

ORIGINAL RESEARCH

Sleep Characteristics and Measures of Glucose Metabolism in Blacks: The Jackson Heart Study

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BACKGROUND: Characterizing associations of sleep characteristics with blood-glucose-level factors among blacks may clarify the underlying mechanisms of impaired glucose metabolism and help identify treatment targets to prevent diabetes mellitus in blacks.

METHODS AND RESULTS: Cross-sectional analyses were conducted in 789 blacks who completed home sleep apnea testing and 7-day wrist actigraphy in 2012–2016. Sleep-disordered breathing measurements included respiratory event index associated with 4% oxygen desaturation and minimum oxygen saturation. Sleep patterns on actigraphy included fragmented sleep indices. Associations between sleep characteristics (8 exposures) and measures of glucose metabolism (3 outcomes) were determined using multivariable linear regression. Mean (SD) age of the participants was 63 (11) years; 581 (74%) were women; 198 (25%) were diabetes mellitus, and 158 (20%) were taking antihyperglycemic medication. After multivariable adjustment, including antihyperglycemic medication use, the betas (95% CI) for fasting glucose and hemoglobin A1c, respectively, for each SD higher level were 0.13 (0.02, 0.24) mmol/L and 1.11 (0.42, 1.79) mmol/mol for respiratory event index associated with 4% oxygen desaturation and 0.16 (0.05, 0.27) mmol/L and 0.77 (0.10, 1.43) mmol/mol for fragmented sleep indices. Among 589 participants without diabetes mellitus, the betas (95% CI) for homeostatic model assessment of insulin resistance for each SD higher level were 1.09 (1.03, 1.16) for respiratory event index associated with 4% oxygen desaturation, 0.90 (0.85, 0.96) for minimum oxygen saturation, and 1.07 (1.01, 1.13) for fragmented sleep indices.

CONCLUSIONS: Sleep-disordered breathing, overnight hypoxemia, and sleep fragmentation were associated with higher blood glucose levels among blacks.

Key Words: blacks ■ glucose metabolism ■ sleep

Blacks have a higher prevalence of insulin resistance and type 2 diabetes mellitus than whites.^{1,2} Over a lifetime, black men are 1.5 times more likely than white men, and black women are 2 times more likely than white women, to develop diabetes mellitus.³ Characterizing factors associated with impaired glucose metabolism among blacks may clarify underlying mechanisms of impaired glucose metabolism and help

identify treatment targets to prevent diabetes mellitus in blacks.

Disrupted sleep, including measurements of sleep-disordered breathing (SDB) and sleep duration and continuity, are associated with blood glucose levels.^{4–8} For example, short sleep (<5 hours per night), long sleep (≥9 hours per night), and obstructive sleep apnea (OSA) are each associated

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CLINICAL PERSPECTIVE

What Is New?

- Adverse sleep characteristics, including sleep-disordered breathing measurements and sleep duration and continuity on actigraphy (sleep fragmentation and variability), were associated with higher blood glucose levels in blacks.

What Are the Clinical Implications?

- Improvement of sleep apnea (eg, continuous positive airway pressure) and sleep patterns (eg, sleep regularity) may improve glycemic control and reduce insulin resistance among blacks.
- Modification of sleep habits may be used as an adjunct treatment to antihyperglycemic therapy for people with diabetes mellitus.

Nonstandard Abbreviations and Acronyms

BMI	Body mass index
JHS	Jackson Heart Study
HbA1c	glycosylated hemoglobin
HOMA1R	homeostatic model assessment of insulin resistance
MinSaO₂	Minimum oxygen saturation
OSA	obstructive sleep apnea
REI	respiratory event index
Sat<90	% sleep time with <90% oxyhemoglobin saturation
SDB	sleep-disordered breathing

with insulin resistance and increased risk for type 2 diabetes mellitus in studies that primarily included Asian and European populations.^{6–8} Sex differences in associations between OSA and impaired glucose metabolism have been reported.^{9–11} However, the results have been inconsistent, potentially because of insufficient assessment of sleep characteristics (eg, snoring and witness of sleep apnea). Given that men are more likely than women to have OSA at an earlier age,¹² cumulative exposure to hypoxemia-related stressors on several organs may be greater in men than in women.

OSA is prevalent in community-dwelling blacks.^{12,13} Studies of children and young adults suggest that OSA may have an earlier onset in blacks than whites, suggesting greater lifelong adverse physiological exposure in blacks.^{14,15} However, few studies have used objective measurements of sleep characteristics to assess their association with blood glucose levels among black men and women. Furthermore, few studies have

assessed associations with multiple measurements of glucose metabolism. Recent data also indicate that night-to-night variability in sleep duration may be associated with abnormalities in glucose homeostasis,¹⁶ but this measurement has not been comprehensively assessed across populations.

Participants in the JHS (Jackson Heart Study) Sleep Study, an exclusively black community-based cohort,^{17,18} conducted objective testing of sleep characteristics concurrently with assessment of blood glucose levels. We utilized these data to assess whether sleep measurements on home sleep apnea tests (ie, respiratory event index [REI] and overnight hypoxemia) and sleep patterns from 7-day actigraphy (ie, sleep duration, sleep maintenance efficiency, night-to-night variability of sleep duration, and sleep fragmentation) are associated with blood glucose levels. As a post hoc analysis, we assessed whether associations between sleep characteristics and glucose levels differed by sex.

METHODS

These data are available to other researchers for purposes of reproducing the results or replicating the procedures by submitting a manuscript proposal to the JHS at jhspub@umc.edu. Data updates for the JHS are also deposited regularly in the National Institutes of Health data repositories, dbGaP and BioLincc.

Study Population

The JHS is a community-based, prospective cohort study designed to identify risk factors for cardiovascular disease among blacks.^{17,18} Between 2000 and 2004, the JHS enrolled 5306 noninstitutionalized blacks aged ≥ 21 years from the tricounty area (Hinds, Madison, and Rankin counties) of the Jackson, Mississippi metropolitan area. This cross-sectional analysis was restricted to 913 JHS participants who completed a sleep study after the third clinical visit (2012–2016). Details of the sleep exam were reported previously.¹⁸ We excluded participants who were using continuous positive airway pressure machines and participants who had invalid sleep apnea test data (<3 hours of data from the oximeter, nasal pressure sensor, and ≥ 1 respiratory bands) or invalid measures of glucose metabolism. The institutional review boards of the University of Mississippi Medical Center and Partners Research Committee approved the JHS Sleep Study protocol. All participants provided written informed consent.

Sleep Measurements Obtained From Sleep Apnea Testing

SDB measurements were assessed with a validated type 3 home sleep apnea testing device

(Embletta-Gold device; Embla, Broomfield, CO) that recorded: nasal pressure (measuring airflow); thoracic and abdominal inductance plethysmography; finger pulse oximetry; body position; and ECG.^{19,20} Sleep time was estimated using a previously reported method.²¹ In brief, sleep onset was identified based on reduction of movement artifact, heart rate, and assumption of rhythmic breathing. Sleep offset was identified by the appearance of sustained movement activity and/or increased heart rate. Obstructive apneas were identified when the amplitude (peak to trough) of the nasal pressure signal was flat or nearly flat for >10 seconds and accompanied by respiratory effort on the abdominal or thoracic inductance plethysmography bands.²² Hypopneas were identified if a $\geq 30\%$ reduction of amplitude was visualized in the nasal pressure signal or, if unclear, in the respiratory inductance bands for ≥ 10 seconds. The desaturation associated with respiratory events was based on the nadir desaturation after termination of the event (20–45 seconds). The REI was derived as the sum of all apneas plus hypopneas associated with 4% oxygen desaturation (REI4P) or 3% oxygen desaturation (REI3P) divided by the estimated sleep time.²¹ Nocturnal hypoxemia was quantified as % sleep time with $<90\%$ oxyhemoglobin saturation (Sat <90). Minimum oxygen saturation (MinSaO₂) was defined as the lowest arterial oxygen saturation recorded during the study period. In the primary analysis, each SDB index was evaluated as a continuous variable. In secondary analyses, REI was analyzed as a categorical variable defined as REI <5 (unaffected OSA); REI ≥ 5 and <15 (mild OSA); REI ≥ 15 and <30 (moderate OSA); or REI ≥ 30 (severe OSA), reflecting clinical definitions of disease severity. Sat <90 was also analyzed as a categorical variable defined as Sat <90 $<5\%$ and Sat <90 of $\geq 5\%$.

Sleep Duration and Continuity Measures Obtained From 7-Day Wrist Actigraphy

Participants completed 7-day wrist actigraphy using a GT3X+ Activity Monitor worn on the nondominant wrist for 7 consecutive days along with completing a sleep diary.²³ Participants had an average (SD) of 6.8 (0.6) days of acceptable actigraphy data. Actigraphic data during 60-second epochs were scored as sleep or wake by ActiLife analysis software (version 6.13; ActiGraph Corp., Pensacola, FL), using a validated algorithm (Cole-Kripke).²⁴ Sleep duration and sleep maintenance efficiency (the percentage of time spent asleep after the onset of sleep until final awaking) were averaged over all night. Sleep records were manually annotated by a single trained research assistant who had experience with actigraphy scoring to identify participants' sleep periods using information from the

sleep diary. Records were scored blindly. Intraclass correlation coefficients, assessing scorer reliability, were 0.95 (95% CI, 0.87, 0.98) for sleep efficiency and 0.97 (0.93, 0.99) for sleep duration. The actigraphy used in the study (a GT3X+ Activity Monitor) has been shown to provide an accuracy of 0.81 to 0.86 when compared with polysomnography.²⁵ Night-to-night sleep duration variability was estimated in minutes using the within-person SD of sleep duration from each night, using an average of 7 nights of actigraphy. Fragmented sleep was derived from software from the sum of the movement index (obtained by dividing the number of minutes with ≥ 1 movements by time in bed and multiplying that by 100) and fragmentation index (an index of restlessness during the sleep period expressed as a percentage). Fragmented sleep index was defined as the average of sleep fragmentation index (%) during sleep over 7 days. In the primary analysis, each actigraphy measure was evaluated as a continuous variable. Nonlinear associations between sleep duration and blood glucose levels have been described previously.^{7,26} Therefore, in the secondary analysis, (1) sleep duration was analyzed as a categorical variable. Only 43 participants had short sleep (defined as <5 hours per night); 19 participants had long sleep (defined as ≥ 9 hours per night).⁶ Therefore, sleep duration was analyzed using tertiles; and (2) we conducted restricted cubic spline regression of sleep duration and measures of glucose metabolism. Knots were established at sleep durations of 5, 7, and 9 hours.

Glucose and Other Measurements

Information on age, sex, education level, height, weight, smoking, alcohol use, medication use, and history of diabetes mellitus and cardiovascular disease were obtained from interviewer-administered questionnaires; height, weight, and waist circumference were directly measured; and fasting laboratory values were obtained by venipuncture after an overnight fast, using standardized protocols²⁷ at a research clinic visit conducted. Fasting glucose concentration was measured on a Roche Cobas Integra 400 analyzer (Roche Diagnostics, Indianapolis, IN), using an enzymatic reference method with hexokinase, and insulin concentrations were measured on a Roche Elecsys 2010, using a sandwich immunoassay method. A high-performance liquid chromatography system (Tosoh Corp) was used to measure glycosylated hemoglobin (HbA1c) concentrations. Diabetes mellitus was defined as fasting plasma glucose ≥ 126 mg/d, use of insulin or hypoglycemic medications, or self-reported diabetes mellitus diagnosis, or self-reported use of diabetes mellitus medications. Insulin resistance was estimated using the homeostatic model assessment of insulin resistance (HOMA-IR), calculated as (fasting plasma

glucose [millimoles per liter]×fasting plasma insulin [milliunits per milliliter]/22.5.²⁸ HOMA-IR is influenced by antihyperglycemic medication, and thus we calculated HOMA-IR only for participants without diabetes mellitus. Body mass index (BMI) was calculated in kg/m² using direct measurements of weight and height.

