to monitor and manage hypo/hyperglycemia, a fear of hypoglycemia, an intensive insulin therapy regimen, and device alarms which can delay bedtimes and disrupt sleep overnight (7-9).

T1D is one of the most common chronic conditions in young adulthood, affecting 45 million people with a rising increase of 3% annually and a projected 70 million people to be affected globally by 2045 (10). Only 1 in 8 young adults achieve glycemic targets (glycosylated hemoglobin A1c [HbA1c] < 7%) (10), and higher HbA1c values predict premature micro- and macrovascular complications (11). HbA1c does not account for glycemic variability or hypoglycemia in those with T1D (11). Glycemic variability detected through continuous glucose monitoring (CGM) contributes to endothelial damage and the onset or progression of premature complications (12-14) and has gained attention in research.

Short sleep leads to impaired glucose metabolism and hormonal and body weight regulation in individuals without chronic conditions and in those with T1D (15-19). Short sleep is associated with higher body mass index (20), lower leptin and higher ghrelin levels (21, 22), and higher cortisol secretion (23). Short sleep is associated with poorer glycemic control in adolescents (24), young adults (25, 26), and middle-aged adults with T1D (27).

Most researchers focus on person-level predictors and outcomes, such as person-specific mean or standard deviation of sleep duration and HbA1c, yielding between-person comparisons. Based on prior studies, it is indicated that, at a group level, young adults without chronic conditions and T1D with short sleep or with higher sleep variability have poorer glycemic control or more glucose variability (7, 28). Those with poorer glycemic control are at greater risk for sleep that is of a shorter duration (27, 29). These findings do not clarify, however, day-to-day associations within a person, eg, whether a young adult with T1D is more likely to have more glucose variability or less time in range with shorter sleep duration or experience shorter sleep duration at an individual level (eg, within-person level of analysis). Given the rising incidence of T1D, more detailed research that addresses objective sleep-wake behaviors at home is critical, including to examine both the between-person and within-person associations. This in turn would inform our understanding of the true nature of the sleep-glucose association in young adults with T1D to uncover modifiable sleep targets to improve glucose variability and glycemic control and reduce premature micro-and macrovascular complications.

The aim of this analysis was to evaluate the extent to which daily variations in objective sleep-wake characteristics (total sleep time, wake after sleep onset, bed/rise times, awakenings, sleep fragmentation index, mid-sleep time) predict subsequent glucose variability (time in range,

J index, coefficient of variation, and high and low blood glucose indices) and the extent to which daily variations in glucose predict sleep-wake characteristics within-person. We hypothesized that poorer person-specific average sleep (shorter total sleep time, lower sleep efficiency, later bedtimes, earlier wake times) and more sleep disruptions (more awakenings, higher sleep fragmentation index) would predict worse next-day glucose variability (less % time in range, higher J index, higher high and low blood glucose indices) and vice versa (within-person). We also hypothesized that poorer sleep and more disruptions would be associated with worse glucose variability at the group level (between persons).

Method

Study Objectives and Design

We reported previously, based on descriptive between-person analyses of person-level averages, that higher sleep variability, daytime sleepiness, and sleep fragmentation were associated with glucose variability (mean of daily differences) in young adults with T1D (30). For this study, in addition to person-level averages, we analyzed daily data from actigraphy and CGM in estimating associations in sleep and glucose patterns. This approach allows us to distinguish associations of glucose variability with a participant's typical sleep pattern (between-person differences in person-level summaries) from associations with prior-day sleep characteristics (within-person analyses of daily-level variables). A between-persons relationship would indicate relationships among interindividual differences in sleep and glucose variables (ie, level-2, group or macro level of analysis) (31). A within-person relationship between sleep and next-day glucose and vice versa would indicate existence of intraindividual variation within a person repeatedly over time. In other words, how a person varies from their own baseline data (ie, level-1, individual or the micro level of analysis) (31). Details pertinent to this report are summarized below:

Young adults monitored their sleep and glucose patterns concurrently for 6 to 14 days with a sleep-wake activity monitor (Phillips Respironics Spectrum Plus) and either their own CGM or a provided blinded Dexcom G4. The CGM was blinded to avoid intervention effects as the intention was to observe the sleep-glucose relationship in a naturalistic setting. Within-person and between-persons variations in sleep and glucose patterns using the actigraphy and CGM data were analyzed. The study followed the World Medical Association Declaration of Helsinki for research involving human subjects (32), and it was approved by both the Case Western Reserve University (#20200650) and the Yale University Human Investigation Committee (#1507016174).

Procedures

Research Electronic Data Capture (REDCap), a secure web-based software, was used to administer the questionnaires at baseline with twice-daily diaries for 14 days. Each diary entry was time-stamped, so it was evident when participants completed each survey, reducing the potential for recall bias. Electronic Medical Record (EMR) data were entered directly into REDCap. Young adults completed sleep diaries daily in the mornings and evenings to track daytime sleep-related behaviors (eg, caffeine use, exercise) and nocturnal sleep-wake characteristics (eg, bedtime, awakening). Actigraphy scoring methods were reported previously (33).

