Sleep and HbA_{1c} in Patients With Type 2 Diabetes: Which Sleep Characteristics Matter Most?

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Diabetes Care 2020;43:235–243 | https://doi.org/10.2337/dc19-0550

OBJECTIVE

Poor sleep has been identified as a risk factor for poor glycemic control in individuals with type 2 diabetes (T2D). As optimal sleep can be characterized in several ways, we evaluated which sleep characteristics are most strongly associated with glycated hemoglobin A_{1c} (HbA_{1c}).

RESEARCH DESIGN AND METHODS

A total of 172 patients with T2D completed 7-day wrist-actigraphy and sleep questionnaires. Linear regression was used to evaluate associations between sleep measures (total sleep duration, variability in sleep duration, midsleep time, variability in midsleep time, sleep efficiency, subjective sleep quality, and subjective insomnia symptoms) and HbA_{1c}, individually and in concert.

RESULTS

Variability in sleep duration was individually most strongly associated with HbA_{1c} ($\beta = 0.239$; $P = 0.002$; $R^2 = 4.9\%$), followed by total sleep duration (U-shaped: $\beta = 1.161/\beta^2 = 1.044$; $P = 0.017/0.032$; $R^2 = 4.3\%$), subjective sleep quality ($\beta = 0.191$; $P = 0.012$; $R^2 = 3.6\%$), variability in midsleep time ($\beta = 0.184$; $P = 0.016$; $R^2 = 3.4\%$), and sleep efficiency ($\beta = -0.150$; $R^2 = 2.3\%$). Midsleep time and subjective insomnia symptoms were not associated with HbA_{1c}. In combination, variability in sleep duration, total sleep duration, and subjective sleep quality were significantly associated with HbA_{1c}, together explaining 10.3% of the variance in HbA_{1c}. Analyses adjusted for covariates provided similar results, although the strength of associations was generally decreased and showing total sleep duration and subjective sleep quality to be most strongly associated with HbA_{1c}, together explaining 6.0% of the variance in HbA_{1c}.

CONCLUSIONS

Sleep in general may be a modifiable factor of importance for patients with T2D. The prevention of sleep curtailment may serve as a primary focus in the sleep-centered management of T2D.

Given the growing number of patients with type 2 diabetes (T2D) worldwide and the considerable burden associated with the disease, it is highly relevant to identify modifiable factors for the risk of poor glycemic control, in order to ultimately prevent complications (1). Sleep, which is regulated by neuroendocrine as well as behavioral processes, has been identified as a candidate factor (2,3). Sleep problems are common in the general population and individuals with T2D and on the rise as a consequence of our modern 24/7 society (1,4,5).

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Received 19 March 2019 and accepted 7 October 2019

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc19-0550/-/DC1.

Optimal sleep can be characterized in various ways, including measures of sleep duration, sleep efficiency (the time asleep as percentage of the time in bed with the intention to sleep), sleep continuity, sleep architecture, sleep debt (the cumulative effect of not getting enough sleep), sleep timing, as well as more subjective variables such as perceived quality of sleep and daytime sleepiness or alertness (6,7).

A number of these sleep measures have been studied in their association with glycemic control in patients with T2D. The association between the total duration of sleep and glycated hemoglobin A_{1c} (HbA_{1c}) in patients with T2D indicates a U-shaped curve, with worse HbA_{1c} in those who sleep shorter or longer than 7 to 8 h a night (8–13). Also, worse subjective sleep quality (8), decreased sleep efficiency (11,13,14), increased subjective insomnia symptoms (15,16), and decreased rapid eye movement sleep latency (17) have been related to higher HbA_{1c} in patients with T2D. Recently, variability in sleep duration, which may reflect partial sleep deprivation alternating with sleep compensation, has gained attention as a sleep characteristic of importance for good health, with higher HbA_{1c} in those with higher variability (13,18). It is thought that primarily shortage and disturbance of sleep underlie these associations, as experimental studies showed that sleep deprivation as well as sleep disruption in healthy individuals induce insulin resistance and β-cell dysfunction (19,20). Apart from quantity and quality of sleep, timing of sleep relative to the natural day appears to be of importance for glycemic control. Those who prefer to sleep later—the evening (chrono)types—and those who show more variability in sleep timing—likely due to a mismatch between the preferred sleep timing and timing of (social) activities (social jetlag)—exhibit higher HbA_{1c} (21–25). It has been suggested that these individuals experience a degree of jetlag (circadian misalignment) on a daily basis (21–25), which may impair glucose homeostasis, independent of sleep loss (26,27).

There is uncertainty as to which sleep characteristic has the strongest impact on glycemic control in patients with T2D. This information is of importance, as it may provide guidance for the development of sleep-focused treatment strategies in the management of T2D. In addition, it is currently unknown how all of the different sleep measures studied relate to one another. Moreover, in previous research, sleep measures were mostly derived from subjective reports, limiting the reliability of these findings.