Statistical Analyses

Descriptive statistics are reported as means (SD), medians (interquartile range) for skewed variables, and proportions, where appropriate. Multivariable linear regression was used to assess associations of sleep characteristics (8 exposures) with measures of glucose metabolism (3 outcomes). Sleep characteristics included: REI4P, REI3P, Sat<90, MinSaO₂, sleep duration, sleep maintenance efficiency, sleep duration variability, and fragmented sleep indices. Glucose metabolism measures included: fasting glucose, HbA1c, and HOMA-IR. We conducted 8 primary tests for each measure of glucose metabolism. Statistical significance was defined as $P<0.05$ using 2-sided tests. In order to minimize false-positive rates, we also calculated false discovery rates and analogous q values.²⁹

Results are reported as standardized regression coefficients (betas) for each SD higher level for each sleep measure. For HOMA-IR, exponential betas were calculated, interpreted as a 1-SD increase in each sleep measure would multiply the expected value of HOMA-IR by $\exp(\text{beta})$. Possible violations of the assumptions of multiple linear regression were examined by visual inspection of the distribution of residuals through both histograms and normal probability plots. We further checked for deviations from linearity and homoscedasticity by visually inspecting scatterplots of standardized residuals by standardized predicted values. In addition, we assessed variance inflation factors to examine the possibility of multicollinearity; values >2.5 were considered to indicate collinearity. Standardized regression coefficients were calculated in an unadjusted model, and after adjustment for age, sex, education level, alcohol use, smoking status, BMI (or waist circumference), antihyperglycemic medication use, prevalent diabetes mellitus, statin use, and sleep duration. Antihyperglycemic medication use and prevalent diabetes mellitus were not used in modeling for HOMA-IR. Sleep duration was not used in modeling of sleep duration as an exposure. Covariates were selected a priori because they may be associated with sleep characteristics and measures of glucose metabolism.^{4,5,30} Assuming that missing data for covariates occurred independently of missing measures of glucose metabolism (ie, arbitrary missing patterns), we imputed missing data for covariates (Table S1), using an iterative Markov chain Monte Carlo method with 5 iterations as described by Schafer.^{31,32} We analyzed

each of the imputed data sets and combined the results from 5 regression models.

As a post hoc analysis, we tested for heterogeneity in the association between each sleep measure and measures of glucose metabolism by sex, smoking status (current smoking versus ex- or never-smoking), and BMI (≥ 30 versus <30 kg/m²) with the inclusion of multiplicative interaction terms. We also tested for heterogeneity by prevalent diabetes mellitus, because antihyperglycemic medication use could affect fasting glucose. Stratified analyses were considered when an interaction was observed ($P<0.05$). In a sensitivity analysis, we performed analyses without imputing missing covariates. All statistical analyses were performed with Stata software (version 15.0; StataCorp LP, College Station, TX).

RESULTS

Of the 913 participants, we excluded 8 who reported continuous positive airway pressure use, 59 who did not have a valid in-home sleep study, and 57 who had missing study values for sleep measures obtained from sleep apnea testing or actigraphy, or measures of glucose metabolism. A final analytical sample size was 789 participants (mean±SD age, 63±11 years, of whom 581 [66%] were women and 198 [26%] met the criteria for diabetes mellitus; Table 1). Of the 789 participants, 8 had missing data for the third clinical visit characteristics. Therefore, we calculated summary statistics for the third clinical visit characteristics of JHS participants who were included (N=781) and not included (N=3038) in the current analysis (Table S2). Compared with JHS participants not included in the analysis, the sample of included participants were younger and had higher educational attainment. Prevalence of diabetes mellitus and statin use was lower among participants included versus not included in the analysis.

Sleep Characteristics (Continuous Variables) and Measures of Glucose Metabolism

Of the 789 participants, 17 had missing data for HbA1c. In unadjusted models, higher REI3P, REI4P, sleep duration variability, and fragmented sleep indices and lower MinSaO₂ and sleep maintenance efficiency each were significantly associated with higher levels of fasting glucose and HbA1c (Table 2). After multivariable adjustment, higher REI3P, REI4P, and fragmented sleep index each were significantly associated with higher levels of fasting glucose and HbA1c. In analyses for HOMA-IR, we excluded participants with diabetes mellitus. In unadjusted models of 589 participants without diabetes mellitus, a higher REI3P, REI4P, Sat<90, and fragmented sleep indices and lower MinSaO₂ and sleep maintenance

Table 1. Characteristics of JHS Sleep Study Participants (n=789)

Characteristics	Mean±SD, Median±IQR, or Counts (Percentages)
Age, y, mean±SD	63.1±10.7
Women, n (%)	518 (66)
Education, n (%)	
<High school	77 (10)
High school or GED	130 (16)
Some college/training or college degree	582 (74)
BMI, kg/m ² , mean±SD	31.9±6.9
Waist circumference, cm, mean±SD	105.9±16.2
Current smokers, n (%)	65 (8)
Habitual drinkers, n (%)	264 (34)
Fasting glucose, mmol/L, mean±SD	6.0±1.8
HOMA-IR, median (IQR)	2.7±2.4
HbA1c, mmol/mol, mean±SD	44.4±10.9
Diabetes mellitus, n (%)	212 (27)
Statin, n (%)	241 (33)
Antihyperglycemic medication, n (%)	158 (21)
Sleep-disordered breathing measures	
REI4P (events/h), median (IQR)	6.3±11.8
REI3P (events/h), median (IQR)	10.8±15.6
Sat<90, %, median (IQR)	0.35±2.20
MinSaO ₂ , %, median (IQR)	86.0±8.0
Sleep duration and continuity measures	
Sleep duration, h, mean±SD	6.7±1.1
Sleep maintenance efficiency, %, median (IQR)	87.7 (5.9)
Sleep duration variability, min, mean±SD	73.4±33.5
Fragmented sleep indices, %, mean±SD	29.3±8.8

Data are expressed as mean±SD, median (IQR), or counts (percentages). Sleep characteristic measures were obtained using polysomnography, and sleep habits were obtained using 7-day actigraphy. BMI indicates body mass index; GED, general educational development; HbA1c, hemoglobin A1c; HOMA-IR, homeostatic model assessment of insulin resistance; IQR, interquartile range; JHS, Jackson Heart Study; MinSaO₂, minimum oxygen saturation; REI3P, apnea-hypopnea index at 3% oxygen desaturation; REI4P, apnea-hypopnea index at 4% oxygen desaturation; Sat<90, % sleep time with <90% oxyhemoglobin saturation.

efficiency each were significantly associated with higher HOMA-IR. After multivariable adjustment, higher REI3P, REI4P, and fragmented sleep indices and lower MinSaO₂ and sleep maintenance efficiency each were significantly associated with higher HOMA-IR (Table 2). When waist circumference instead of BMI was used as an adjustment, results were unchanged (Tables S3 and S4). We calculated the false discovery rates for each association (Table S5). The analogous *q* values were 0.05 for the associations of REI3P, REI4P, and sleep maintenance efficiency with fasting glucose; of sleep duration variability and fragmented sleep indices with HbA1c; and

of fragmented sleep indices with HOMA-IR. The *q* value was 0.08 for the association of sleep maintenance efficiency with HOMA-IR.

There was evidence of interaction of REI4P and MinSaO₂ with sex in the association with fasting glucose levels (both *P*<0.05: Table S6). In stratified analyses, adjusted beta estimates describing the association of REI4P and MinSaO₂ with fasting glucose were higher in men than in women (Table S7).

There was no evidence of interaction of sleep characteristics with smoking status and BMI (≥30 versus <30 kg/m²) in the associations with measures of glucose metabolism (all *P*>0.09; Tables S8 and S9), except for the interaction of Sat<90 with BMI (≥30 versus <30 kg/m²) in the association with HbA1c (*P*=0.03). In stratified analyses, the adjusted beta (95% CI) for the association between HbA1c and each SD increase in Sat<90 (per 8.03%) was -0.14 (-0.88, 0.62) mmol/L among participants with BMI ≥30 kg/m² and 1.43 (0.25, 2.60) mmol/L among participants with BMI <30 kg/m².

There was evidence of interaction of REI4P, sleep duration variability, and fragmented sleep indices with prevalent diabetes mellitus in the association with fasting glucose and HbA1c (all *P*<0.05: Table S10). In stratified analyses, adjusted beta estimates describing the association of REI4P, sleep duration variability, and fragmented sleep indices with fasting glucose and HbA1c were higher in participants with diabetes mellitus compared with those without diabetes mellitus (Table S11).

Sleep Characteristics (Categorical Variables) and Measures of Glucose Metabolism

Of the 789 participants, 340 (43.1%) had REI4P <5; 263 (33.3%) had REI4P ≥5 and <15, 116 (14.7%) had REI4P ≥15 and <30, and 70 (8.9%) had REI4P ≥30. In unadjusted models, the group with REI4P ≥30 had higher levels of fasting glucose (mean, 0.86; 95% CI, 0.41, 1.31 mmol/L), HbA1c (mean, 6.40; 95% CI, 3.63, 9.18 mmol/mol), and HOMA-IR (mean, 1.54; 95% CI, 1.24, 1.92) compared with their counterparts with REI4P <5 (Table 3). After multivariable adjustment, glucose, HbA1c levels, and HOMA-IR remained higher in the group with REI4P ≥30 compared with those with REI4P <5. Table S12 shows the differences in measures of glucose metabolism across the groups when the groups were defined using REI3P. In Table 3 models, there was evidence of interaction with sex (both *P*<0.05), but not with prevalent diabetes mellitus, in the association of REI4P subgroups with fasting glucose and HbA1c. In stratified analyses, adjusted beta estimates describing the association of REI4P ≥30 (versus REI4P <5)

Table 2. Associations Between Sleep Disturbances and Measures of Glucose Metabolism, JHS Sleep Study, 2012–2016

	Fasting Glucose, mmol/L (n=789)		HbA1c, mmol/mol (n=772)		HOMA-IR (n=576)	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
Sleep-disordered breathing measures						
REI4P (events/h)	0.22 (0.09, 0.34)*	0.13 (0.02, 0.24)†	1.54 (0.78, 2.30)*	1.11 (0.43, 1.78)‡	1.17 (1.11, 1.24)*	1.09 (1.03, 1.16)‡
REI3P (events/h)	0.23 (0.11, 0.35)*	0.13 (0.02, 0.25)†	1.60 (0.85, 2.36)*	1.11 (0.42, 1.79)‡	1.19 (1.12, 1.26)*	1.11 (1.05, 1.18)*
Sat<90, %	0.13 (0.01, 0.26)†	0.07 (−0.03, 0.18)	0.71 (−0.05, 1.47)	0.28 (−0.36, 0.93)	1.12 (1.05, 1.19)*	1.05 (0.99, 1.11)
MinSaO ₂ , %	−0.19 (−0.31, −0.07)†	−0.04 (−0.16, 0.07)	−1.39 (−2.16, −0.63)*	−0.45 (−1.15, 0.25)	0.82 (0.78, 0.87)*	0.90 (0.85, 0.96)‡
Sleep duration and continuity measures						
Sleep duration, h	0.10 (−0.03, 0.22)	0.08 (−0.03, 0.19)	0.08 (−0.70, 0.85)	−0.13 (−0.80, 0.53)	0.98 (0.93, 1.04)	1.02 (0.96, 1.08)
Sleep maintenance efficiency, %	−0.12 (−0.25, −0.00)†	−0.14 (−0.25, −0.02)†	−0.84 (−1.62, −0.06)†	−0.67 (−1.37, 0.04)	0.92 (0.87, 0.98)‡	0.94 (0.89, 1.00)†
Sleep duration variability, min	0.20 (0.08, 0.33)†	0.21 (0.10, 0.31)*	0.87 (0.10, 1.64)†	0.72 (0.08, 1.37)†	1.02 (0.96, 1.08)	0.99 (0.93, 1.04)
Fragmented sleep indices, %	0.18 (0.06, 0.31)†	0.16 (0.05, 0.27)†	0.95 (0.18, 1.72)†	0.77 (0.10, 1.43)†	1.08 (1.01, 1.14)†	1.07 (1.01, 1.13)†