Participants

A total of 46 participants consented and completed baseline questionnaires. Of these, 42 successfully wore the CGM and Spectrum Plus concurrently for 7 continuous days/nights (mean = 7.4 ± 3.3 days/nights) and were included in this analysis. Each of 42 participants provided 7 consecutive days of data. Because daily-level predictors were lagged by 1 day, eg, sleep on day 1 predicting glycemic outcomes on day 2, analyses included 6 observations per participant. The data presented for this article represent daily CGM and sleep actigraphy data for a total of 252 reports. A sample size of 42 and 252 reports are comparable to previously published studies using daily actigraphy data or glucose among adolescents/young adults (18, 34-36).

The participants were: between 18 to 30 years, had been diagnosed with T1D for at least 6 months, with no other major health problems (eg, chronic medical conditions or severe psychiatric illness), not participating in any intervention studies, and understood English. Those with a previous obstructive sleep apnea (OSA) diagnosis, night shift workers, and current pregnancy were not eligible to participate. The Berlin Questionnaire was used to screen participants for inclusion in the study (37). Participants considered to be at high risk for sleep apnea were referred for treatment and not included in the study.

Measures

Demographics and clinical characteristics

Clinical and demographic data were extracted from the EMR, including age, body mass index (in kg/m^2), duration of diabetes, most recent HbA1c, and medical history. Ethnicity, education, primary caregiver, employment status, full-time student status, work hours, marital status,

residence, household count, income, cigarette smoking, alcohol or other substance use, insulin therapy regimen (eg, insulin injections or an insulin pump), CGM pump brand (if applicable), and last menstrual period (for females) data were collected via self-report survey. Self-report data were cross-validated with the EMR.

Objective sleep-wake characteristics

Actigraphy is a valid, reliable method to objectively estimate sleep-wake based on activity and inactivity measures (38). Actigraph data were collected in 30-second epochs (39). Participants were instructed to wear the actigraph continuously on their nondominant wrist for 7 to 14 days. They were instructed to depress the event marker at "lights out" and "lights on" times to demarcate time in bed. The following objective sleep-wake characteristics were derived: bedtime, waketime, total sleep time, sleep efficiency (indicator of sleep quality) (%), wake after sleep onset (minutes), awakenings (number), and sleep fragmentation index (% movement index + % fragmentation index). Midsleep time was determined as the midpoint between sleep onset (bedtime plus sleep onset latency) and sleep offset (waketime) (40). Actigraphy provides the greatest agreement and least bias compared with polysomnography in young adults with T1D (41).

Glucose variability

CGM data from the time the wrist actigraph was worn were downloaded directly from each young adult's existing or provided blinded Dexcom G4 Professional CGM to capture daily glucose patterns. Participants inserted a small sensor wire just under their skin using an automatic inserter (42). CGMs are accurate across a wide range of levels (43). CGM systems provide real-time, dynamic glucose information every 5 minutes—up to 288 readings in a 24-hour period—and values are measured in mg/dL (43). Glucose variability was calculated from CGM with the following indices: Mean ± SD, J index (calculated as $0.001 \times [\text{mean} + \text{SD}]^2$), low (LGBI) and high blood glucose risk indices (HGBI), time in range (calculated as % in target range 70-180 mg/dL, hypoglycemia < 70 mg/dL and severe hypoglycemia < 54 mg/dL, and hyperglycemia > 180 mg/dL and severe hyperglycemia > 250 mg/dL) (44).

Data Analysis Plan

Actigraphy data were scored with Actiware v. 6.0.9 software. GlyCulator 2.0 was used to calculate glycemic variability indices from raw CGM data. GlyCulator 2.0 follows CGM reporting guidelines specified in the International Consensus on Use of Continuous Glucose Monitoring (45). Prior to the analysis, data were screened for missing or out-of-range values and distributions of continuous variables. Descriptive statistics were calculated for all variables and analyzed using Statistical Package for Social Sciences (SPSS) version 27 for Mac (Armonk, NY: IBM Corp) and Statistical Analysis Software (SAS) version 9.4 (SAS Institute, Inc., Cary, NC, USA).

A series of multilevel models were performed to examine the associations of sleep-wake characteristics with glucose variability at both the day- and person-level; the day-level predictor reflects within-person differences, and the person-level predictor reflects between-person differences (46). Daily sleep reports comprised level-1 variables (N = 252) nested within-person at level-2 (N = 42 individuals). Models were run using all available data in collection days 1 to 7, assuming missingness at random (47). The multilevel models were set with a random intercept for individual variability to place the fewest restrictions on the models and allow variances and covariances to be freely estimated from the data. All models included a contrast indicator of weekend = 1 (Friday or Saturday) vs weekday = 0 (Sunday to Thursday) at level-1 to examine weekly differences between weekday and weekend sleep-wake and glucose patterns. All models also included sex (male = 1, female = 0), as a level-2 covariate.