With this cross-sectional study in patients with T2D, we aimed to evaluate which objective and subjective sleep measures, alone and in combination, are most strongly associated with HbA_{1c}.

We first examined if and how individual sleep measures are associated and cluster together, in order to discern whether the various sleep measures represent differential underlying sleep characteristics. Secondly, we examined which of the sleep measures explain most of the variance in HbA_{1c}, individually and in concert. Lastly, we examined effects of confounding and potential explanatory variables.

RESEARCH DESIGN AND METHODS

Design

We conducted a cross-sectional study in a sample of 205 patients with T2D, recruited from two diabetes centers affiliated to the Amsterdam UMC. The study was executed in accordance with the Helsinki Declaration 2013 and with approval from the Medical Ethics Committee of Amsterdam UMC (Vrije Universiteit Medical Center). All participants gave written informed consent before participation.

Participants

Patients were eligible when ≥18 years old and diagnosed with T2D. Exclusion criteria were performing shift work or being unable to comply with the study protocol due to language deficiency or practical problems. Health care providers asked whether patients were interested in participation at their annual diabetes checkup at the diabetes outpatient clinic of the Vrije Universiteit Medical Center (2013 to 2014) and the primary care clinic Ketenzorg West-Friesland (Hoorn, the Netherlands) (2016 to 2017). Interested patients were informed by a research assistant and enrolled after completion of the informed consent procedure.

In total, 291 patients received information about the study from research assistants (Amsterdam, $N = 179$; Hoorn, $N = 112$). Of these, 75 declined participation, and 9 were excluded: 7 patients were unable to take part in study procedures (language barrier [$N = 5$], deafness [$N = 1$], and cognitive problems [$N = 1$]), and 2 patients were not diagnosed with T2D (type 1 latent autoimmune diabetes in adults and type 1 diabetes).

Measures

We obtained objective measures of sleep using a wrist-worn microelectromechanical (accelerometer) system (GENEActiv; Activinsights Ltd, Kimbolton, U.K.), which was worn for 1 week continuously. Objective sleep measures were derived from accelerometer data using a previously validated algorithm, which combines actigraphy data with patient-report daily bed time and wake time information (28), and has shown good comparability with sleep measures derived from polysomnography, the gold standard for measuring sleep (29). Sleep measures calculated included total sleep duration (mean), variability in sleep duration (SD total sleep duration), sleep efficiency (mean; time asleep/time intention to sleep per night) (30), midsleep time (mean), a proxy for chronotype, the propensity for an individual to sleep at a particular time during a 24-h period (e.g., being a morning type) (31,32), and variability in midsleep time (SD midsleep time), a proxy for social jetlag, a mismatch between the preferred sleep timing and timing of (social) activities. Subjective measures of sleep, sleep quality, and insomnia symptoms were obtained using the self-report Pittsburgh Sleep Quality Index (PSQI) (33) (scores ≥6 indicate poor sleep) and self-report Insomnia Severity Index (ISI) (34) (scores ≥10 indicate clinically relevant insomnia), respectively.

HbA_{1c}, a measure of average blood glucose levels in the past 3 months, was determined in fasting whole blood samples by automated high-performance liquid chromatography (Amsterdam: ADAMS A1c, Menarini Diagnostics, Firenze, Italy; Hoorn: Diamat, Bio-Rad, Veenendaal, the Netherlands).

Potential confounding and explanatory variables tested included age, sex, country of birth, highest educational level, employment status, number of medications, glucose-lowering medication, BMI, physical activity, risk for sleep apnea, use of alcohol, depressive symptoms, diabetes distress, anxiety symptoms,

and length of natural day (short vs. long). Physical activity in metabolic equivalent of task minutes was derived from the International Physical Activity Questionnaire, sleep apnea risk from the Berlin Questionnaire of sleep apnea, and use of alcohol from the Alcohol Use Disorders Identification Test. Depressive symptoms were measured using the Inventory of Depressive Symptomatology; a score ≥14 indicates clinically significant symptoms. Diabetes distress was measured using the 5-item Problem Areas in Diabetes Questionnaire; a score ≥8 indicates possible diabetes-related emotional distress. Anxiety symptoms were measured using the Beck Anxiety Inventory; a score ≥22 indicates clinically significant anxiety symptoms.

Statistical Analyses

Data were checked for normality and transformed when appropriate. Significance was set at a *P* value of 0.05, unless indicated otherwise. Missing data were not imputed. Statistics were performed using SPSS IBM Statistics 22.