Sleep-disordered breathing measures were obtained through home sleep apnea testing, and sleep duration and continuity measures were obtained using 7-day actigraphy. β=standardized regression coefficient. Adjusted βs (95% CIs) associated with a 1-SD increase in each sleep measure are shown. For HOMA-IR, exponential βs were calculated, interpreted as a 1-SD increase in each sleep measure would multiply the expected value of HOMA-IR by exp(β). The 1-SD increments for each sleep measure are as follows: REI4P, 13.68 events/h; REI3P, 15.89 events/h; Sat <90, 8.03%; MinSaO₂, 6.37%; sleep duration, 1.13 h; sleep efficiency, 4.83%; sleep duration variability, 33.54 min; fragmented sleep indices, 8.75%. Each sleep measure was analyzed in a separate model. Regression coefficients and P values for each multiplicative interaction term are shown. Each sleep measure was analyzed in a separate model. Models include adjustment for age, sex, educational level, alcohol use, smoking status, BMI, antihyperglycemic medication use and prevalent diabetes mellitus, statin use, and sleep duration. Antihyperglycemic medication use and prevalent diabetes mellitus were not used in modeling for HOMA-IR. Sleep duration was not used in modeling of sleep duration as an exposure. BMI indicates body mass index; HbA1c, hemoglobin A1c; HOMA-IR, homeostatic model assessment of insulin resistance; JHS, Jackson Heart Study; MinSaO₂, minimum oxygen saturation; REI3P, apnea-hypopnea index at 3% oxygen desaturation; REI4P, apnea-hypopnea index at 4% oxygen desaturation; Sat<90, % sleep time with <90% oxyhemoglobin saturation.

*P<0.001.

†P<0.05.

‡P<0.01.

Table 3. Differences in Measures of Glucose Metabolism Across REI4P Subgroups: A Multiple Imputation Sample

	Fasting Glucose, mmol/L (n=789)	HbA1c, mmol/mol (n=772)	HOMA-IR (n=576)
	Reference	Reference	Reference
Unadjusted model REI4P <5			
5 ≤REI4P <15	0.21 (−0.07, 0.49)	0.86 (−0.90, 2.61)	1.22 (1.07, 1.39)*
15 ≤REI4P <30	0.29 (−0.08, 0.66)	1.79 (−0.50, 4.08)	1.58 (1.33, 1.88)†
REI4P ≥30	0.86 (0.41, 1.31)‡	6.40 (3.63, 9.18)‡	1.54 (1.24, 1.92)‡
Adjusted model REI4P <5			
5 ≤REI4P <15	0.03 (−0.22, 0.28)	−0.09 (−1.61, 1.43)	1.11 (0.99, 1.26)
15 ≤REI4P <30	0.03 (−0.30, 0.36)	0.20 (−1.77, 2.17)	1.31 (1.11, 1.55)*
REI4P ≥30	0.49 (0.08, 0.90)‡	4.44 (2.02, 6.85)‡	1.30 (1.05, 1.62)‡

Differences in adjusted β s (95% CIs) associated with 5 ≤REI4P <15, 15 ≤REI4P <30, or REI4P ≥30 (vs REI4P <5) are shown. For HOMA-IR, exponential β s were calculated, interpreted as a 1-SD increase in each sleep measure would multiply the expected value of HOMA-IR by $\exp(\beta)$. Of the 789 participants included in analyses for fasting glucose, 340 had REI4P <5, 263 had REI4P ≥5 and <15, 116 had REI4P ≥15 and <30, and 70 had REI4P ≥30. Of the 772 participants included in analyses for HbA1c, 330 had REI4P <5, 257 had REI4P ≥5 and <15, 115 had REI4P ≥15 and <30, and 70 had REI4P ≥30. Of the 589 participants included in analyses for HOMA-IR, 266 had REI4P <5, 187 had REI4P ≥5 and <15, 79 had REI4P ≥15 and <30, and 44 had REI4P ≥30. Regression coefficients and *P* values for each multiplicative interaction term are shown. Each sleep measure was analyzed in a separate model. Models include adjustment for age, sex, educational level, alcohol use, smoking status, BMI, antihyperglycemic medication use and prevalent diabetes mellitus, statin use, and sleep duration. Antihyperglycemic medication use and prevalent diabetes mellitus were not used in modeling for HOMA-IR. BMI indicates body mass index; HbA1c, hemoglobin A1c; HOMA-IR, homeostatic model assessment of insulin resistance; REI3P, apnea-hypopnea index at 3% oxygen desaturation; REI4P, apnea-hypopnea index at 4% oxygen desaturation.

**P*<0.01.

†*P*<0.001.

‡*P*<0.05.

with fasting glucose and HbA1c were higher in men than in women (Table S13).

In analyses using Sat<90 as a categorical variable, HbA1c was higher in participants with Sat<90 of ≥5% compared with those with Sat<90 of <5% (Table S14). Similar to REI4P, there was evidence of interaction with sex in the association of the groups defined using Sat<90 of ≥5% (versus <5%) with fasting glucose (*P*=0.01). In stratified analyses, adjusted beta estimates describing the association of Sat<90 of ≥5% (versus <5%) with fasting glucose and HbA1c were higher in men than women (Table S15). No significant differences in fasting glucose, HbA1c, and HOMA-IR were present across tertiles of sleep duration (Table S16), with no interaction by sex or prevalent diabetes mellitus (each *P*>0.25). Restricted cubic spline curves showed no association of sleep duration with fasting glucose, HbA1c, and HOMA-IR (Figure S1).

Sensitivity Analyses

Table S17 shows results without imputed missing covariates. Results with and without imputed missing covariates were similar in terms of the point estimate for measures of glucose metabolism for each sleep measure.

DISCUSSION

In this community-based study of blacks, higher REI and fragmented sleep indices were significantly associated with higher levels of fasting glucose and HbA1c

after multivariable adjustment. This suggests that SDB and fragmented sleep are associated with abnormal glucose metabolism in blacks. Moreover, the significant associations of higher REI and fragmented sleep indices and lower MinSaO₂ and sleep maintenance efficiency with higher HOMA-IR among individuals without diabetes mellitus suggest that disturbed sleep and hypoxia during sleep were associated with increased insulin resistance. There was evidence of differences in the strength of the associations of several sleep characteristics with measures of glucose metabolism by sex and diabetes mellitus status. Notably, the associations of REI and MinSaO₂ with fasting glucose levels were stronger in men than women. The associations of REI, sleep duration variability, and sleep fragmentation with fasting glucose or HbA1c levels were stronger in participants with diabetes mellitus compared with those without diabetes mellitus. The association of Sat<90 with HbA1c was stronger among participants with BMI <30 kg/m² compared with those with BMI ≥30 kg/m². Overall, our data suggest that multiple aspects of disturbed sleep, including SDB, sleep fragmentation, and sleep duration variability, are adversely associated with glucose metabolism in community-dwelling blacks.

In the MESA (Multi-Ethnic Study of Atherosclerosis), a prospective, population-based cohort, including white, black, Hispanic, and Chinese participants, blacks had an ≈2-fold higher likelihood of OSA, defined as REI4P ≥5 events per hour plus daytime sleepiness, compared with whites (13% versus 7%).¹³ In the MESA, blacks with moderate-to-severe OSA (REI4P ≥15) had a higher likelihood of having glucose abnormalities,

defined as fasting glucose levels ≥ 100 mg/dL or antihyperglycemic medication use, compared with their counterparts with REI4P < 5 (odds ratio, 1.69; 95% CI, 1.05–2.72).⁸ In a more recent analysis from the MESA, participants without diabetes mellitus who also had severe OSA (REI4P ≥ 30) had higher HbA1c compared with their counterparts with REI4P < 5 (5.75% versus 5.67%), but the HbA1c differences between the groups with severe OSA and with REI4P < 5 were not observed among participants with diabetes mellitus.¹⁶ However, blacks comprised $< 30\%$ of the MESA cohort (560 blacks), which might preclude robust assessments of associations within blacks. In addition, sleep and measures of glucose metabolism were measured approximately a year apart in the MESA, which might reduce the strength of the associations between sleep characteristics and measures of glucose metabolism. The present study advanced this earlier work by focusing on a large sample of well-characterized blacks, showing that: (1) Associations of REI with fasting glucose or HbA1c levels were present in blacks; (2) those associations were stronger in men than women and in participants with diabetes mellitus compared with those without diabetes mellitus; (3) associations with abnormal glucose metabolism were stronger for measurements that utilize REI indices that capture higher levels of oxyhemoglobin desaturation; and (4) higher REI was associated with insulin resistance among participants without diabetes mellitus.

Sex differences in cardiovascular outcomes (including hypertension and cardiovascular disease) that are associated with adverse sleep measurements have been inconsistent.^{33–35} These inconsistencies may be attributable to differences in study population characteristics, including age, medication, and comorbidities. However, little is known about whether associations between sleep characteristics and glucose metabolism differ by sex. A study using objective polysomnographic evaluation suggested that among people without diabetes mellitus ($n=145$; 70% blacks), men with OSA were more likely than women with OSA to have greater insulin resistance and more impaired beta-cell function during the oral glucose tolerance test.⁹ In the current study, associations of higher REI, lower MinSaO_2 , and longer sleep time at low oxygen saturation ($\text{Sat} < 90$ of $\geq 5\%$) with higher fasting glucose and HbA1c were stronger in men than women. Stronger associations in men may reflect differences in duration of untreated OSA, given that OSA appears at younger ages in men than in women,¹² potentially contributing to a longer cumulative duration of exposure to hypoxemia-related stressors that adversely affect pancreatic beta-cell function and peripheral insulin sensitivity. It is also possible that physiological responses to hypoxia during sleep (eg, neurohumoral factors, inflammation, and oxidative stress) differ by

sex. However, given the secondary nature of the interaction analyses, our results require further testing in an independent cohort to determine whether associations between sleep characteristics and glucose metabolism differ by sex.

Using multiday actigraphy data, we quantified 2 measures of disturbed sleep continuity: sleep maintenance efficiency (the proportion of the sleep period consisting of sleep) and the sleep fragmentation index (the percentage of brief bouts of sleep during the sleep period). A low sleep efficiency may reflect multiple periods of brief awakenings or fewer periods of prolonged awakening. Etiologies for each form of sleep disturbance may vary, with multiple shorter periods of awakenings likely reflecting repetitive arousals from sleep attributed to respiratory events, periodic limb movements, environmental disturbances, or spontaneously. Our data suggest that a higher sleep fragmentation index and lower sleep maintenance efficiency were associated with higher levels of fasting glucose and HOMA-IR, and these indices may be a target for intervention studies aimed at improving sleep health in blacks. In healthy adults, fragmented sleep was associated with impaired glucose metabolism through alternating sensitivity of peripheral tissue to insulin.³⁶ Experimental disturbance of sleep also results in release of cortisol, systemic inflammation, and surges in blood pressure.^{36–38} Our data suggest that sleep fragmentation was associated with all measures of glucose metabolism, with evidence of stronger associations among participants with diabetes mellitus compared with those without diabetes mellitus. Further investigation is needed to determine whether different triggers for arousal differ in their impact on metabolic health and identify strategies for improving sleep disturbances in individuals with diabetes mellitus.