In the first set of models, sleep-wake characteristics—prior-day sleep (level 1) and person-specific average sleep (level 2)—were examined as a predictor of glucose variability outcomes. Each participant had 6 observations due to the lagged predictor (eg, day 1 glucose variable to predict day 2 sleep variable, and vice versa). Next, parallel models with all glucose indices as predictors of sleep-wake characteristics indices were examined. In supplemental analyses, daily glucose outcomes were modeled as a function of person-specific variability in each sleep characteristic, where variability was operationalized as mean of squared successive daily differences (MSSD) (48). Outcomes were transformed as needed, such as by square root or Tobit (49), to satisfy model assumptions, including normally distributed residuals.

Results

Descriptive Analyses

Young adults in the study (N = 42) had a mean age of 22.2 ± 3.0 years, were 66.7% female, and were 83.3% non-Hispanic white. The mean T1D duration was 10.3 ± 6.1 years, mean HbA1c was 7.2% ± 1.1%, and most used an insulin pump (78.6%) and CGM (80.9%) for treatment. Participants used various CGM systems including Dexcom G6 (54.8%, n = 23), Dexcom G5 (19.0%, n = 8),

Medtronic MiniMed 670G (11.9%, n = 5), and Freestyle Libre (2.4%, n = 1). Participants without a CGM were provided with a blinded Dexcom G4 (11.9%, n = 5). The mean glucose was 163.0 (SD = 30.5) mg/dL, mean coefficient of variation (CV) was 36.8 (SD = 5.9), mean amplitude of glycemic excursions was 152.5 (*SD* = 40.0), and the mean of daily differences was 64.9 (SD = 21.4), measured via CGM across the 6 to 14 days. Descriptive statistics for sleep-wake characteristics and glucose variability indices are presented in Table 1.

Sex and Weekend Differences

Females with a later bedtime and later mid-sleep time had less glucose variability (J index, $P = 0.008$ and CV $P = 0.009$), lower low and high blood glucose index risk scores ($P = 0.006$ and $P = 0.008$, respectively), less time in range ($P = 0.01$), less time spent in hypoglycemia/severe hypoglycemia ($P = 0.002$ & $P = 0.008$ & $P = 0.002$, respectively), and hyperglycemia/severe hyperglycemia ($P = 0.009$ and $P = 0.009$ respectively). On weekends those with a later waketime had higher glucose variability (J index $P = 0.032$ and CV $P = 0.016$), higher low and high blood glucose index risk scores ($P = 0.027$ and $P = 0.032$ respectively), more time in range ($P = 0.026$), and more time spent in hyperglycemia and hypoglycemia (all $P < 0.04$).

Temporal Models of Sleep-Wake Predicting Glucose

We present the temporal models of sleep-wake characteristics predicting glucose indices in Tables 2 and 3. Higher sleep efficiency predicted more time in range ($P = 0.036$) and less time in hyperglycemia ($P = 0.037$) within-person. Higher sleep efficiency predicted a higher low blood glucose index risk ($P = 0.042$) within-person. More awakenings predicted higher glucose variability ($P = 0.040$), a higher high blood glucose risk score ($P = 0.036$), and more time spent in hyperglycemia ($P = 0.037$) between persons.

Temporal Models of Glucose Variability Predicting Sleep-Wake

We present the temporal models of glucose indices predicting sleep-wake characteristics in Tables 4 and 5. Lower glucose variability (CV), a lower low blood glucose index risk score, a higher blood glucose index risk score, and more time spent in hyperglycemia/severe hyperglycemia delayed bedtime within-person ($P = 0.047$, $P = 0.006$, $P = 0.040$, $P = 0.014$, and 0.027 respectively). More time in range and less time spent in hyperglycemia delayed waketime within-person ($P = 0.048$ and 0.040 respectively). A higher high blood glucose index, less time in range, and more time spent in hyperglycemia predicted a later mid-sleep time within-person (all $P < 0.05$).

Table 1. Descriptive statistics of sleep-wake characteristics and glucose variability indices (N = 42) days 1 to 7

Variables	Participant-specific daily average	Participant-specific standard deviations
	Mean (SD)	Mean (SD)
Sleep-wake characteristics		
Bedtime (hh:mm)	22:32 (6:34)	1:01 (0:31)
Wake time (hh:mm)	8:05 (1:30)	1:16 (0:41)
Sleep midpoint (hh:mm)	04:18 (1:18)	1:03 (0:45)
Total sleep time (min)	421.53 (64.37)	72.49 (32.42)
Sleep efficiency (%)	85.02 (4.80)	7.05 (4.87)
Wake after sleep onset (min)	36.66 (17.61)	15.64 (15.15)
Awakenings*	35.42 (9.48)	9.64 (4.79)
Sleep fragmentation index	17.82 (5.67)	5.66 (3.52)
Glucose indices		
J index	50.14 (19.18)	15.94 (9.21)
Coefficient of variation (CV)	31.58 (5.56)	8.50 (4.47)
Low blood glucose index	1.07 (1.38)	0.77 (0.68)
High blood glucose index	8.50 (5.00)	4.23 (2.71)
Time in range of 70-180 mg/dL, %	60.00 (17.86)	17.49 (7.07)
Hypoglycemia (time < 70 mg/dL), %	4.32 (7.22)	3.76 (3.56)
Severe hypoglycemia (time < 54 mg/dL), %	0.96 (2.05)	0.99 (1.42)
Hyperglycemia (time > 180 mg/dL), %	35.68 (19.57)	17.76 (8.34)
Severe hyperglycemia (time > 250 mg/dL), %	12.61 (11.11)	10.23 (8.44)

Note: Awakenings is the number of wake bouts.