First, we performed an exploratory factor analysis to evaluate the association between the different individual sleep measures and potential underlying sleep characteristics (latent variables or constructs; explanatory sleep variables that are not directly observable). Factor matrixes were extracted using the maximum likelihood method and varimax orthogonal rotations with Kaiser normalization. Scree plot analysis (cutoff of 1) was used to determine the appropriate number of factors to retain. The underlying sleep characteristics were derived from the rotated factor matrix; a factor-loading cutoff of 0.4 was used to discern factor characteristics. Factor analysis was acceptable in this data set, as indicated by the Kaiser-Meyer-Olkin measure of sampling adequacy (0.498) and Bartlett test of sphericity (χ^2 = 8,676.712; df 66; $P < 0.001$).

Second, in order to assess which sleep measures were most strongly associated with HbA_{1c}, we performed linear regression analyses, including all participants with complete data sets regarding all sleep measures as well as HbA_{1c}. For sleep duration, we tested whether a linear or quadratic (U-shaped) association best described the relationship with HbA_{1c} in our sample. Results were reported in standardized β coefficients with 95% CIs, *P* value, and explained variance (R^2 [%]; [explained variance/total variance] * 100), for comparability of model parameters among the individual sleep measures. For the unadjusted analyses, we additionally reported unstandardized *B* (the outcome measure of HbA_{1c} was not transformed). Backward stepwise regression analysis was performed in order to assess which sleep measures together were most strongly associated with HbA_{1c}. The backward elimination approach involves starting with all candidate sleep measures, deleting the sleep measure for which loss gives the least deterioration of the model fit, and repeating this process until no further sleep measures can be deleted without a significant loss of fit (i.e., defined as $P < 0.1$ for the individual sleep measures).

Third, we assessed effects of confounding and potential explanatory variables. First, nonmodifiable covariates were added to the models (model 2), subsequently adding modifiable covariates (model 3).

Lastly, we tested whether associations were moderated by age, sex, sleep apnea risk, depressive symptoms, and the number of medications used, as a proxy for the number of comorbidities. For this purpose, we used linear regression with HbA_{1c} as dependent variables and the sleep variable, the moderator, and their two-way interaction as predictors. A candidate moderator was declared an effect-moderator when the two-way interaction was significant.

RESULTS

Sample Characteristics

In total, 205 participants took part in the study (Amsterdam, $N = 105$; Hoorn, $N = 100$). Complete data sets regarding all sleep measures as well as HbA_{1c} were available from 172 participants (Supplementary Table 1). This subsample did not differ from the total sample regarding the primary sample characteristics of age, sex, average HbA_{1c}, and the subjective sleep measures sleep quality and insomnia symptoms (results not shown).

A total of 62% of the participants were men, and 78% of the participants worked <12 h/week or not at all. On average, participants were 66.4 (range 33–85) years old, obese (BMI 30.8), and had T2D for 13 (range 1–44) years, with a mean HbA_{1c} of 57 mmol/mol (range 29–107 mmol/mol; 7.3%, range 4.5–11.9%). A total of 42.9% of the participants used insulin therapy. At least mild depressive symptoms, anxiety, and diabetes distress were present in, respectively, 41%, 6%, and 22% of the participants. Participants slept on average 6 h and 29 min, with midsleep time at 3:50 A.M. and a median sleep efficiency of 88% (≥80% is considered normal). Participants reported on average poor subjective sleep quality (PSQI score median 10), but few subjective insomnia symptoms (ISI score median 5). The majority of the participants were at high risk for having sleep apnea (69%), and 15% used sleep medication weekly. Characteristics of the sample are shown in Table 1.

Sleep Measures: Distinct Characteristics of Sleep?

Associations among individual sleep measures ranged from $r = 0.779$ ($P < 0.001$) to $r = 0.004$ ($P = 0.479$) (Supplementary Table 2). Factor analysis suggested three underlying sleep characteristics: factor 1 linking the subjective measures (insomnia symptoms and sleep quality; sleep complaints), factor 2 linking both variability measures (variability in sleep duration and variability in midsleep time; sleep variability), and factor 3 linking duration and efficiency (sleep efficiency and total sleep duration; sleep quantity) (Fig. 1 and Supplementary Table 3). Midsleep time appears to bridge the three sleep characteristics statistically, which may suggest that midsleep time is a sleep characteristic on its own, even though it was not identified as a separate factor in the current analysis (Fig. 1 and Supplementary Table 3).

Which Sleep Measures Are Most Strongly Associated With HbA_{1c}?

Total sleep duration was significantly associated with HbA_{1c} in a U-shaped manner, indicating worse glycemic control with both short and long sleep compared with sleep medium duration, with the nadir at 436 min (7 h 16 min) (Table 2). Also, sleep efficiency, variability in sleep duration, variability in midsleep time, and subjective sleep quality were significantly associated with HbA_{1c}, with higher HbA_{1c} in individuals with lower efficiency, higher variability, and worse quality (Table 2). Insomnia symptoms and midsleep time were not associated with HbA_{1c} (Table 2).