In this cross-sectional study, greater sleep duration variability was associated with higher fasting glucose and HbA1c, and the associations were stronger in participants with diabetes mellitus compared with those without diabetes mellitus. Although average sleep duration has been a focus of most epidemiological studies of sleep and metabolic health, emerging data suggest that sleep duration variability is also associated with adverse cardiovascular and metabolic outcomes.^{39,40} Greater sleep duration variability correlates with increased consumption of high-calorie food.⁴¹ Variability in sleep duration also may result in circadian misalignment and metabolic dysfunction. Consistent with a report in the MESA,¹⁶ we found that increased sleep duration variability was associated with poorer glycemic control (higher HbA1C concentration) in participants with diabetes mellitus, but not in those without diabetes mellitus. These data suggest potential benefit from interventions that aim to improve sleep schedule consistency, such

as sleep hygiene, among participants with diabetes mellitus. Furthermore, the MESA and JHS studies both suggest that individuals with diabetes mellitus and variable sleep schedule have poor glucose control. This suggests that the effects of mild circadian misalignment, which may occur with variable sleep patterns, may be harmful in individuals with diabetes mellitus.

Strengths of this study include the well-characterized, community-based cohort of blacks and the use of standardized data collection protocols in the JHS Sleep Study. Furthermore, the JHS Sleep Study is one of the few community-based studies that has a comprehensive set of anthropometric, physiological, and sleep measurements collected concurrently. However, there are several limitations to the current analysis. Because the findings are based on a cross-sectional analysis, we are unable to determine the causal relationships of the associations observed. Possible residual confounding, including physical activity, diets (eg, fat intake and processed foods), occupation types, family environment, and weekday-weekend variation, may be affecting the associations between sleep characteristics and measures of glucose metabolism.^{42–44} Only a subset of JHS participants underwent sleep assessments, and participants who underwent sleep assessments differed from those who did not undergo the procedure. Use of a type 3 sleep apnea monitor precluded assessment of sleep stages; furthermore, these devices may underestimate REI by 10% to 15%.⁴⁵ However, we edited sleep time using a validated approach that minimizes misclassification.²¹ Direct measurements of EEG arousal and limb movements were unavailable. An additional limitation is that antihyperglycemic medication use can affect the association between sleep measurements and measures of glucose metabolism. We thus provided results stratified by prevalent diabetes mellitus. Our analyses were not hypothesis free, that is, this study was executed based on earlier studies that illustrated the associations of sleep characteristics with measures of glucose metabolism.^{6–8} However, multiple testing problems might occur. Therefore, we calculated false discovery rates; the probability of having ≥ 1 false positives was $\leq 5\%$ for most reported associations, other than for sleep maintenance efficiency and HOMA-IR, where the false-positive rate was 8%. Finally, blacks were recruited from a single site in the United States. Therefore, participants in this study might not be representative of the general US population of blacks.

CONCLUSIONS

In the current study, adverse sleep characteristics, including SDB measurements and sleep duration and

continuity on actigraphy (sleep fragmentation and variability), were associated with higher blood glucose levels in blacks. Further studies are needed to determine whether improvement of sleep apnea (eg, continuous positive airway pressure) and sleep patterns (eg, sleep regularity) could improve glycemic control and reduce insulin resistance, and whether modification of sleep habits could be used as an adjunct treatment to antihyperglycemic therapy for people with diabetes mellitus.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Materials

Tables S1–S17

Figure S1

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Supplemental Material

Table S1. The observation number of imputed covariates.

Total number after imputing missing covariates	n=789
	Number of imputed observations for each variable
Age, years	n=0
Women, n (%)	n=0
Education, n (%)	n=0
BMI, kg/m ²	n=6
Waist circumference, cm	n=10
Current smokers, n (%)	n=6
Habitual drinkers, n (%)	n=10
Measures of glucose metabolism	
Fasting glucose, mmol/l	n=0
HOMA-IR,	n=0
HbA1c, mmol/mol	n=0
History of diabetes	n=18
Statin	n=54
Antihyperglycemic medication	n=55
Sleep disordered breathing measures	
REI4P (events/hour)	n=0
REI3P (events/hour)	n=0
Sat<90, %	n=0
MinSaO ₂ , %	n=0
Sleep duration and continuity measures	
Sleep duration, hours	n=0
Sleep maintenance efficiency, %	n=0
Sleep duration variability, minutes	n=0
Fragmented sleep indices, %	n=0

BMI=body mass index; HOMA-IR= homeostatic model assessment of insulin resistance; HbA1c= hemoglobin A1c; REI4P= apnea-hypopnea index at 4% oxygen desaturation; REI3P= apnea-hypopnea index at 3% oxygen desaturation; Sat<90, % sleep time with <90% oxyhemoglobin saturation; MinSaO₂=minimum oxygen saturation.

Table S2. Characteristics at the third clinical visit (2012-2016) of JHS participants who were included in the current study and those who were not included.

Characteristics at the third clinical visit	Means \pm SD or counts (percentages)		P value
	Sleep Exam (n=781)	JHS Exam 3 participants (n=3,038)	
Age, years, mean \pm SD	59.84 (10.31)	63.13 (12.43)	<0.001
Women, n (%)	513 (66%)	1924 (63%)	0.222
Education, n (%)			<0.001
< High school	76 (10%)	584 (19%)	
High school or GED	130 (17%)	539 (18%)	
Some college/training, or college degree	575 (74%)	1910 (63%)	
BMI, kg/m ² , mean \pm SD	31.94 (6.58)	32.18 (7.40)	0.598
Waist circumference, cm, mean \pm SD	102.48 (14.69)	103.55 (16.34)	0.185
Current smokers, n (%)	79 (10%)	354 (12%)	0.228
Habitual drinkers, n (%)	367 (47%)	1310 (43%)	0.057
Fasting glucose, mmol/l, median (IQR)	5.39 \pm 0.89	5.39 \pm 1.06	0.132
HOMA-IR, median (IQR)	2.48 \pm 2.16	2.44 \pm 2.20	0.314
HbA1c, mmol/mol, median (IQR)	40.99 \pm 6.56	40.99 \pm 8.74	0.001
Diabetes, n (%)	189 (24%)	1006 (33%)	<0.001
Statin use, n (%)	264 (36%)	1193 (41%)	0.006
Insulin or hypoglycemic medication use, n (%)	145 (20%)	777 (27%)	<0.001

Data are expressed as mean (standard deviation) or percentage. P values were calculated by Kruskal–Wallis test or chi-square test. GED= general educational development; BMI=body mass index; HOMA-IR= homeostatic model assessment of insulin resistance; HbA1c= hemoglobin A1c.

Table S3. Associations between sleep disturbances and measures of glucose metabolism, JHS Sleep Study, 2012-2016.

	Fasting glucose, mmol/l (n=789)		HbA1c, mmol/mol (n=772)		HOMA-IR (n=576)	
	Adjusted for body mass index	Adjusted for waist circumference	Adjusted for body mass index	Adjusted for waist circumference	Adjusted for body mass index	Adjusted for waist circumference
Sleep disordered breathing measures						
REI4P (events/hour)	0.13 (0.02,0.24)*	0.12 (0.00,0.23)*	1.11 (0.43,1.78)†	1.07 (0.41,1.74)†	1.09 (1.03,1.16)†	1.09 (1.03,1.15) †
REI3P (events/hour)	0.13 (0.02,0.25)*	0.12 (0.00,0.23)*	1.11 (0.42,1.79)†	1.07 (0.39,1.74)†	1.11 (1.05,1.18)‡	1.10 (1.04,1.17) ‡
Sat<90, %	0.07 (-0.03,0.18)	0.06 (-0.04,0.17)	0.28 (-0.36,0.93)	0.27 (-0.37,0.91)	1.05 (0.99,1.11)	1.04 (0.98,1.10)
MinSaO2, %	-0.04 (-0.16,0.07)	-0.03 (-0.14,0.08)	-0.45 (-1.15,0.25)	-0.43 (-1.11,0.25)	0.90 (0.85,0.96)†	0.90 (0.85,0.96) ‡
Sleep duration and continuity measures						
Sleep duration, hours	0.08 (-0.03,0.19)	0.09 (-0.02,0.20)	-0.13 (-0.80,0.53)	-0.08 (-0.75,0.59)	1.02 (0.97,1.08)	1.02 (0.97,1.08)
Sleep maintenance efficiency, %	-0.14 (-0.25,-0.02)*	-0.14 (-0.25,-0.02)*	-0.67 (-1.37,0.04)	-0.68 (-1.38,0.03)	0.94 (0.89,1.00)*	0.94 (0.88,0.99)*
Sleep duration variability, mins	0.21 (0.10,0.31)‡	0.21 (0.11,0.32)‡	0.72 (0.08,1.37)*	0.73 (0.09,1.37)	0.99 (0.93,1.04)	1.00 (0.94,1.05)
Fragmented sleep indices, %	0.16 (0.05,0.27)†	0.15 (0.04,0.26)†	0.77 (0.10,1.43)*	0.75 (0.09,1.41)	1.07 (1.01,1.13)*	1.06 (1.01,1.12)*

Sleep disordered breathing measures were obtained through home sleep apnea testing, and sleep duration and continuity measures were obtained using 7-day actigraphy. β = standardized regression coefficient. Adjusted β s (95% CIs) associated with a one-SD increase in each sleep measure are shown. For HOMA-IR, exponential β s were calculated, interpreted as a one-SD increase in each sleep measure would multiplies the expected value of HOMA-IR by $\exp(\beta)$. The one-SD increments for each sleep measure are as follows: REI4P, 13.68 events/hour; REI3P, 15.89 events/hour; Sat<90, 8.03%; MinSaO2, 6.37%; sleep duration, 1.13 hours; sleep efficiency, 4.83%; sleep duration variability, 33.54 mins; fragmented sleep indices, 8.75%. Each sleep measure was analyzed in a separate model. Models include adjustment for age, sex, educational level, alcohol use, smoking status, BMI (or waist circumference), antihyperglycemic medication use and prevalent diabetes, statin use, and sleep duration. Antihyperglycemic medication use and prevalent diabetes were not used in modeling for HOMA-IR. Sleep duration was not used in modeling of sleep duration as an exposure. * $P<0.05$; † $P<0.01$; ‡ $P<0.001$. HOMA-IR = homeostatic model assessment of insulin resistance; HbA1c = hemoglobin A1c; REI4P = apnea-hypopnea index at 4% oxygen desaturation; REI3P = apnea-hypopnea index at 3% oxygen desaturation; Sat<90, % = sleep time with <90% oxyhemoglobin saturation; MinSaO2 = minimum oxygen saturation.

Table S4. Differences in measures of glucose metabolism across REI4P subgroups: a multiple imputation sample.