Higher glucose variability (J index) and more time spent in severe hyperglycemia were associated with a lower sleep efficiency between persons (P = 0.041 and P = 0.046, respectively). A higher high blood glucose index risk score and more time spent in severe hyperglycemia were associated with a longer wake after sleep onset between persons (P = 0.044 and 0.021 respectively). More time spent in severe hyperglycemia was associated with a higher sleep fragmentation index between persons (P = 0.039).

Supplemental analyses of within-person MSSD in sleep characteristics and glucose variability outcomes (data not shown) identified only 2 marginally statistically significant (P < 0.10) associations. Higher within-person variability in bedtime was associated with higher CV (β = 0.61, P = 0.0725), whereas higher within-person variability in total sleep time was associated with less time spent in hypoglycemia (< 70 mg/dL) (β = –0.36, P = 0.0573).

Discussion

This is the first study in young adults with T1D where both between- and within-person variations in objective sleep-wake characteristics and the link to glucose variability indices were examined. Results showed significant temporal associations where poorer sleep led to poorer achievement of glucose targets and vice versa within-person. Higher sleep efficiency predicted better achievement of glucose targets within-person (eg, more time in range and less time in hyperglycemia). More time in range led to an earlier bedtime and later waketime,

Table 2. Person- and day-level effects of sleep-wake characteristics on glucose variability—multilevel models (N = 42)

Predictors		Bedtime β±SE (P value)	Wake time β±SE (P value)	Total sleep time β±SE (P value)	Sleep efficiency β±SE (P value)
Outcomes					
J index[a]	Person level	0.08 ± 0.15 (0.6081)	0.19 ± 0.13 (0.1608)	0.10 ± 0.13 (0.4772)	-0.24 ± 0.12 (0.0543)
	Day level	0.02 ± 0.07 (0.8026)	0.01 ± 0.07 (0.8396)	-0.001 ± 0.06 (0.9844)	-0.06 ± 0.05 (0.1999)
CV	Person level	-0.01 ± 0.12 (0.9568)	0.07 ± 0.11 (0.5547)	0.09 ± 0.10 (0.4151)	-0.01 ± 0.10 (0.9397)
	Day level	-0.04 ± 0.09 (0.6757)	-0.05 ± 0.09 (0.5595)	0.001 ± 0.08 (0.9913)	0.07 ± 0.07 (0.2806)
Low blood glucose index[b]	Person level	-0.08 ± 0.15 (0.5969)	-0.10 ± 0.14 (0.4979)	0.01 ± 0.13 (0.9278)	0.23 ± 0.12 (0.0744)
	Day level	-0.04 ± 0.07 (0.5646)	-0.01 ± 0.06 (0.8399)	0.03 ± 0.06 (0.5522)	**0.11 ± 0.05 (0.0416)**
High blood glucose index[a]	Person level	0.07 ± 0.15 (0.6222)	0.21 ± 0.13 (0.1312)	0.12 ± 0.13 (0.3662)	-0.23 ± 0.12 (0.0728)
	Day level	0.01 ± 0.07 (0.8792)	0.01 ± 0.06 (0.8971)	-0.004 ± 0.06 (0.9463)	-0.08 ± 0.05 (0.0899)
% Time in range 70-180 mg/dL	Person level	-0.05 ± 0.14 (0.7138)	-0.20 ± 0.13 (0.1446)	-0.16 ± 0.13 (0.2013)	0.10 ± 0.12 (0.4043)
	Day level	0.03 ± 0.07 (0.7236)	0.02 ± 0.07 (0.8002)	0.02 ± 0.06 (0.7594)	**0.11 ± 0.05 (0.0364)**
% Hypoglycemia <70 mg/dL[b]	Person level	-0.16 ± 0.19 (0.4010)	-0.13 ± 0.18 (0.4898)	0.07 ± 0.17 (0.6716)	0.31 ± 0.16 (0.0578)
	Day level	-0.09 ± 0.11 (0.4131)	-0.07 ± 0.09 (0.4177)	0.01 ± 0.09 (0.9402)	0.16 ± 0.08 (0.0614)
% Hypoglycemia <54 mg/dL[b]	Person level	-0.39 ± 0.41 (0.3488)	0.11 ± 0.38 (0.7778)	0.48 ± 0.36 (0.1838)	-0.26 ± 0.34 (0.4408)
	Day level	-0.03 ± 0.27 (0.9256)	-0.27 ± 0.24 (0.2758)	-0.19 ± 0.23 (0.4234)	-0.97 ± 0.66 (0.1473)
% Hyperglycemia >180 mg/dL[b]	Person level	0.09 ± 0.15 (0.5543)	0.23 ± 0.14 (0.1009)	0.16 ± 0.13 (0.2456)	-0.20 ± 0.12 (0.1106)
	Day level	-0.03 ± 0.07 (0.6412)	-0.003 ± 0.06 (0.9573)	0.002 ± 0.06 (0.9781)	**-0.11 ± 0.05 (0.0373)**
% Hyperglycemia >250 mg/dL[b]	Person level	0.04 ± 0.21 (0.8670)	0.22 ± 0.20 (0.2687)	0.13 ± 0.19 (0.5170)	-0.32 ± 0.18 (0.0785)
	Day level	0.09 ± 0.11 (0.4178)	0.08 ± 0.09 (0.3908)	0.01 ± 0.09 (0.9346)	-0.09 ± 0.08 (0.2564)

