Association between Glucose Metabolism and Sleep-disordered Breathing during REM Sleep

Hassan A. Chami^{1,2}, Daniel J. Gottlieb^{3,4}, Susan Redline⁴, and Naresh M. Punjabi⁵

¹Department of Medicine, American University of Beirut, Beirut, Lebanon; ²Department of Medicine, Boston University School of Medicine, Boston, Massachusetts; ³VA Boston Healthcare System, Boston, Massachusetts; ⁴Department of Medicine, Brigham and Women's Hospital and Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts; and ⁵Johns Hopkins University School of Medicine, Baltimore, Maryland

Abstract

Rationale: Sleep-disordered breathing (SDB) has been associated with impaired glucose metabolism. It is possible that the association between SDB and glucose metabolism is distinct for non-REM versus REM sleep because of differences in sleep-state-dependent sympathetic activation and/or degree of hypoxemia.

Objectives: To characterize the association between REM-related SDB, glucose intolerance, and insulin resistance in a community-based sample.

Methods: A cross-sectional analysis that included 3,310 participants from the Sleep Heart Health Study was undertaken (53% female; mean age, 66.1 yr). Full montage home-polysomnography and fasting glucose were available on all participants. SDB severity during REM and non-REM sleep was quantified using the apnea-hypopnea index in REM (AHI_{REM}) and non-REM sleep (AHI_{NREM}), respectively. Fasting and 2-hour post-challenge glucose levels were assessed during a glucose tolerance test (n = 2,264). The homeostatic

model assessment index for insulin resistance (HOMA-IR) was calculated (n = 1,543). Linear regression was used to assess the associations of AHI_{REM} and AHI_{NREM} with fasting and post-prandial glucose levels and HOMA-IR.

Measurements and Main Results: AHI_{REM} and AHI_{NREM} were associated with fasting glycemia, post-prandial glucose levels, and HOMA-IR in models that adjusted for age, sex, race, and site. However, with additional adjustment for body mass index, waist circumference, and sleep duration, AHI_{REM} was only associated with HOMA-IR ($\beta = 0.04$; 95% CI, 0.1–0.07; $P = 0.01$), whereas AHI_{NREM} was only associated with fasting ($\beta = 0.93$; 95% CI, 0.14–1.72; $P = 0.02$) and post-prandial glucose levels ($\beta = 3.0$; 95% CI, 0.5–5.5; $P = 0.02$).

Conclusions: AHI_{REM} is associated with insulin resistance but not with fasting glycemia or glucose intolerance.

Keywords: sleep apnea; REM sleep; insulin resistance; glucose intolerance; epidemiology

Sleep-disordered breathing (SDB) is independently associated with impaired glucose metabolism including insulin resistance, fasting hyperglycemia, and impaired glucose tolerance in multiple clinic-based (1–11) and community-based studies (12). Although disordered breathing

events often occur during non-REM and REM sleep, a subset of patients has events that occur primarily during REM sleep (13). In fact, the term “REM-related SDB” is commonly used in clinical practice to describe the predominant occurrence of apneas and hypopneas during REM sleep.

In clinical samples, the prevalence of REM-related SDB is estimated to be in the range of 10–36%, with a relatively higher prevalence in women, younger individuals, and those with mild to moderate SDB (13–17). Given that REM sleep constitutes approximately 25% of the sleep period, the

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Correspondence and requests for reprints should be addressed to Hassan A. Chami, M.D., M.S., American University of Beirut, Internal Medicine, Beirut, Lebanon. E-mail: hchami@aub.edu.lb

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At a Glance Commentary

Scientific Knowledge on the

Subject: The association of REM and non-REM-related sleep-disordered breathing with impaired glucose metabolism has not been well investigated.

What This Study Adds to the

Field: In this community-based sample, REM-related sleep-disordered breathing is associated with insulin resistance, whereas non-REM-related sleep-disordered breathing is associated with glucose intolerance.

number of SDB events that can occur during REM sleep and their overall frequency relative to total sleep is limited. Thus, the relative contribution of SDB events during REM sleep to the overall apnea-hypopnea index (AHI) tends to be smaller than that of events that occur during non-REM sleep, and their potential impact on clinical sequelae may also be limited; however, it is well recognized that SDB events during REM sleep are generally longer than those during non-REM sleep and are often associated with pronounced hypoxemia (13, 18), and might therefore be more detrimental. Furthermore, REM sleep is associated with heightened sympathetic activation, which may further modulate physiologic responses (19).

Thus, the possibility exists that REM-related SDB may have relevant clinical effects despite a smaller total number of SDB events. In fact AHI_{REM} was recently shown to predict prevalent and incident hypertension in a community-based sample, whereas AHI_{NREM} did not (20). In the present study, we sought to evaluate the relation of REM-related SDB to glucose intolerance and insulin resistance in a large community-based cohort. It was hypothesized that the degree of REM-related SDB as measured by AHI_{REM} would be associated with fasting glycemia, glucose intolerance, and insulin resistance independent of such factors as age, body mass index (BMI), and sleep duration.