In unadjusted analyses of individual sleep measures that were modeled

Table 1—Sample characteristics

Sample size, *N*	172
Age, years, mean (SD)	66.4 (8.5)
Sex, %, men/women	62.2/37.8
Country of birth, %, European/non-European	88.4/11.6
Time of year in protocol, %, spring/summer/autumn/winter	15.7/46.5/25.6/12.2
Educational level, %, elementary not completed/elementary/ lower vocational/lower secondary/intermediate secondary/ intermediate vocational/higher secondary/college/university	2.9/4.1/ 19.2/1.7/9.9/ 26.2/2.9/25.6/7.6
Employment status, %, employed ≥12 h/week/other	22.1/77.9
Number of medications, mean (SD)	7.5 (3.8)
Polypharmacy (≥5 medications), %, yes/no	81/19
Diabetes duration, years, mean (SD)	13.3 (8.1)
Glucose-lowering medication, %, insulin/oral only/none	41.9/43.0/15.1
BMI, kg/m^2, mean (SD)	30.0 (5.6)
Physical activity, MET minutes, median (IQR)	2,684 (971–5,513)
Sleep apnea risk, %, low/high	30.7/69.3
Use of alcohol, %, less than weekly/weekly	61.2/38.8
Sleep medication, %, less than weekly/weekly	85.5/14.5
Depressive symptoms, IDS score, median (IQR)	11 (6–19)
Diabetes distress, PAID-5 score, median (IQR)	2 (0–7)
Anxiety, BAI score, median (IQR)	5 (2–11)
Sleep measures	
Sleep duration, min (h:min), mean (SD)	389 (6:29) (64)
Variability in sleep duration, min, median (IQR)	45 (30–63)
Midsleep time, time, mean (SD)	3:50 (0:59)
Variability in midsleep time, min, median (IQR)	31 (20–47)
Sleep efficiency, %, median (IQR)	88 (82–91)
Sleep quality, PSQI score, median (IQR)	10 (7–12)
Insomnia symptoms, ISI score, median (IQR)	5 (1–13)
Glycemic control	
HbA_{1c}, mmol/mol/ and %, mean (SD)	57 (14)/7.3 (1.3)

BAI, Beck Anxiety Inventory; IDS, Inventory of Depressive Symptomatology; IQR, interquartile range; MET, metabolic equivalent of task; PAID-5, 5-item Problem Areas in Diabetes Questionnaire.

separately, variability in sleep duration had the greatest standardized β coefficient of all sleep measures tested (β = 0.222) and explained most of the variance in HbA_{1c} (4.9%) (Fig. 1) (Table 2). The average difference in HbA_{1c} between the lowest and highest quartile in variability in sleep duration was 11 mmol/mol (1.0%). Variability in sleep duration was followed by total sleep duration (4.3%), subjective sleep quality (3.6%), variability in midsleep time (3.4%), and sleep efficiency (2.3%) (Fig. 1) (Table 2).

Stepwise regression, in which all sleep measures were entered in a single model, suggested that the combination of variability in sleep duration, total sleep duration, and subjective sleep quality was most strongly associated with HbA_{1c} (β = 0.179 [95% CI 0.030–0.327], P = 0.019; β = −0.931 [95% CI −1.873 to 0.012], P = 0.053/0.810 [95% CI −0.133 to 1.753], P = 0.092; and 0.136 [95% CI −0.0 14 to 0.286], P = 0.076, respectively) (Table 3). Together, these sleep measures explained 10.3% of the variance in HbA_{1c} (Table 3).

What Are the Effects of Confounding and Potential Explanatory Factors?

The following variables were identified as confounding or potential explanatory factors: age, country of birth, employment status, diabetes distress, natural day length, and glucose-lowering medication (Supplementary Table 4).

When we adjusted for the nonmodifiable covariates age and country of birth, associations between individual sleep measures and HbA_{1c} weakened slightly, thereby rendering the associations of sleep efficiency and variability in mid sleep time insignificant and now suggesting total sleep duration as the sleep measure explaining most of the variance in HbA_{1c} (difference in R^2 between total sleep duration and variability in sleep duration: 0.7%) (Table 2). Additional adjustment for the modifiable covariates employment status, diabetes distress, natural day length, and glucose-lowering medication weakened the associations further, rendering all associations insignificant, except the association between total sleep duration and HbA_{1c} (Table 2). After adjustment, total sleep duration explained most of the variance in HbA_{1c}, followed by subjective sleep quality (difference in R^2 between total sleep duration and sleep quality: 0.6%), and sleep efficiency (R^2 difference between total sleep duration and sleep efficiency: 1.0%).