Note: β values are unstandardized coefficients in general linear mixed model of repeatedly measured sleep characteristic with glucose variability index as predictor. The person level represents how the sleep characteristic predicts each glucose variability index (between persons) and day level represents how each sleep characteristic predicts the daily level of glucose variability (within-person). **Bolded values are significant.**

[a]Variables were square root transformed.

[b]Variables were Tobit transformed.

Table 3. Person- and day-level effects of sleep-wake characteristics on glucose variability—multilevel models (N = 42)

Predictors		Wake after sleep onset β±SE (*P* value)	Awakenings β±SE (*P* value)	Sleep fragmentation index β±SE (*P* value)	Mid-sleep time β±SE (*P* value)
Outcomes					
J index[a]	Person level	**0.31 ± 0.12 (0.0149)**	**0.28 ± 0.13 (0.0402)**	0.23 ± 0.13 (0.0862)	0.13 ± 0.14 (0.3517)
	Day level	-0.01 ± 0.06 (0.8689)	0.001 ± 0.06 (0.9884)	-0.01 ± 0.06 (0.9137)	0.07 ± 0.06 (0.2535)
CV	Person level	0.04 ± 0.10 (0.7296)	0.14 ± 0.11 (0.2005)	-0.02 ± 0.11 (0.8442)	0.06 ± 0.11 (0.6134)
	Day level	-0.07 ± 0.08 (0.4047)	-0.02 ± 0.08 (0.7609)	0.03 ± 0.08 (0.6389)	-0.06 ± 0.08 (0.4539)
Low blood glucose index[b]	Person level	-0.16 ± 0.13 (0.2193)	-0.08 ± 0.14 (0.5656)	-0.09 ± 0.14 (0.5028)	-0.09 ± 0.14 (0.5236)
	Day level	-0.06 ± 0.07 (0.3913)	0.02 ± 0.06 (0.7143)	-0.00 ± 0.06 (0.9648)	-0.05 ± 0.06 (0.4045)
High blood glucose index[a]	Person level	**0.31 ± 0.12 (0.0149)**	**0.28 ± 0.13 (0.0363)**	0.24 ± 0.13 (0.0824)	0.13 ± 0.14 (0.3459)
	Day level	-0.00 ± 0.06 (0.9556)	0.003 ± 0.06 (0.9527)	-0.02 ± 0.06 (0.7664)	0.07 ± 0.06 (0.2544)
% Time in range 70-180 mg/dL	Person level	-0.20 ± 0.12 (0.1001)	-0.24 ± 0.13 (0.0597)	-0.16 ± 0.13 (0.2084)	-0.10 ± 0.14 (0.4760)
	Day level	-0.05 ± 0.06 (0.3799)	-0.02 ± 0.06 (0.7681)	-0.03 ± 0.06 (0.6177)	-0.05 ± 0.07 (0.4521)
% Hypoglycemia <70 mg/dL[b]	Person level	-0.24 ± 0.17 (0.1630)	-0.14 ± 0.18 (0.4402)	-0.14 ± 0.18 (0.4448)	-0.13 ± 0.19 (0.5002)
	Day level	-0.06 ± 0.10 (0.5552)	0.04 ± 0.09 (0.6247)	0.02 ± 0.09 (0.8717)	-0.16 ± 0.10 (0.1249)
% Hypoglycemia <54 mg/dL[b]	Person level	-0.06 ± 0.35 (0.8553)	0.02 ± 0.36 (0.9456)	0.02 ± 0.36 (0.9483)	-0.15 ± 0.40 (0.7049)
	Day level	-0.23 ± 0.26 (0.3887)	-0.05 ± 0.21 (0.8123)	-0.20 ± 0.26 (0.4415)	-0.25 ± 0.28 (0.3816)
% Hyperglycemia >180 mg/dL[b]	Person level	**0.28 ± 0.12 (0.0304)**	0.25 ± 0.13 (0.0605)	0.20 ± 0.13 (0.1526)	0.14 ± 0.14 (0.3258)
	Day level	0.05 ± 0.06 (0.4133)	0.03 ± 0.06 (0.6381)	0.02 ± 0.06 (0.7901)	0.05 ± 0.07 (0.4129)
% Hyperglycemia >250 mg/dL[b]	Person level	**0.52 ± 0.18 (0.0050)**	**0.40 ± 0.19 (0.0373)**	0.36 ± 0.19 (0.0645)	0.13 ± 0.20 (0.5287)
	Day level	0.00 ± 0.09 (0.9969)	0.00 ± 0.09 (0.9814)	-0.04 ± 0.09 (0.6368)	0.17 ± 0.10 (0.0802)