	Fasting glucose, mmol/l (n=789)		HbA1c, mmol/mol (n=772)		HOMA-IR (n=576)	
	Adjusted for body mass index	Adjusted for waist circumference	Adjusted for body mass index	Adjusted for waist circumference	Adjusted for body mass index	Adjusted for waist circumference
Adjusted model REI4P < 5	Reference	Reference	Reference	Reference	Reference	Reference
5 ≤ REI4P < 15	0.03 (-0.22,0.28)	0.02 (-0.23,0.26)	-0.09 (-1.61,1.43)	-0.10 (-1.58,1.37)	1.11 (0.99,1.26)	1.15 (1.01,1.29)*
15 ≤ REI4P < 30	0.03 (-0.30,0.36)	0.00 (-0.32,0.33)	0.20 (-1.77,2.17)	0.11 (-1.83,2.06)	1.31 (1.11,1.55)†	1.32 (1.12,1.56)‡
REI4P ≥ 30	0.49 (0.08,0.90)*	0.47 (0.06,0.87)*	4.44 (2.02,6.85)‡	4.44 (2.04,6.83)‡	1.30 (1.05,1.62)*	1.27 (1.04,1.59)*

Differences in adjusted β s (95% CIs) associated with $5 \leq \text{REI4P} < 15$, $15 \leq \text{REI4P} < 30$, or $\text{REI4P} \geq 30$ (vs. $\text{REI4P} < 5$) are shown. For HOMA-IR, exponential β s were calculated, interpreted as a one-SD increase in each sleep measure would multiplies the expected value of HOMA-IR by $\exp(\beta)$. Of the 789 participants in analyses for fasting glucose, 340 had $\text{REI4P} < 5$, 263 had $\text{REI4P} \geq 5$ and < 15 , 116 had $\text{REI4P} \geq 15$ and < 30 , and 70 had $\text{REI4P} \geq 30$. Of the 772 participants in analyses for HbA1c, 330 had $\text{REI4P} < 5$; 257 had $\text{REI4P} \geq 5$ and < 15 , 115 had $\text{REI4P} \geq 15$ and < 30 , and 70 had $\text{REI4P} \geq 30$. Of the 576 participants in analyses for HOMA-IR, 266 had $\text{REI4P} < 5$; 187 had $\text{REI4P} \geq 5$ and < 15 , 79 had $\text{REI4P} \geq 15$ and < 30 , and 44 had $\text{REI4P} \geq 30$. Models include adjustment for age, sex, educational level, alcohol use, smoking status, BMI (or waist circumference), antihyperglycemic medication use and prevalent diabetes, statin use, and sleep duration. Antihyperglycemic medication use and prevalent diabetes were not used in modeling for HOMA-IR. * $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$. HOMA-IR = homeostatic model assessment of insulin resistance; HbA1c = hemoglobin A1c; REI4P = apnea-hypopnea index at 4% oxygen desaturation.

Table S5. Associations between sleep disturbances and measures of glucose metabolism, JHS Sleep Study, 2012-2016.

	Fasting glucose, mmol/l (n=789)			HbA1c, mmol/mol (n=772)			HOMA-IR (n=576)		
	Adjusted	p values	q values	Adjusted	p values	q values	Adjusted	p values	q values
Sleep disordered breathing measures									
REI4P (events/hour)	0.13 (0.02,0.24)	0.03	0.05	1.11 (0.43,1.78)	0.001	0.008	1.09 (1.03,1.16)	0.003	0.01
REI3P (events/hour)	0.13 (0.02,0.25)	0.03	0.05	1.11 (0.42,1.79)	0.002	0.008	1.11 (1.05,1.18)	0.001	0.01
Sat<90, %	0.07 (-0.03,0.18)	0.18	0.26	0.28 (-0.36,0.93)	0.38	0.48	1.05 (0.99,1.11)	0.11	0.17
MinSaO2, %	-0.04 (-0.16,0.07)	0.48	0.57	-0.45 (-1.15,0.25)	0.20	0.27	0.90 (0.85,0.96)	0.001	0.01
Sleep duration and continuity measures									
Sleep duration, hours	0.08 (-0.03,0.19)	0.16	0.23	-0.13 (-0.80,0.53)	0.69	0.69	1.02 (0.96,1.08)	0.52	0.57
Sleep maintenance efficiency, %	-0.14 (-0.25,-0.02)	0.02	0.05	-0.67 (-1.37,0.04)	0.06	0.10	0.94 (0.89,1.00)	0.045	0.08
Sleep duration variability, mins	0.21 (0.10,0.31)	0.0001	0.002	0.72 (0.08,1.37)	0.03	0.05	0.99 (0.93,1.04)	0.61	0.70
Fragmented sleep indices, %	0.16 (0.05,0.27)	0.006	0.02	0.77 (0.10,1.43)	0.02	0.05	1.07 (1.01,1.13)	0.02	0.05

In order to minimize low false positive rates, we calculated false discovery rates and analogous q-values. β = standardized regression coefficient. Adjusted β s (95% CIs) associated with a one-SD increase in each sleep measure are shown. For HOMA-IR, exponential β s were calculated, interpreted as a one-SD increase in each sleep measure would multiplies the expected value of HOMA-IR by $\exp(\beta)$. The one-SD increments for each sleep measure are as follows: REI4P, 13.68 events/hour; REI3P, 15.89 events/hour; Sat<90, 8.03%; MinSaO2, 6.37%; sleep duration, 1.13 hours; sleep efficiency, 4.83%; sleep duration variability, 33.54 mins; fragmented sleep indices, 8.75%. Each sleep measure was analyzed in a separate model. Models include adjustment for age, sex, educational level, alcohol use, smoking status, BMI, antihyperglycemic medication use and prevalent diabetes, statin use, and sleep duration. Antihyperglycemic medication use and prevalent diabetes were not used in modeling for HOMA-

IR. Sleep duration was not used in modeling of sleep duration as an exposure. HOMA-IR = homeostatic model assessment of insulin resistance; HbA1c = hemoglobin A1c; REI4P = apnea-hypopnea index at 4% oxygen desaturation; REI3P = apnea-hypopnea index at 3% oxygen desaturation; Sat<90, % = sleep time with <90% oxyhemoglobin saturation; MinSaO2 = minimum oxygen saturation.

Table S6. Interaction by sex for associations between sleep disturbances and measures of glucose metabolism using multiplicative interaction terms.

	Fasting glucose, mmol/l (n=789)		HbA1c, mmol/mol (n=772)		HOMA-IR (n=576)	
	Regression coefficient for interaction term	P values	Regression coefficient for interaction term	P values	Regression coefficient for interaction term	P values
Sleep disordered breathing measures						
REI4P (events/hour)	0.25 (0.04,0.46)	0.0224	1.77 (0.50,3.04)	0.0063	1.03 (0.93,1.15)	0.5574
REI3P (events/hour)	0.23 (0.01,0.44)	0.0395	1.84 (0.56,3.12)	0.0050	1.04 (0.93,1.16)	0.4996
Sat<90, %	0.05 (-0.16,0.27)	0.6283	0.25 (-1.04,1.55)	0.6999	1.03 (0.91,1.16)	0.6651
MinSaO2, %	-0.26 (-0.48,-0.05)	0.0170	-1.26 (-2.56,0.03)	0.0555	0.95 (0.85,1.06)	0.3493
Sleep duration and continuity measures						
Sleep duration, hours	-0.01 (-0.24,0.21)	0.8973	-0.06 (-1.42,1.30)	0.9258	0.98 (0.87,1.09)	0.6669
Sleep maintenance efficiency, %	-0.19 (-0.40,0.03)	0.0865	-0.57 (-1.90,0.76)	0.4027	1.01 (0.91,1.13)	0.8183
Sleep duration variability, minutes	-0.10 (-0.33,0.12)	0.3670	-0.12 (-1.49,1.25)	0.8647	0.89 (0.79,0.99)	0.0395
Fragmented sleep indices, %	0.06 (-0.15,0.28)	0.5587	0.11 (-1.18,1.40)	0.8704	0.99 (0.89,1.11)	0.9231

Interactions by sex for associations between sleep characteristic measures and measures of glucose metabolism were evaluated with the inclusion of multiplicative interaction terms (i.e., each sleep measure × sex). Regression coefficient and p values for each multiplicative interaction term are shown. Each sleep measure was analyzed in a separate model. Models include adjustment for age, sex, educational level, alcohol use, smoking status, BMI, antihyperglycemic medication use and prevalent diabetes, statin use, and sleep duration. Antihyperglycemic medication use and prevalent diabetes were not used in modeling for HOMA-IR. Sleep duration was not used in modeling of sleep duration as an exposure. Of the 789 participants included in analyses for fasting glucose, 271 were men and 518 were women. Of the 772 participants included in analyses for HbA1c, 265 were men and 507 were women. Of the 576 participants included in analyses for HOMA-IR, 203 were men and 373 were women. HOMA-IR= homeostatic model assessment of insulin resistance; HbA1c= hemoglobin A1c; REI4P= apnea-hypopnea index at 4% oxygen desaturation; REI3P= apnea-hypopnea index at 3% oxygen desaturation; Sat<90, % sleep time with <90% oxyhemoglobin saturation; MinSaO2=minimum oxygen saturation.

Table S7. Associations between sleep disturbances and measures of glucose metabolism by sex in a multiple imputation sample.						
	Fasting glucose, mmol/l		HbA1c, mmol/mol		Log-transformed HOMA-IR	
	Women (n= 518)	Men (n= 271)	Women (n= 507)	Men (n= 265)	Women (n=373)	Men (n=203)
Sleep disordered breathing measures						
REI4P (events/hour)	-0.01 (-0.16,0.15)	0.27 (0.10,0.44)†	0.14 (-0.73,1.01)	2.16 (1.05,3.28)‡	1.10 (1.01,1.20)*	1.06 (0.98,1.15)
REI3P (events/hour)	0.01 (-0.14,0.16)	0.27 (0.09,0.45)†	0.15 (-0.69,0.99)	2.30 (1.11,3.49)‡	1.12 (1.03,1.21)†	1.08 (0.99,1.18)
Sat<90, %	0.06 (-0.07,0.19)	0.09 (-0.11,0.28)	0.25 (-0.48,0.98)	0.33 (-0.93,1.60)	1.05 (0.97,1.13)	1.02 (0.92,1.14)
MinSaO2, %	0.08 (-0.07,0.23)	-0.20 (-0.40,-0.00)*	0.17 (-0.64,0.98)	-1.21 (-2.53,0.11)	0.90 (0.83,0.97)†	0.92 (0.83,1.01)
Sleep duration and continuity measures						
Sleep duration, hours	0.05(-0.07,0.16)	0.11(-0.06,0.29)	-0.24(-0.90,0.42)	-0.06(-1.22,1.10)	1.02(0.96,1.09)	1.00(0.93,1.08)
Sleep maintenance efficiency, %	-0.06 (-0.20,0.08)	-0.26 (-0.46,-0.07)†	-0.41 (-1.20,0.38)	-0.98 (-2.35,0.38)	0.93 (0.86,1.01)	0.96 (0.88,1.05)
Sleep duration variability, minutes	0.27 (0.14,0.39)‡	0.08 (-0.12,0.29)	0.87 (0.17,1.57)*	0.39 (-0.98,1.77)	1.03 (0.96,1.10)	0.91 (0.84,1.00)
Fragmented sleep indices, %	0.12 (-0.02,0.26)	0.20 (0.03,0.38)*	0.64 (-0.16,1.44)	0.82 (-0.34,1.99)	1.08 (1.00,1.17)	1.06 (0.98,1.14)

Sleep disordered breathing measures were obtained through home sleep apnea testing, and sleep duration and continuity measures were obtained using 7-day actigraphy. β = standardized regression coefficient. Adjusted β s (95% CIs) associated with a one-SD increase in each sleep measure are shown. For HOMA-IR, exponential β s were calculated, interpreted as a one-SD increase in each sleep measure would multiplies the expected value of HOMA-IR by $\exp(\beta)$. The one-SD increments for each sleep measure in women are as follows: REI4P, 11.87 events/hour; REI3P, 14.30 events/hour; Sat<90, 7.77 %; MinSaO2, 6.14 %; sleep duration, 1.09 hours; sleep efficiency, 4.68 %; sleep duration variability, 34.23 minutes; fragmented sleep indices, 7.77%. The one-SD increments for each sleep measure in men are as follows: REI4P, 16.01 events/hour; REI3P, 17.81 events/hour; Sat<90, 8.46 %; MinSaO2, 6.72 %; sleep duration, 1.18 hours; sleep maintenance efficiency, 6.38%; sleep duration variability, 32.11 minutes; fragmented sleep indices, 9.93 %. Each sleep measure was analyzed in a separate model. Models include adjustment for age, educational level, alcohol use, smoking status, BMI, antihyperglycemic medication use and prevalent diabetes, statin use, and sleep duration. Antihyperglycemic medication use and prevalent diabetes were not used in modeling for HOMA-IR. Sleep duration was not used in modeling of sleep duration as an exposure. * $P<0.05$; † $P<0.01$; ‡ $P<0.001$. HOMA-IR= homeostatic model assessment of insulin resistance; HbA1c= hemoglobin A1c; REI4P=

apnea-hypopnea index at 4% oxygen desaturation; REI3P= apnea-hypopnea index at 3% oxygen desaturation; Sat<90, % sleep time with <90% oxyhemoglobin saturation; MinSaO2=minimum oxygen saturation.