Stepwise regression analysis, in which all sleep measures and nonmodifiable covariates were entered in a single model, identified age as a covariate strongly associated with HbA_{1c} (β = −0.160 [95% CI −0.309 to 0.012], P = 0.035, and explaining 4.5% of the variance in HbA_{1c}). In line with the unadjusted stepwise regression analysis, results suggest

that the combination of subjective sleep quality, variability in sleep duration, and total sleep duration was most strongly associated with HbA_{1c} (β = 0.148 [95% CI 0.000–0.296], $P = 0.050$; β = 0.148 [95% CI −0.004 to 0.300], $P = 0.056$; and β = −0.127 [95% CI −0.271 to 0.017], $P = 0.084$, respectively) (Table 3). Together, these sleep measures explained 6.7% of the variance in HbA_{1c} (Table 3).

Stepwise regression analysis that included both the nonmodifiable and modifiable covariates identified employment status and glucose-lowering medication as covariates strongly associated with HbA_{1c} (β = 0.241 [95% CI 0.098–0.378], $P = 0.001$; and β = 0.242 [95% CI 0.101–0.378], $P = 0.001$, respectively). In combination, these covariates explained 13.3% of the variance in HbA_{1c}. The combination of subjective sleep quality and total sleep duration was most strongly associated with HbA_{1c} (β = 0.179 [95% CI 0.037–0.317], $P = 0.014$; and β = −0.892 [95% CI −1.783 to 0.012], $P = 0.053/\beta^2 = 0.805$ [95% CI −0.100 to 1.697], $P = 0.081$, respectively) (Table 3). Together, these sleep measures explained 6.0% of the variance in HbA_{1c} (Table 3).

Associations were not moderated by age, sex, depressive symptoms, or the number of medications used (Supplementary Table 5). Sleep apnea risk moderated the association between (variability) in midsleep time and HbA_{1c}, but none of the other sleep measures. Midsleep time was strongly associated with HbA_{1c} in those with low risk for sleep apnea (β = 0.516 [95% CI 0.159–0.873]; $P = 0.006$, and explaining 23.1% of the variance in HbA_{1c}), but not in those with high risk for sleep apnea (Supplementary Table 6). Variability in midsleep time was strongly associated with HbA_{1c} in those with high risk for sleep apnea (β = 0.308 [95% CI 0.075–0.541]; $P = 0.010$, and explaining 9.3% of the variance in HbA_{1c}), but not in those with low risk for sleep apnea (Supplementary Table 6).

CONCLUSIONS

In this study, we investigated which sleep measures represent distinct characteristics of sleep, and are most strongly associated with HbA_{1c}, in patients with T2D. Sleep measures tested included total sleep duration, variability in sleep duration, midsleep time, variability in midsleep time, sleep efficiency, subjective sleep quality, and subjective insomnia symptoms.

Three underlying sleep characteristics were identified: sleep complaints, sleep variability, and sleep quantity. Midsleep time appears to be a sleep characteristic on its own. Variability in sleep duration, which may reflect partial sleep deprivation alternating with sleep compensation, was individually most strongly associated with HbA_{1c}, explaining 4.9% of the variance in HbA_{1c}. Variability in sleep duration was followed by total sleep duration (4.3%), subjective sleep quality (3.6%), variability in midsleep time (3.4%), and sleep efficiency (2.3%). Midsleep time and subjective insomnia symptoms were not associated with HbA_{1c}. In combination, variability in sleep duration, total sleep duration, and subjective sleep quality were most strongly associated with HbA_{1c}; together explaining 10.3% of the variance in HbA_{1c}. Analyses adjusted for covariates also identified these sleep measures as being most strongly associated with HbA_{1c}, though the strength of associations was generally decreased (sleep measures together explained 6.0–6.7% of the variance in HbA_{1c}), and pointed to total sleep duration and sleep quality as the sleep measures most strongly associated with HbA_{1c}.

Our findings support the idea that sleep optimization could improve HbA_{1c} and be used as adjunct treatment in the management of T2D. More specifically, the prevention of sleep curtailment may serve as a primary focus in the sleep-centered management of T2D. The magnitude of the difference in average HbA_{1c} between participants in the lowest and highest quartile of variability in sleep duration—11 mmol/mol or 1.0%—for