Note: *β* values are standardized coefficients in general linear mixed models. The person level represents how sleep each characteristics predicts each glucose variability index (between persons) and day level represents (within-person). **Bolded values are significant.**

[a]Variables were square root transformed.

[b]Variables were Tobit transformed.

providing an opportunity for more sleep while more time spent in hyperglycemia delayed bedtime within-person. Poorer achievement of glucose targets led to poorer sleep within-person (eg, delayed bedtime, waketime, mid-sleep time, and lower sleep efficiency). In comparison, poorer achievement of glucose targets was associated with poorer sleep and more disruptions between persons (eg, lower efficiency, longer wake after sleep onset, and a higher sleep fragmentation index). Short sleep was not a predictor of glucose variability nor time in range, and glucose variability was not a predictor of short sleep within-person or between persons in the current study.

Sleep quantity (total sleep time) and quality (sleep efficiency) are different dimensions of sleep health. Sleep efficiency is the ratio of time in bed to total time asleep and is an indicator of sleep quality. Therefore, sleep efficiency < 90% or < 85% would indicate excessive time in bed and potential for clinically significant sleep disturbance (3, 6). Multiple dimensions of sleep health (eg, higher sleep efficiency and total sleep time within range) are associated with better physical and mental health outcomes in the literature (5, 25, 50). The association between sleep variables and glucose between persons is limited to the average of the variables across the monitoring period. On the other hand, at the individual level (within-person) a relationship would indicate existence of intraindividual variation within a person repeatedly over time with sleep variables and glucose variability.

Table 4. Person- and day-level effects of glucose variability on sleep-wake characteristics—multilevel models (N = 42)

Outcomes		Bedtime β±SE (*P* value)	Wake time β±SE (*P* value)	Total sleep time β±SE (*P* value)	Sleep efficiency β±SE (*P* value)
Predictors					
J index	Person level	0.02 ± 0.13 (0.878)	0.13 ± 0.13 (0.294)	0.08 ± 0.12 (0.472)	**-0.22 ± 0.11 (0.041)**
	Day level	0.08 ± 0.06 (0.164)	0.05 ± 0.06 (0.432)	-0.03 ± 0.07 (0.688)	0.05 ± 0.08 (0.547)
CV	Person level	-0.02 ± 0.12 (0.883)	0.06 ± 0.12 (0.618)	0.09 ± 0.10 (0.395)	-0.02 ± 0.10 (0.831)
	Day level	**-0.09 ± 0.05 (0.047)**	-0.08 ± 0.05 (0.103)	-0.01 ± 0.06 (0.878)	0.09 ± 0.07 (0.151)
Low blood glucose Index[a]	Person level	-0.04 ± 0.12 (0.765)	-0.15 ± 0.12 (0.214)	-0.09 ± 0.11 (0.409)	0.12 ± 0.10 (0.234)
	Day level	**-0.16 ± 0.06 (0.006)**	-0.06 ± 0.06 (0.293)	0.08 ± 0.07 (0.279)	0.08 ± 0.08 (0.301)
High blood glucose index	Person level	-0.02 ± 0.12 (0.901)	0.12 ± 0.12 (0.358)	0.09 ± 0.11 (0.424)	-0.21 ± 0.11 (0.051)
	Day level	0.12 ± 0.06 (0.040)	0.08 ± 0.06 (0.200)	-0.02 ± 0.07 (0.753)	0.04 ± 0.08 (0.649)
%Time in range 70-180 mg/dL	Person level	0.09 ± 0.12 (0.474)	-0.08 ± 0.12 (0.534)	-0.13 ± 0.11 (0.246)	0.14 ± 0.11 (0.202)
	Day level	**-0.13 ± 0.06 (0.019)**	**-0.12 ± 0.06 (0.048)**	-0.03 ± 0.07 (0.654)	-0.05 ± 0.08 (0.554)
% Hypoglycemia <70 mg/dL[a]	Person level	-0.16 ± 0.12 (0.177)	-0.22 ± 0.12 (0.073)	-0.06 ± 0.11 (0.585)	0.15 ± 0.10 (0.153)
	Day level	-0.10 ± 0.05 (0.054)	-0.02 ± 0.05 (0.657)	0.07 ± 0.06 (0.261)	-0.00 ± 0.07 (0.951)
% Hypoglycemia <54 mg/dL[a]	Person level	-0.07 ± 0.12 (0.591)	-0.04 ± 0.12 (0.752)	0.03 ± 0.11 (0.780)	0.10 ± 0.10 (0.322)
	Day level	-0.02 ± 0.05 (0.633)	-0.03 ± 0.05 (0.545)	-0.01 ± 0.06 (0.928)	0.01 ± 0.07 (0.891)
% Hyperglycemia >180 mg/dL	Person level	-0.07 ± 0.13 (0.576)	0.09 ± 0.12 (0.493)	0.12 ± 0.11 (0.310)	-0.19 ± 0.11 (0.076)
	Day level	**0.14 ± 0.06 (0.014)**	**0.123 ± 0.06 (0.040)**	0.01 ± 0.07 (0.843)	0.04 ± 0.08 (0.604)
% Hyperglycemia >250 mg/dL	Person level	-0.01 ± 0.12 (0.955)	0.13 ± 0.12 (0.298)	0.09 ± 0.11 (0.417)	**-0.20 ± 0.10 (0.046)**
	Day level	**0.12 ± 0.05 (0.027)**	0.04 ± 0.06 (0.523)	-0.06 ± 0.07 (0.343)	0.04 ± 0.07 (0.559)