Table S8. Interaction by body mass index (≥ 30 versus < 30 kg/m²) for associations between sleep disturbances and measures of glucose metabolism using multiplicative interaction terms.

	Fasting glucose, mmol/l (n=789)		HbA1c, mmol/mol (n=772)		HOMA-IR (n=576)	
	Regression coefficient for interaction term	P values	Regression coefficient for interaction term	P values	Regression coefficient for interaction term	P values
Sleep disordered breathing measures						
REI4P (events/hour)	-0.03 (-0.28,0.22)	0.82	0.34 (-1.11,1.78)	0.65	0.93 (0.82,1.05)	0.24
REI3P (events/hour)	-0.03 (-0.28,0.22)	0.81	0.44 (-1.02,1.89)	0.56	0.90 (0.80,1.03)	0.12
Sat<90, %	-0.20 (-0.44,0.03)	0.09	-1.56 (-2.97,-0.16)	0.03	0.92 (0.78,1.07)	0.27
MinSaO ₂ , %	0.12 (-0.12,0.36)	0.31	-0.05 (-1.47,1.38)	0.95	1.06 (0.94,1.20)	0.33
Sleep duration and continuity measures						
Sleep duration, hours	0.16 (-0.06,0.37)	0.15	0.15 (-1.15,1.44)	0.82	0.98 (0.88,1.09)	0.71
Sleep maintenance efficiency, %	0.01 (-0.20,0.23)	0.89	-0.64 (-1.96,0.69)	0.35	0.95 (0.85,1.06)	0.39
Sleep duration variability, minutes	0.04 (-0.17,0.25)	0.72	0.28 (-0.98,1.55)	0.66	0.96 (0.86,1.07)	0.46
Fragmented sleep indices, %	0.03 (-0.19,0.24)	0.82	0.44 (-0.87,1.75)	0.51	1.08 (0.97,1.21)	0.15

Interactions by categorical BMI (≥ 30 versus < 30 kg/m²) for associations between sleep characteristic measures and measures of glucose metabolism were evaluated with the inclusion of multiplicative interaction terms (i.e., each sleep measure \times categorical BMI). Regression coefficients and p values for each multiplicative interaction term are shown. Each sleep measure was analyzed in a separate model. Models include adjustment for age, sex, educational level, alcohol use, smoking status, categorical BMI, antihyperglycemic medication use and prevalent diabetes, statin use, and sleep duration. Antihyperglycemic medication use and prevalent diabetes were not used in modeling for HOMA-IR. Sleep duration was not used in modeling of sleep duration as an exposure. Of the 789 participants included in analyses for fasting glucose, 352 were non-obese and 437 were obese. Of the 772 participants included in analyses for HbA1c, 347 were non-obese and 425 were obese. Of the 576 participants included in analyses for HOMA-IR, 278 were non-obese, and 298 were obese. HOMA-IR = homeostatic model assessment of insulin resistance; HbA1c = hemoglobin A1c; REI4P = apnea-hypopnea index at 4% oxygen desaturation; REI3P= apnea-hypopnea index at 3% oxygen desaturation; Sat<90, % = sleep time with <90% oxyhemoglobin saturation; MinSaO₂ = minimum oxygen saturation.

Table S9. Interaction by smoking status for associations between sleep disturbances and measures of glucose metabolism using multiplicative interaction terms.

	Fasting glucose, mmol/l (n=789)		HbA1c, mmol/mol (n=772)		HOMA-IR (n=576)	
	Regression coefficient for interaction term	P values	Regression coefficient for interaction term	P values	Regression coefficient for interaction term	P values
Sleep disordered breathing measures						
REI4P (events/hour)	-0.03 (-0.34,0.28)	0.86	0.96 (-0.87,2.79)	0.30	1.05 (0.91,1.22)	0.47
REI3P (events/hour)	0.02 (-0.29,0.33)	0.89	1.33 (-0.50,3.15)	0.15	1.05 (0.91,1.22)	0.50
Sat<90, %	0.01 (-0.28,0.29)	0.96	0.41 (-1.30,2.12)	0.64	1.05 (0.92,1.20)	0.44
MinSaO2, %	-0.01 (-0.35,0.33)	0.96	-0.57 (-2.60,1.46)	0.58	0.98 (0.84,1.15)	0.80
Sleep duration and continuity measures						
Sleep duration, hours	-0.01 (-0.35,0.32)	0.94	0.89 (-1.13,2.91)	0.39	0.96 (0.83,1.11)	0.55
Sleep maintenance efficiency, %	-0.05 (-0.35,0.26)	0.76	-0.02 (-1.83,1.80)	0.98	0.96 (0.83,1.11)	0.57
Sleep duration variability, minutes	-0.10 (-0.41,0.21)	0.53	0.24 (-1.63,2.11)	0.80	1.13 (0.97,1.31)	0.12
Fragmented sleep indices, %	0.00 (-0.33,0.34)	0.98	0.06 (-1.93,2.04)	0.95	0.96 (0.82,1.13)	0.61

Interactions by smoking status for the associations between sleep characteristic measures and measures of glucose metabolism were evaluated with the inclusion of multiplicative interaction terms (i.e., each sleep measure × smoking status). Non-current smokers (ex- or never-smokers) were treated as the reference group. Regression coefficients and p values for each multiplicative interaction term are shown. Each sleep measure was analyzed in a separate model. Models include adjustment for age, sex, educational level, alcohol use, smoking status, BMI, antihyperglycemic medication use and prevalent diabetes, statin use, and sleep duration. Antihyperglycemic medication use and prevalent diabetes were not used in modeling for HOMA-IR. Sleep duration was not used in modeling of sleep duration as an exposure. Of the 789 participants included in analyses for fasting glucose, 65 were current smokers and 724 were

non-current smokers. Of the 772 participants included in analyses for HbA1c, 65 were current smokers and 707 were non-current smokers. Of the 576 participants included in analyses for HOMA-IR, 56 were current smokers and 520 were non-current smokers. HOMA-IR = homeostatic model assessment of insulin resistance; HbA1c = hemoglobin A1c; REI4P = apnea-hypopnea index at 4% oxygen desaturation; REI3P = apnea-hypopnea index at 3% oxygen desaturation; Sat<90, % = sleep time with <90% oxyhemoglobin saturation; MinSaO2 = minimum oxygen saturation.

Table S10. Interaction by prevalent diabetes for associations between sleep disturbances and measures of glucose metabolism using multiplicative interaction terms.

	Fasting glucose, mmol/l (n= 773)		HbA1c, mmol/mol (n= 756)	
	Regression coefficient for interaction term	P values	Regression coefficient for interaction term	P values
Sleep disordered breathing measures				
REI4P (events/hour)	0.24 (0.00,0.48)	0.0471	2.38 (0.97,3.78)	0.0009
REI3P (events/hour)	0.19 (-0.04,0.43)	0.1102	1.88 (0.48,3.28)	0.0085
Sat<90, %	0.14 (-0.08,0.36)	0.2038	1.25 (-0.06,2.55)	0.0612
MinSaO2, %	0.01 (-0.22,0.24)	0.9375	-0.40 (-1.76,0.96)	0.5617
Sleep duration and continuity measures				
Sleep duration, hours	0.17 (-0.06,0.41)	0.1513	0.03 (-1.39,1.45)	0.9678
Sleep maintenance efficiency, %	-0.17 (-0.40,0.06)	0.1459	-1.25 (-2.67,0.18)	0.0860
Sleep duration variability, minutes	0.83 (0.60,1.06)	<0.001	3.50 (2.10,4.89)	<0.001
Fragmented sleep indices, %	0.27 (0.03,0.50)	0.0255	1.48 (0.05,2.90)	0.0420

We did not impute missing data for a variable “history of diabetes” in this stratified analysis by a history of diabetes. Therefore, the sample size was reduced. Interactions by prevalent diabetes for associations between sleep characteristic measures and measures of glucose metabolism were evaluated with the inclusion of multiplicative interaction terms (i.e., each sleep measure × prevalent diabetes). Regression coefficient and p values for each multiplicative interaction term are shown. Each sleep measure was analyzed in a separate model. Models include adjustment for age, sex, educational level, alcohol use, smoking status, BMI, antihyperglycemic medication use and prevalent diabetes, statin use, and sleep duration. Sleep duration was not used in modeling of sleep duration as an exposure. Of the 789 participants included in analyses for fasting glucose, 212 were participants with diabetes and 561 were participants without diabetes. Of the 772 participants included in analyses for HbA1c, 207 were participants with diabetes and 549 were participants without diabetes. HbA1c= hemoglobin A1c; REI4P= apnea-hypopnea index at 4% oxygen desaturation; REI3P= apnea-hypopnea index at 3% oxygen desaturation; Sat<90, % sleep time with <90% oxyhemoglobin saturation; MinSaO2=minimum oxygen saturation.

Table S11. Associations between sleep disturbances and measures of glucose metabolism by prevalent diabetes in a multiple imputation sample.

	Fasting glucose, mmol/l		HbA1c, mmol/mol	
	Non-diabetes (n= 561)	Diabetes (n= 212)	Non-diabetes (n=549)	Diabetes (n= 207)
Sleep disordered breathing measures				
REI4P (events/hour)	0.00(-0.00,0.01)	0.03(-0.00,0.06)	0.03(-0.00,0.06)	0.22(0.06,0.39)†
REI3P (events/hour)	0.00(0.00,0.01)*	0.02(-0.00,0.05)	0.03(0.00,0.06)*	0.16(0.02,0.31)*
Sat<90, %	0.00(-0.00,0.01)	0.03(-0.01,0.07)	-0.02(-0.07,0.03)	0.17(-0.06,0.40)
MinSaO2, %	-0.01(-0.01,0.00)	-0.01(-0.07,0.05)	-0.05(-0.12,0.02)	-0.10(-0.44,0.25)
Sleep duration and continuity measures				
Sleep duration, hours	-0.01(-0.05,0.04)	0.23(-0.10,0.57)	-0.35(-0.71,0.01)	0.39(-1.52,2.30)
Sleep maintenance efficiency, %	-0.01(-0.02,-0.00)*	-0.07(-0.15,0.01)	-0.04(-0.12,0.05)	-0.32(-0.80,0.16)
Sleep duration variability, minutes	-0.00(-0.00,0.00)	0.02(0.01,0.03)‡	-0.00(-0.02,0.01)	0.09(0.02,0.15)†
Fragmented sleep indices, %	0.01(0.00,0.01)*	0.05(0.01,0.09)*	0.04(-0.01,0.08)	0.23(-0.03,0.48)

We did not impute missing data for a variable “history of diabetes” in this stratified analysis by a history of diabetes. Therefore, the sample size was reduced. β = standardized regression coefficient. Adjusted β s (95% CIs) associated with a one-SD increase in each sleep measure are shown. The one-SD increments for each sleep measure in the diabetes group are as follows: REI4P, 13.82 events/hour; REI3P, 16.36 events/hour; Sat<90, 9.55%; MinSaO2, 6.91 %; sleep duration, 1.19 hours; sleep efficiency, 5.04 %; sleep duration variability, 34.40 minutes; fragmented sleep indices, 8.96 %. The one-SD increments for each sleep measure in the non-diabetes group are as follows: REI4P, 13.69 events/hour; REI3P, 15.74 events/hour; Sat<90, 7.55 %; MinSaO2, 6.19 %; sleep duration, 1.07 hours; sleep efficiency, 4.78 %; sleep duration variability, 33.37 minutes; fragmented sleep indices, 8.65 %. Each sleep characteristic was analyzed in a separate model. Models include adjustment for age, sex, educational level, alcohol use, smoking status, BMI, antihyperglycemic medication use and prevalent diabetes, statin use, and sleep duration. Sleep duration was not used in modeling of sleep duration as an exposure. * $P<0.05$; † $P<0.01$; ‡ $P<0.001$. HbA1c= hemoglobin A1c; REI4P= apnea-hypopnea index at

4% oxygen desaturation; REI3P= apnea-hypopnea index at 3% oxygen desaturation; Sat<90, % sleep time with <90% oxyhemoglobin saturation;
MinSaO2=minimum oxygen saturation.