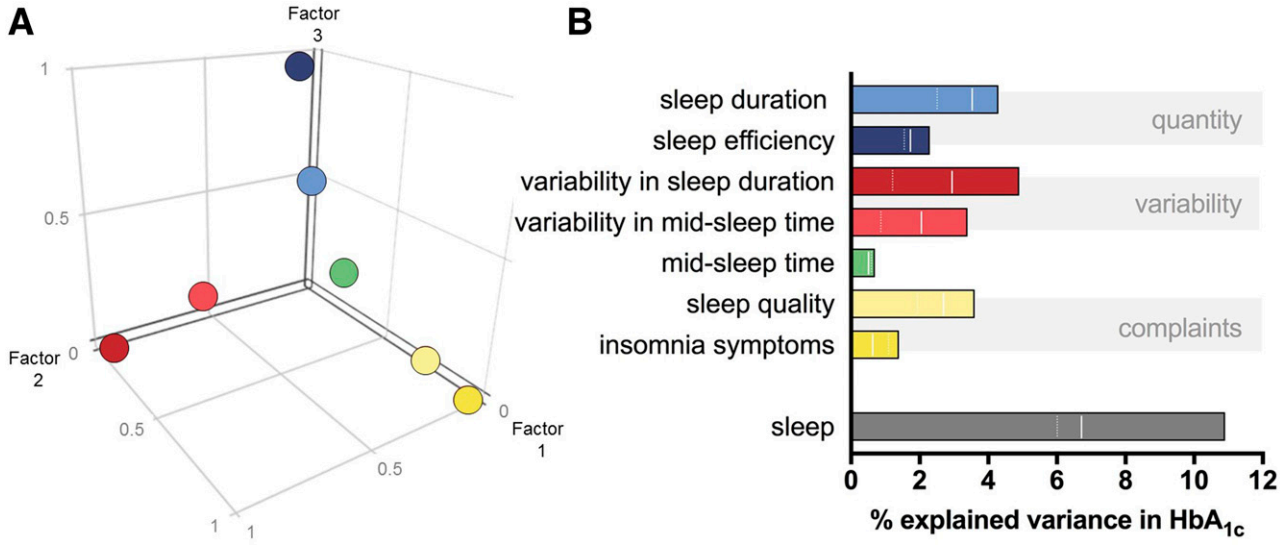

Figure 1—*A*: Association among sleep measures: spatial representation of relationships between derived factors and individual sleep measures. *B*: Percentage of explained variance in HbA_{1c} for individual sleep measures, as well as sleep in general (contributing sleep measures according to stepwise regression analyses: total sleep duration + variability in sleep duration + subjective sleep quality). Horizontal bars indicate the explained variance in HbA_{1c} derived from unadjusted analyses (model 1). Lines within the bars indicate the percentage of explained variance in HbA_{1c} derived from adjusted analyses: continuous lines when adjusted for nonmodifiable covariates (age and country of birth; model 2) and dashed lines when additionally adjusted adjustment for modifiable covariates (employment status, diabetes distress, natural day length, and glucose-lowering medication; model 3).

Table 2—Associations between individual sleep measures and HbA_{1c} (parameters of unadjusted and adjusted regression models)

		Model 1, unadjusted				Model 2, adjusted for nonmodifiable covariates (age and country of birth; R^2 = 5.2%)			Model 3, additionally adjusted for modifiable covariates (employment status, diabetes distress, natural day length, and glucose-lowering medication; R^2 = 15.9%)			
Underlying sleep variable	Sleep measure	Unstandardized coefficient B ($/B^2$)	95% CI	Standardized coefficient β ($/β^2$)	95% CI	*P* value	R^2, %	Standardized coefficient β ($/β^2$)	95% CI	*P* value	R^2, %	Standardized coefficient β ($/β^2$)	95% CI	*P* value	R^2, %
Sleep quantity	Sleep duration, min	−0.248/0.000	−0.452 to −0.044/ 0.000 to 0.001	−1.161/ 1.044	−2.117 to −0.206/ 0.089 to 2.000	**0.017**/ **0.032***	4.3	−1.062/ 0.954	−2.003 to −0.121/ 0.013 to 1.985	**0.027**/ **0.047**	8.8	−0.936/ 0.857	−1.845 to −0.026/ −0.054 to 1.768	**0.044**/ 0.065	18.4
	Sleep efficiency, %	−0.263	−0.526 to −0.001	−0.150	−0.300 to 0.000	**0.049**	2.3	−0.132	−0.280 to 0.016	0.081	6.9	−0.124	−0.266 to 0.019	0.089	17.4
Sleep variability	Variability in sleep duration, minutes	0.109	0.036–0.181	0.222	0.074–0.369	**0.003**	4.9	0.175	0.024–0.326	**0.023**	8.1	0.117	−0.031 to 0.265	0.121	17.1
	Variability in midsleep time, min	0.002	0.000–0.004	0.184	0.035–0.333	**0.016**	3.4	0.148	−0.001 to 0.297	0.052	7.3	0.091	−0.054 to 0.237	0.216	16.7
Midsleep time	Midsleep time, time	0.000	0.000–0.001	0.085	−0.066 to 0.236	0.267	0.7	0.074	−0.075 to 0.222	0.328	5.7	0.080	−0.065 to 0.225	0.276	16.5
Sleep complaints	Sleep quality, PSQI score	0.645	0.143–1.146	0.191	0.042–0.340	**0.012**	3.6	0.167	0.019–0.315	**0.027**	7.9	0.148	−0.003 to 0.299	0.055	17.8
	Insomnia symptoms, ISI score	0.220	−0.059 to 0.500	0.119	−0.032 to 0.269	0.121	1.4	0.078	−0.074 to 0.229	0.312	5.8	0.045	−0.115 to 0.206	0.576	17.0

$P < 0.05$ in boldface. *The linear association (β = 0.090 [95% CI 0.280–0.020]; P = 0.090) was inferior.

example, appears clinically relevant. By comparison: established glucose-lowering drugs and newer glucose-lowering drugs under investigation provide HbA_{1c} reductions in the range of 0.5–1.25% (35) and 0.3–0.5%, respectively (36). Clinical trials need to discern whether the findings of this study demonstrate clinical significance as well. A study in habitually sleep-restricted healthy individuals already demonstrated that sleep extension is a feasible real-life intervention and improves insulin sensitivity (37).