Note: *β* values are standardized coefficients in general linear mixed models. The person level represents how the sleep characteristic predicts each glucose variability index (between persons) and day level represents how each sleep characteristic predicts the daily level of glucose variability (within-person). **Bolded values are significant.**

[a]Variables were natural log transformed.

Shorter total sleep time was not associated with glucose variability within or between persons in the present study. Findings in the present study were consistent with some other studies of adults and adolescents with T1D (15, 51-53) and inconsistent with other studies of adults with T1D (26, 27). The methods in previous adult studies were between-person designs (15, 51, 52), with 1 study of adolescents with T1D also not finding a significant relationship between glucose variability and total sleep time within-person (53). Shorter total sleep time was associated between persons with poorer glycemic control in 2 previous studies of adults with T1D (26, 27). This may be partially explained due to the use of intermittent glucometer testing to determine glucose variability in 1 study (15), and researchers in other studies using self-reported sleep duration (51, 52).

Higher sleep efficiency predicted better achievement of glucose targets (eg, more time in range and less time in hyperglycemia within-person). More time spent asleep while in bed (eg, time in bed to total sleep time ratio) reflects a higher sleep efficiency. However, it should be noted that sleep efficiency should not be considered in isolation of total sleep time even though the relationship with total sleep time was not significant. For example, if a person were to only sleep 4 hours and spend all of those 4 hours asleep, they would have 100% sleep efficiency; however, 4 hours is not an adequate sleep duration as indicated by several studies where total or partial sleep deprivation led to impaired glucoregulation (15-19). Contrary to the hypothesis, higher sleep efficiency predicted a higher low blood glucose index risk within-person. Spending more time in range increases the risk of hypoglycemia (54).

In the models with glucose indices as predictors, poorer achievement of glucose targets led to poorer sleep. Our findings were consistent with other studies of adolescents and adults with T1D (28, 36, 50). In line with our findings, higher glucose variability was associated with a later chronotype (delayed mid-sleep time) between persons in 2 studies of adults with T1D (28, 50). Also, higher glucose variability and less time in range predicted poorer sleep within-person in a study of adolescents with T1D (53).

Table 5. Person- and day-level effects of glucose variability indices on sleep-wake characteristics—multilevel models (N = 42)