Table S12. Differences in measures of glucose metabolism across REI3P subgroups: a multiple imputation sample.

	Fasting glucose, mmol/l (n=789)	HbA1c, mmol/mol (n=772)	HOMA-IR (n=576)
Unadjusted model			
REI3P < 5	Reference	Reference	Reference
5 ≤ REI3P < 15	-0.18 (-0.49,0.14)	-1.69 (-3.67,0.29)	1.24 (1.08,1.43)†
15 ≤ REI3P < 30	0.34 (-0.02,0.69)	0.70 (-1.54,2.95)	1.68 (1.42,1.99)‡
REI3P ≥ 30	0.39 (-0.00,0.79)	3.04 (0.57,5.50)*	1.62 (1.35,1.96)‡
Adjusted model			
REI3P < 5	Reference	Reference	Reference
5 ≤ REI3P < 15	-0.15 (-0.44,0.13)	-1.20 (-2.93,0.53)	1.17 (1.02,1.35)*
15 ≤ REI3P < 30	0.08 (-0.25,0.42)	-0.71 (-2.75,1.33)	1.47 (1.23,1.73)‡
REI3P ≥ 30	0.13 (-0.24,0.51)	1.69 (-0.56,3.94)	1.39 (1.15,1.69)‡

Differences in adjusted β s (95% CIs) associated with $5 \leq \text{REI3P} < 15$, $15 \leq \text{REI3P} < 30$, or $\text{REI3P} \geq 30$ (vs. $\text{REI3P} < 5$) are shown. For HOMA-IR, exponential β s were calculated, interpreted as a one-SD increase in each sleep measure would multiply the expected value of HOMA-IR by $\exp(\beta)$. Of the 789 participants included in analyses for fasting glucose, 192 had $\text{REI3P} < 5$, 301 had $\text{REI3P} \geq 5$ and < 15 , 173 had $\text{REI3P} \geq 15$ and < 30 , and 123 had $\text{REI3P} \geq 30$. Of the 772 participants included in analyses for HbA1c, 185 had $\text{REI3P} < 5$, 295 had $\text{REI3P} \geq 5$ and < 15 , 170 had $\text{REI3P} \geq 15$ and < 30 , and 122 had $\text{REI3P} \geq 30$. Of the 576 participants included in analyses for HOMA-IR, 143 had $\text{REI3P} < 5$, 237 had $\text{REI3P} \geq 5$ and < 15 , 114 had $\text{REI3P} \geq 15$ and < 30 , and 82 had $\text{REI3P} \geq 30$. Models include adjustment for age, sex, educational level, alcohol use, smoking status, BMI, antihyperglycemic medication use and prevalent diabetes, statin use, and sleep duration. Antihyperglycemic medication use and prevalent diabetes were not used in modeling for HOMA-IR. * $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$. HOMA-IR= homeostatic model assessment of insulin resistance; HbA1c= hemoglobin A1c; REI4P= apnea-hypopnea index 4% oxygen desaturation; REI3P= apnea-hypopnea index 3% oxygen desaturation.

Table S13. Differences in measures of glucose metabolism across REI4P subgroups by sex: a multiple imputation sample.

	Fasting glucose, mmol/l (n=789)		HbA1c, mmol/mol (n=772)		HOMA-IR (n=576)	
	Women (n= 518)	Men (n= 271)	Women (n= 507)	Men (n= 265)	Women (n= 373)	Men (n=203)
Unadjusted model						
REI4P < 5	Reference	Reference	Reference	Reference	Reference	Reference
5 ≤ REI4P < 15	0.23 (-0.10,0.57)	0.19 (-0.33,0.71)	1.48 (-0.51,3.47)	0.19 (-3.29,3.68)	1.23 (1.05,1.45)*	1.24 (1.00,1.54)*
15 ≤ REI4P < 30	0.09 (-0.35,0.54)	0.65 (0.01,1.30)*	1.04 (-1.61,3.69)	3.57 (-0.79,7.92)	1.59 (1.28,1.98)‡	1.61 (1.21,2.14)†
REI4P ≥ 30	0.36 (-0.29,1.02)	1.29 (0.62,1.95)‡	3.05 (-0.82,6.92)	9.79 (5.36,14.21)‡	1.55 (1.12,2.17)†	1.65 (1.23,2.23)†
Adjusted model						
REI4P < 5	Reference	Reference	Reference	Reference	Reference	Reference
5 ≤ REI4P < 15	-0.02 (-0.32,0.28)	0.09 (-0.38,0.55)	-0.01 (-1.69,1.67)	-0.63 (-3.69,2.43)	1.14 (0.97,1.33)	1.06 (0.87,1.29)
15 ≤ REI4P < 30	-0.14 (-0.53,0.26)	0.31 (-0.28,0.91)	-0.41 (-2.61,1.79)	0.97 (-2.93,4.87)	1.35(1.09,1.68)†	1.18 (0.90,1.55)
REI4P ≥ 30	0.12 (-0.46,0.70)	0.83 (0.21,1.45)†	1.50 (-1.71,4.70)	6.93 (2.90,10.96)‡	1.29 (0.93,1.79)	1.20 (0.90,1.61)

Differences in adjusted β s (95% CIs) associated with $5 \leq \text{REI4P} < 15$, $15 \leq \text{REI4P} < 30$, or $\text{REI4P} \geq 30$ (vs. $\text{REI4P} < 5$) are shown. For HOMA-IR, exponential β s were calculated, interpreted as a one-SD increase in each sleep measure would multiplies the expected value of HOMA-IR by $\exp(\beta)$. Of the 518 women included in analyses for fasting glucose, 247 had $\text{REI4P} < 5$, 170 had $\text{REI4P} \geq 5$ and < 15 , 72 had $\text{REI4P} \geq 15$ and < 30 , and 29 had $\text{REI4P} \geq 30$. Of the 507 women included in analyses for HbA1c, 241 had $\text{REI4P} < 5$, 165 had $\text{REI4P} \geq 5$ and < 15 , 72 had $\text{REI4P} \geq 15$ and < 30 , and 29 had $\text{REI4P} \geq 30$. Of the 373 women included in analyses for HOMA-IR, 189 had $\text{REI4P} < 5$, 115 had $\text{REI4P} \geq 5$ and < 15 , 50 had $\text{REI4P} \geq 15$ and < 30 , and 19 had $\text{REI4P} \geq 30$. Of the 271 men included in analyses for fasting glucose, 93 had $\text{REI4P} < 5$, 93 had $\text{REI4P} \geq 5$ and < 15 , 44 had $\text{REI4P} \geq 15$ and < 30 , and 41 had $\text{REI4P} \geq 30$. Of the 265 men included in analyses for HbA1c, 89 had $\text{REI4P} < 5$, 92 had $\text{REI4P} \geq 5$ and < 15 , 43 had $\text{REI4P} \geq 15$ and < 30 , and 41 had $\text{REI4P} \geq 30$. Of the 203 men included in analyses for HOMA-IR, 77 had $\text{REI4P} < 5$, 72 had $\text{REI4P} \geq 5$ and < 15 , 29 had $\text{REI4P} \geq 15$ and < 30 , and 25 had $\text{REI4P} \geq 30$. Models include adjustment for age, educational level, alcohol use, smoking status, BMI, antihyperglycemic medication use and prevalent diabetes, statin use, and sleep duration. Antihyperglycemic medication use and prevalent diabetes were not used in modeling for HOMA-IR. * $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$. HOMA-IR= homeostatic model assessment of insulin resistance; HbA1c= hemoglobin A1c; REI4P= apnea-hypopnea index at 4% oxygen desaturation; REI3P= apnea-hypopnea index at 3% oxygen desaturation.

Table S14. Differences in measures of glucose metabolism by Sat<90 in a multiple imputation sample.

	Fasting glucose, mmol/l	HbA1c, mmol/mol	HOMA-IR
Sat<90 less than 5%	Reference	Reference	Reference
Sat<90 5% or more	0.15(-0.18,0.48)	2.03(0.09,3.97)*	1.11(0.93,1.33)

Of the 798 participants included in analyses for fasting glucose, 686 had Sat<90 less than 5% and 103 had Sat<90 5% or more. Of the 772 participants included in analyses for HbA1c, 669 had Sat<90 less than 5% and 103 had Sat<90 5% or more. Of the 576 participants included in analyses for HOMA-IR, 514 had Sat<90 less than 5% and 62 had Sat<90 5% or more. Differences in adjusted β s (95% CIs) by Sat<90 are shown. Models include adjustment for age, sex, educational level, alcohol use, smoking status, BMI, antihyperglycemic medication use and prevalent diabetes, statin use, and sleep duration. Antihyperglycemic medication use and prevalent diabetes were not used in modeling for HOMA-IR. * $P<0.05$; † $P<0.01$; ‡ $P<0.001$. HOMA-IR= homeostatic model assessment of insulin resistance; HbA1c= hemoglobin A1c; Sat<90, % sleep time with <90% oxyhemoglobin saturation.

Table S15. Sex-specific differences in measures of glucose metabolism by Sat<90 in a multiple imputation sample.

	Fasting glucose, mmol/l	HbA1c, mmol/mol	HOMA-IR
Men			
Sat<90 less than 5 %	Reference	Reference	Reference
Sat<90 5% or more	0.63(0.12,1.13)*	4.12(0.79,7.45)*	1.12(0.87,1.43)
Women			
Sat<90 less than 5 %	Reference	Reference	Reference
Sat<90 5% or more	-0.30(-0.74,0.13)	-0.01(-2.41,2.39)	1.06(0.82,1.37)

Of the 271 men included in analyses for fasting glucose, 220 had Sat<90 less than 5% and 51 had Sat<90 5% or more. Of the 518 women included in analyses for fasting glucose, 466 had Sat<90 less than 5% and 52 had Sat<90 5% or more. Of the 265 men included in analyses for HbA1c, 214 had Sat<90 less than 5% and 51 had Sat<90 5% or more. Of the 507 women included in analyses for HbA1c, 455 had Sat<90 less than 5% and 52 had Sat<90 5% or more. Of the 203 men included in analyses for HOMA-IR, 173 had Sat<90 less than 5% and 30 had Sat<90 5% or more. Of the 373 women included in analyses for HOMA-IR, 341 had Sat<90 less than 5% and 32 had Sat<90 5% or more. Differences in adjusted β s (95% CIs) by Sat<90 are shown. For HOMA-IR, exponential β s were calculated, interpreted as a one-SD increase in each sleep measure would multiplies the expected value of HOMA-IR by $\exp(\beta)$. Models include adjustment for age, educational level, alcohol use, smoking status, BMI, antihyperglycemic medication use and prevalent diabetes, statin use, and sleep duration. Antihyperglycemic medication use and prevalent diabetes were not used in modeling for HOMA-IR. * $P<0.05$; † $P<0.01$; ‡ $P<0.001$. HOMA-IR= homeostatic model assessment of insulin resistance; HbA1c= hemoglobin A1c; Sat<90, % sleep time with <90% oxyhemoglobin saturation.