Only recently, variability in sleep duration has gained attention as a factor of importance for glycemic control in patients with T2D (13,18), as well as type 1 diabetes (38,39). The question arises why variability in sleep duration of all sleep measures tested individually explains most of the variance in HbA_{1c}. Possibly, variability in sleep duration best reflects individual sleep deprivation, as the optimal sleep duration may differ among individuals. Experimental studies have convincingly shown that sleep deprivation induces insulin resistance and increased glucose levels (19,20). Yet, variability in sleep duration may also be associated with HbA_{1c} through other mechanisms than sleep deprivation. For example, variability in sleep duration may induce a degree of jetlag, as evidenced by its association with variability in midsleep time, which may have additional negative effects on glycemic control (26). Variability in sleep duration may also be related to variability in other behaviors that affect glycemic control, such as eating and physical activity, or may be reflective of a number of unhealthy behaviors in general. Future research should address the mechanism by which higher variability in sleep duration is related to higher HbA_{1c}.

Strengths of the study include the evaluation of a comprehensive set of sleep measures, including self-reported and wrist actigraphy–derived sleep measures, and measures of sleep timing. This is one of the larger sample-size studies investigating objective measures of sleep in people with T2D.

A limitation of the study is that the sample is characterized by individuals mainly of European descent, living in a single geographical location (i.e., the Netherlands) and therefore latitude, with on average a relatively short sleep duration, high risk for sleep apnea, and

Table 3—Stepwise regression of sleep measures on HbA_{1c} (parameters of unadjusted and adjusted regression models)

		Model 1, unadjusted							Model 2, adjusted for nonmodifiable covariates (age and country of birth)							Model 3, additionally adjusted for modifiable covariates (employment status, diabetes distress, natural day length, and glucose-lowering medication)						
		Step 1			Final step (step 5)				Step 1			Final step (step 7)				Step 1			Final step (step 10)			
Underlying sleep variable	Sleep measure	β (/$β^2$)	95% CI	*P* value	β (/$β^2$)	95% CI	*P* value	R^2, %	β (/$β^2$)	95% CI	*P* value	β (/$β^2$)	95% CI	*P* value	R^2,%	β (/$β^2$)	95% CI	*P* value	β (/$β^2$)	95% CI	*P* value	R^2,%
Sleep quantity	Sleep duration, min	−0.976/ 0.880	−1.967 to −0.015/ −0.110 to 1.869	0.054/ 0.081	−0.931/ 0.810	−1.873 to 0.012/ −0.133 to 1.753	0.053/ 0.092	10.3	−0.950/ 0.859	−1.933 to −0.034/ −0.123 to 1.841	0.058/ 0.086	−0.127	−0.271 to 0.017	0.084	6.7	−0.867/ 0.810	−1.810 to −0.088/ −0.146 to 1.753	0.075/ 0.097	−0.892/ 0.805	−1.783 to 0.012/ −0.100 to 1.697	0.053/ 0.081	6.0
	Sleep efficiency, %	−0.016	−0.195 to 0.162						−0.016	−0.193 to 0.161	0.860					−0.040	−0.214 to 0.135	0.656				
Sleep variability	Variability in sleep duration, min	0.136	−0.042 to 0.313		0.179	0.030–0.327	**0.019**		0.100	−0.078 to 0.279	0.268	0.148	−0.004 to 0.300	0.056		0.060	−0.114 to 0.232	0.500				
	Variability in midsleep time, min	0.083	−0.090 to 0.256						0.071	−0.100 to 0.243	0.414					0.033	−0.133 to 0.199	0.697				
Midsleep time	Midsleep time, time	−0.018	−0.186 to 0.149						−0.023	−0.189 to 0.143	0.788					−0.004	−0.165 to 0.158	0.965				
Sleep complaints	Sleep quality, PSQI score	0.261	−0.006 to 0.527		0.136	−0.014 to 0.286	0.076		0.290	0.026–0.555	0.026	0.148	0.000–0.296	0.050		0.290	0.030–0.544	**0.029**	0.179	0.037–0.317	**0.014**	
	Insomnia symptoms, ISI score	−0.146	−0.404 to 0.111						−0.196	−0.455 to 0.063	0.137					−0.225	−0.485 to 0.041	0.098				
Nonmodifiable covariates	Age								−0.144	−0.303 to 0.014	0.073	−0.160	−0.309 to −0.012	0.035	4.5	0.003	−0.178 to 0.184	0.975				13.3
	Country of birth								0.066	−0.090 to 0.223	0.404					0.018	−0.142 to 0.178	0.827				
Modifiable covariates	Employment status															0.223	0.052–0.390	**0.011**	0.241	0.098–0.378	**0.001**	
	Diabetes distress															0.113	−0.066 to 0.290	0.215				
	Glucose-lowering medication															0.190	0.042–0.336	**0.012**	0.242	0.101–0.379	**0.001**	
	Natural day length															−0.086	−0.237 to 0.067	0.270				