Outcomes		Wake after sleep onset β ± SE (*P* value)	Sleep fragmentation index β ± SE (*P* value)	Awakenings β ± SE (*P* value)	Mid-sleep time β ± SE (*P* value)
Predictors					
J index	Person level	0.22 ± 0.12 (0.069)	0.15 ± 0.12 (0.227)	0.16 ± 0.11 (0.169)	0.07 ± 0.12 (0.582)
	Day level	0.01 ± 0.07 (0.921)	0.04 ± 0.07 (0.609)	0.03 ± 0.07 (0.644)	0.11 ± 0.07 (0.105)
CV	Person level	0.01 ± 0.12 (0.936)	0.00 ± 0.12 (0.984)	0.13 ± 0.10 (0.211)	0.01 ± 0.11 (0.942)
	Day level	0.02 ± 0.06 (0.685)	0.01 ± 0.06 (0.877)	-0.01 ± 0.06 (0.926)	-0.04 ± 0.05 (0.401)
Low blood glucose index[a]	Person level	-0.21 ± 0.12 (0.084)	-0.05 ± 0.12 (0.679)	-0.07 ± 0.11 (0.547)	-0.10 ± 0.12 (0.376)
	Day level	0.04 ± 0.07 (0.575)	-0.04 ± 0.07 (0.593)	-0.01 ± 0.07 (0.922)	-0.10 ± 0.06 (0.091)
High blood glucose index	Person level	**0.25 ± 0.12 (0.044)**	0.18 ± 0.12 (0.152)	0.17 ± 0.11 (0.142)	0.05 ± 0.12 (0.698)
	Day level	-0.02 ± 0.07 (0.732)	0.01 ± 0.07 (0.855)	0.02 ± 0.07 (0.728)	**0.13 ± 0.06 (0.041)**
% Time in range 70-180 mg/dL	Person level	-0.20 ± 0.12 (0.108)	-0.14 ± 0.12 (0.242)	-0.19 ± 0.11 (0.083)	-0.01 ± 0.12 (0.958)
	Day level	0.04 ± 0.07 (0.574)	0.01 ± 0.07 (0.848)	0.01 ± 0.07 (0.928)	**-0.14 ± 0.06 (0.022)**
% Hypoglycemia <70 mg/dL[a]	Person level	-0.16 ± 0.12 (0.198)	-0.05 ± 0.01 (0.710)	-0.10 ± 0.11 (0.350)	-0.22 ± 0.11 (0.064)
	Day level	0.01 ± 0.06 (0.870)	-0.03 ± 0.06 (0.659)	0.03 ± 0.06 (0.670)	-0.04 ± 0.05 (0.439)
% Hypoglycemia <54 mg/dL[a]	Person level	-0.04 ± 0.12 (0.721)	-0.09 ± 0.12 (0.456)	-0.03 ± 0.11 (0.766)	-0.07 ± 0.12 (0.577)
	Day level	-0.04 ± 0.06 (0.532)	0.00 ± 0.06 (0.946)	-0.07 ± 0.06 (0.237)	-0.04 ± 0.06 (0.471)
% Hyperglycemia >180 mg/dL	Person level	0.24 ± 0.12 (0.056)	0.16 ± 0.12 (0.211)	0.19 ± 0.11 (0.094)	0.02 ± 0.12 (0.877)
	Day level	-0.03 ± 0.07 (0.660)	0.00 ± 0.07 (0.979)	0.01 ± 0.07 (0.904)	**0.15 ± 0.06 (0.016)**
% Hyperglycemia >250 mg/dL	Person level	**0.27 ± 0.12 (0.021)**	**0.25 ± 0.12 (0.039)**	0.20 ± 0.11 (0.072)	0.05 ± 0.12 (0.706)
	Day level	-0.06 ± 0.07 (0.327)	-0.04 ± 0.06 (0.543)	-0.01 ± 0.06 (0.815)	**0.12 ± 0.06 (0.033)**

Note: *β* values are standardized coefficients in general linear mixed models. The person level represents how the sleep characteristic predicts each glucose variability index (between persons) and day level represents how each sleep characteristic predicts the daily level of glucose variability (within-person). **Bolded values are significant.**

[a]Variables were natural log transformed.

A few limitations should be considered within the context of interpreting these results. The causal mechanisms for the sleep components can only be speculative due to the observational nature of the study. The delayed sleep in the young adults with T1D in the current study may reflect social engagement or a need to self-manage high glucose levels. Alternatively, a shared risk factor (eg, diet, exercise, and other lifestyle behaviors) may increase the likelihood of higher glucose variability and delayed sleep timing. The lack of association between total sleep time and glucose variability may be due to a limited representation of short sleep in the sample. The study also had several strengths. We excluded those with a previous OSA diagnosis or with high risk for sleep apnea, reducing the risk for an independent impact of OSA on glycemic control. However, lab polysomnography was not used, so sleep apnea still may be a confounder in the sample. Despite not controlling for these factors in the current study, our findings are novel in demonstrating that these associations persist over a longer period of time at the individual level. Future studies where hormonal, dietary, and insulin treatment effects are controlled in addition to what we controlled for (weekend and sex) capturing more than 1 or 2 weeks can provide further insight into our findings.

Overall, the findings in this study support the need to assess sleep components as a part of routine care of young adults with T1D. Optimizing sleep health and targeting a euglycemic range overnight is important, given the nature

of their reciprocal relationships. Addressing barriers to bedtime, time in bed, sleep regularity, and sleep efficiency may improve diabetes self-management, achievement of glucose targets, waketime alertness, and quality of life outcomes in this population. Keeping glucose values higher than the target range at night in this population may be the result of fear of hypoglycemia (7-9) but may be detrimental to sleep health and daytime function. These findings provide insight into the design of experimental studies to evaluate causal relationships among sleep profiles and diabetes outcomes among young adults with T1D.

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Author Contributions

S.G. and P.I., on the grants (K99NR018886/ R00NR018886 and AASM220-BS-19), secured the funding, designed the study, collected, analyzed, and interpreted the data, and wrote the manuscript. S.C. and S.M. analyzed and interpreted the data and co-wrote the results. R.L.H. contributed to the study design, interpreted the findings, and co-wrote the manuscript. K.P.S., M.G., S.K., C.S.R.L., and S.R. reviewed the content and critically revised the manuscript. All authors have seen and approved the final version of this manuscript.

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