Table S16. Differences in measures of glucose metabolism by tertiles of sleep duration in a multiple imputation sample.

	Fasting glucose, mmol/l	HbA1c, mmol/mol	HOMA-IR
1 st tertile of sleep duration	0.06 (-0.20,0.32)	1.03 (-0.55,2.61)	0.97 (0.86,1.11)
2 nd tertile of sleep duration	Reference	Reference	Reference
3 rd tertile of sleep duration	0.21 (-0.05,0.47)	0.65 (-0.92,2.22)	1.04 (0.91,1.18)

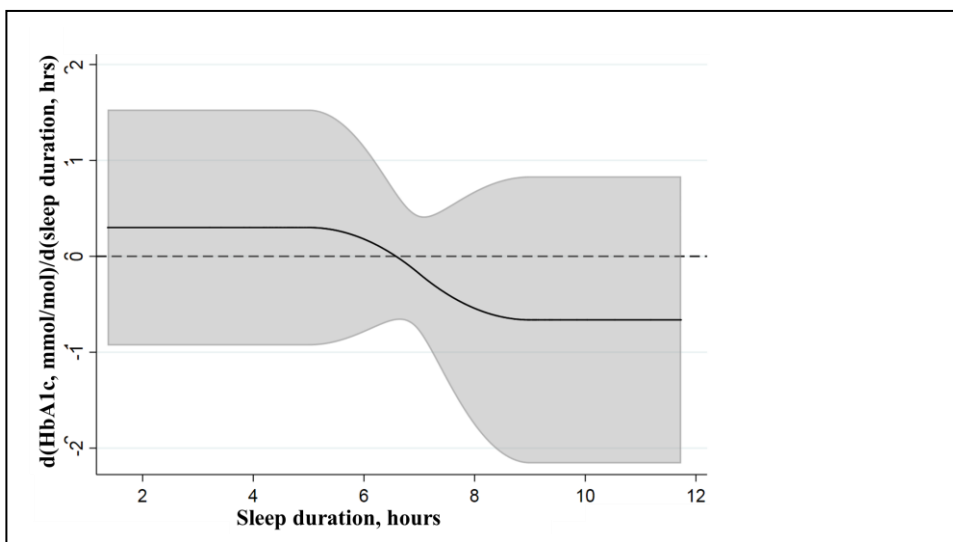
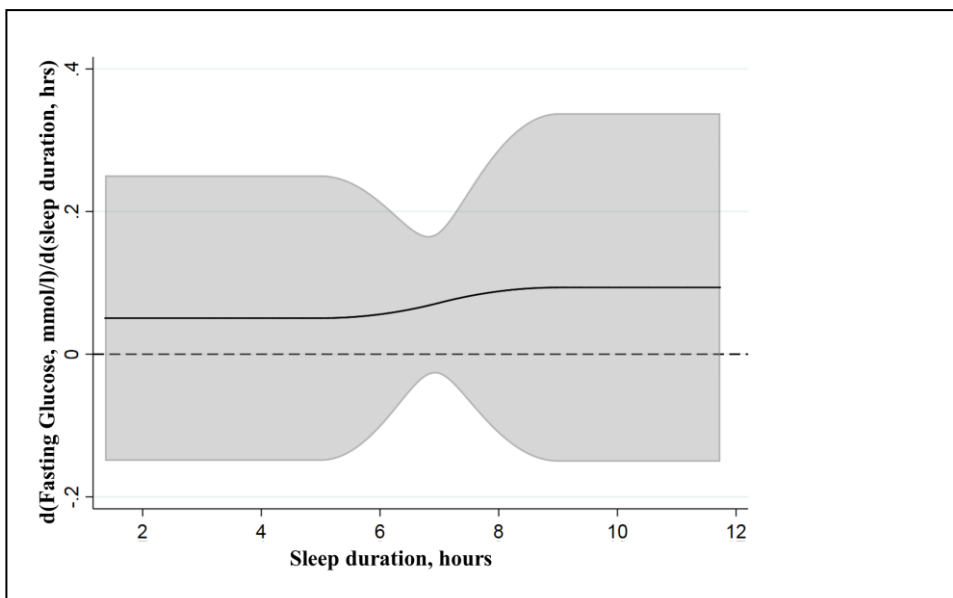
Differences in adjusted β s (95% CIs) by tertiles of sleep duration are shown. For HOMA-IR, exponential β s were calculated, interpreted as a one-SD increase in each sleep measure would multiply the expected value of HOMA-IR by $\exp(\beta)$. The range of sleep duration for each group is as follows: 1st tertile; 1.37-6.2, 2nd tertile; 6.22-7.15; and 3rd tertile, 7.17-11.73 hours per night. Of the 789 participants included in analyses for fasting glucose, 265 were categorized into the 1st tertile group, 263 were categorized into the 2nd tertile group, and 261 were categorized into the 3rd tertile group. Of the 772 participants included in analyses for HbA1c, 259 were categorized into the 1st tertile group, 257 were categorized into the 2nd tertile group, and 256 were categorized into the 3rd tertile group. Of the 576 participants included in analyses for HOMA-IR, 198 were categorized into the 1st tertile group, 197 were categorized into the 2nd tertile group, and 181 were categorized into the 3rd tertile group. Models include adjustment for age, sex, educational level, alcohol use, smoking status, BMI, antihyperglycemic medication use and prevalent diabetes, and statin use. Antihyperglycemic medication use and prevalent diabetes were not used in modeling for HOMA-IR. HOMA-IR= homeostatic model assessment of insulin resistance; HbA1c= hemoglobin A1c.

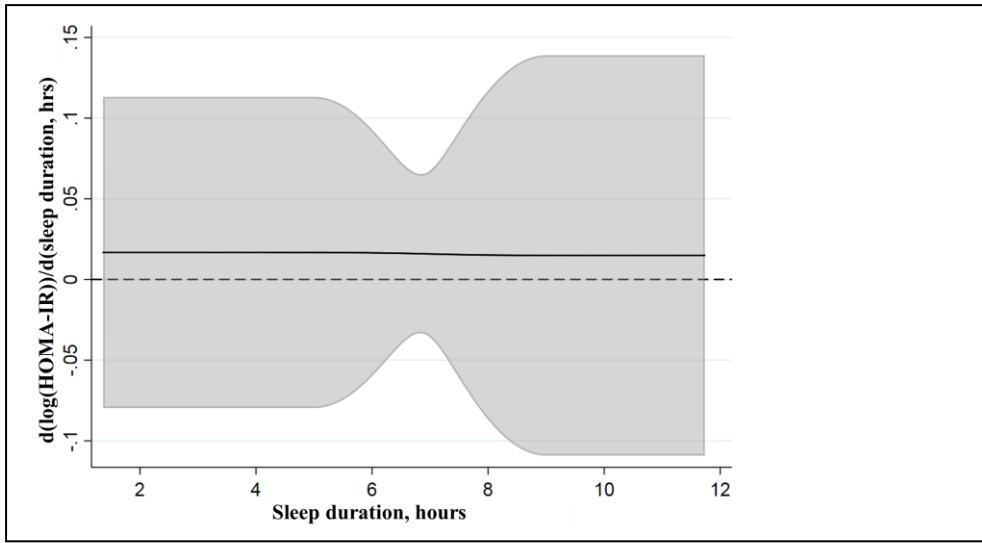
Table S17. Associations between sleep disturbances and measures of glucose metabolism: a complete case analysis.

	Fasting glucose, mmol/l		HbA1c, mmol/mol		HOMA-IR	
	Unadjusted (n=789)	Adjusted (n=714)	Unadjusted (n=772)	Adjusted (n=697)	Unadjusted (n=589)	Adjusted (n=538)
Sleep disordered breathing measures						
REI4P (events/hour)	0.22 (0.09,0.34)‡	0.19 (0.08,0.30)‡	1.54 (0.78,2.30)‡	1.35 (0.70,2.01)‡	1.17 (1.11,1.24)‡	1.10 (1.03,1.17)†
REI3P (events/hour)	0.23 (0.11,0.35)‡	0.20 (0.09,0.31)‡	1.60 (0.85,2.36)‡	1.36 (0.70,2.02)‡	1.19 (1.12,1.26)‡	1.11 (1.05,1.19)†
Sat<90, %	0.13 (0.01,0.26)*	0.09 (-0.01,0.19)	0.71 (-0.05,1.47)	0.45 (-0.15,1.06)	1.12 (1.05,1.19)‡	1.03 (0.97,1.10)
MinSaO2, %	-0.19 (-0.31,-0.07)†	-0.13 (-0.24,-0.02)*	-1.39 (-2.16,-0.63)‡	-0.79 (-1.45,-0.12)*	0.82 (0.78,0.87)‡	0.91 (0.86,0.97)†
Sleep duration and continuity measures						
Sleep duration, hours	0.10 (-0.03,0.22)	0.11 (0.00,0.21)*	0.08 (-0.70,0.85)	0.00 (-0.62,0.62)	0.98 (0.93,1.04)	1.01 (0.95,1.07)
Sleep maintenance efficiency, %	-0.12 (-0.25,-0.00)*	-0.12 (-0.23,-0.02)*	-0.84 (-1.62,-0.06)*	-0.66 (-1.32,-0.00)*	0.92 (0.87,0.98)†	0.96 (0.90,1.01)
Sleep duration variability, minutes	0.20 (0.08,0.33)†	0.23 (0.13,0.32)‡	0.87 (0.10,1.64)*	0.85 (0.26,1.44)†	1.02 (0.96,1.08)	0.98 (0.92,1.03)
Fragmented sleep indices, %	0.18 (0.06,0.31)†	0.16 (0.06,0.27)†	0.95 (0.18,1.72)*	0.89 (0.27,1.51)†	1.08 (1.01,1.14)*	1.08 (1.02,1.14)*

β = standardized regression coefficient. Adjusted β s (95% CIs) associated with a one-SD increase in each sleep measure are shown. For HOMA-IR, exponential β s were calculated, interpreted as a one-SD increase in each sleep measure would multiplies the expected value of HOMA-IR by $\exp(\beta)$. Each sleep measure was analyzed in a separate model. Models include adjustment for age, sex, educational level, alcohol use, smoking status, BMI, antihyperglycemic medication use and prevalent diabetes, statin use, and sleep duration. Antihyperglycemic medication use and prevalent diabetes were not used in modeling for HOMA-IR. Sleep duration was not used in modeling of sleep duration as an exposure. * $P<0.05$; † $P<0.01$; ‡ $P<0.001$. HOMA-IR= homeostatic model assessment of insulin resistance; HbA1c= hemoglobin A1c; REI4P= apnea-hypopnea index at 4% oxygen desaturation; REI3P= apnea-hypopnea index at 3% oxygen desaturation; Sat<90, % sleep time with <90% oxyhemoglobin saturation; MinSaO2=minimum oxygen saturation.

Figure S1. Restricted cubic spline regression of sleep duration and measures of glucose metabolism were shown.





Knots were established at sleep durations of 5, 7, and 9 hours.