$P < 0.05$ in boldface.

low levels of employment. This limits the generalizability of the findings and comparison with other studies in the field. Measures of sleep apnea and sleep architecture were not included in the study, as reliable measurement of sleep apnea and measurement of sleep architecture requires polysomnography. Also, alertness during the day, another sleep dimension proposed by Buysse (6), and other measures of glycemic control, such as hypoglycemia and glucose variability, were not assessed. Furthermore, we gathered no information on (timing of) food intake, timing of exercise, treatment adherence, and self-care, which all may be considered important, yet difficult to measure, potential confounding or explanatory variables. Hence, we cannot discern whether these variables contributed to the observed associations between sleep variables and HbA_{1c}. Lastly, analyses were not corrected for multiple comparisons.

The fact that we could not establish a significant relationship between midsleep time and HbA_{1c}, unlike previous studies that reported higher HbA_{1c} concentration with later chronotype (21–25), may be due to the use of objective rather than subjective measures of sleep timing, as well as the conceptual difference between midsleep time and chronotype, which in other studies has been defined as midsleep time on free days adjusted for sleep debt accumulated at work days (35). We did not collect information on work/free days. Differences in sample characteristics could also play a role. The range in midsleep time was limited, and our sample consisted largely of individuals with high risk for sleep apnea. Effect moderation analyses provided evidence for a possible association between midsleep time and HbA_{1c} exclusively in those with low risk for sleep apnea.

To test the robustness of our findings, analyses were performed in which we adjusted for nonmodifiable (age and country of birth) and modifiable covariates (employment status, diabetes distress, natural day length, and glucose-lowering medication). The following variables were considered but not identified as potential confounding or explanatory factors and therefore not adjusted for: sex, highest educational level, number of medications, BMI, physical activity, risk for sleep apnea, use of alcohol, depressive symptoms, and anxiety symptoms. Adjustment of analyses for covariates weakened the associations between sleep and HbA_{1c}. This may be a better reflection of the actual association among sleep measures and HbA_{1c}, but may also be the result of overcorrection. It remains unknown whether the covariates are true confounders or potential explanatory factors, as cross-sectional study designs do not allow causal inference. Hence, we cannot ascertain which proportion of the association can be truly attributed to the particular sleep measures. In addition, reversed causation cannot be ruled out. For example, individuals with higher HbA_{1c}, may use insulin therapy more often, which may disturb sleep due to (fear for) the occurrence of nocturnal hypoglycemic events (36); similarly, increased HbA_{1c} may induce diabetes distress, worry, and thereby poor sleep. Nonetheless, experimental studies provided robust evidence that sleep restriction, but also sleep disruption, produces insulin resistance without adequate compensatory β-cell insulin response, with increased glucose concentrations as a result (19,20). The fact that the strength of the association between variability in sleep duration and HbA_{1c} is reduced, also relatively to other sleep measures, after adjustment for covariates might imply that variability in sleep is generally more strongly associated with (and possibly affected by) other variables compared with total sleep duration and subjective sleep quality.

In conclusion, sleep may be an important modifiable factor associated with HbA_{1c} in patients with T2D who already receive regular care and may deserve a place in the clinical evaluation and management of the patient with T2D. Particularly variability in sleep duration, which may reflect partial sleep deprivation alternating with sleep compensation, may be a promising therapeutic target. Further research should evaluate whether interventions aimed at the prevention of sleep curtailment may improve glycemic control, as well as other health outcomes.

Funding. This study is supported by Fonds Psychische Gezondheid/MIND and Diabetes Fonds Nederland.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. A.B. conceived of the research question addressed, performed analyses, and drafted the manuscript. D.H.v.R. and F.R. helped with recruitment of participants. F.R. coordinated practical research assistance. F.J.S. and A.T.F.B. helped conceive of the study and participated in the study design. M.A.B. conceived of the study, set up the study design, and coordinated the study and is the principal investigator of this study. A.B., D.H.v.R., F.R., P.J.M.E., F.J.S., A.T.F.B., and M.A.B. contributed to the interpretation of the results and helped to draft the manuscript. A.B. and M.A.B. are the guarantors of this work and, as such, had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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