Methods

Sample

The study sample included participants from the Sleep Heart Health Study (SHHS),

a multicenter study of the cardiovascular consequences of SDB. The design of the SHHS has been previously described (21). Subjects selected for the current analysis included 3,757 SHHS participants who had evaluation of glucose metabolism as part of examinations conducted through their parent cohorts: the Atherosclerosis Risk in Communities Study, the Cardiovascular Health Study, and the Framingham Heart Study. Of the 3,757 participants with polysomnography data and parameters of glucose metabolism, adequate scoring of REM and non-REM was possible in 3,310. Of those, 204 individuals were excluded for being on treatment with either insulin or an oral hypoglycemic agent, resulting in a study sample of 3,086 participants for analysis of fasting glucose levels. Of these, 2,264 participants had an oral glucose tolerance test and 1,531 participants had fasting insulin measurement with a fasting glucose less than 126 mg/dl and were included in the glucose tolerance and insulin resistance analyses, respectively.

Assessment of SDB

Participants underwent full-montage polysomnography at home. The techniques used for monitoring of sleep and breathing, staging of sleep, and scoring of disordered breathing events, and the associated quality-assurance procedures have been previously reported (21–23). The high reliability of the AHI and sleep stage scoring in the SHHS has also been reported (23, 24). The AHI_{REM} and the AHI_{NREM} were calculated as the number of apneas plus hypopneas per hour of REM or non-REM sleep, respectively. The scoring of SDB events was based on the requirement of a 4% or greater decrease in oxyhemoglobin saturation. SDB events scored based on 3% or greater decrease in oxyhemoglobin saturation were evaluated in secondary analyses. The arousal index in REM (Ai_{REM}) and non-REM (Ai_{NREM}) were calculated as the number of arousals per hour of REM and non-REM sleep respectively.

Assessment of Glucose Metabolism

Procedures for collection of blood samples were established independently for each cohort. Fasting morning blood samples were collected by venipuncture after 12 hours of an overnight fast. A second blood sample was collected 2 hours after administration of 75 g of glucose orally to participants without

diabetes that were recruited from the Atherosclerosis Risk in Communities Study and the Cardiovascular Health Study. Extracted serum was stored at -70°C . Serum glucose was measured in the fasting and the 2-hour post-prandial samples using the hexokinase method. Serum insulin level was measured on the fasting samples using a commercial radioimmunoassay in the subset of participants from the Atherosclerosis Risk in Communities Study. The homeostatic model assessment insulin resistance (HOMA-IR) index was used as a measure of insulin resistance in participants with data on fasting insulin level and fasting glucose less than 126 g/dl (25). The HOMA-IR was calculated as the product of fasting glucose (mmol/L) and fasting insulin ($\mu\text{U/L}$) divided by 22.5. HOMA-IR correlates well with the hyperinsulinemic euglycemic clamp, the gold standard measure of insulin resistance (26, 27), and accurately identifies individuals with insulin resistance in clinical (28) and epidemiologic samples (29).

Assessment of Covariates

During the SHHS baseline home visit, usual sleep duration was assessed using an interviewer-administered questionnaire. Weight was measured using a portable scale with the participant in light clothes. Height and waist-hip ratio were obtained at the baseline home visit only if not already measured within 3 months in the parent cohort. BMI was calculated as weight in kilograms divided by the square of height in meters. Sex and race were obtained from parent cohorts.

Statistical Analysis

The primary exposure variables were AHI_{REM} and AHI_{NREM} . Secondary exposure variables included Ai_{REM} and Ai_{NREM} . In analyses that treated SDB as a continuous variable both AHI_{REM} and AHI_{NREM} were natural log transformed because the distributions of these variables were skewed. The main analysis was repeated in confirmatory analyses without log transformation of AHI_{REM} and AHI_{NREM} . The outcome variables were the measures of glucose metabolism: fasting glucose, 2-hour post-prandial glucose, and HOMA-IR index. The HOMA-IR index was natural log transformed in the analysis because of right skewed distribution and the results back transformed for ease of interpretation in the categorical analysis.

In the main analysis, we evaluated the association of AHI_{REM} with measures of glucose metabolism using multiple linear regression treating AHI_{REM} as a continuous variable: $\log(AHI_{REM} + 1)$. To adjust for a possible confounding effect of AHI_{NREM} and evaluate the association of AHI_{REM} with glucose metabolism both AHI_{REM} and AHI_{NREM} were included in the same model. Because AHI_{REM} and AHI_{NREM} are highly correlated ($r = 0.61$), colinearity diagnostics were performed by assessing variance inflation measures and condition indices. Because the samples with measured fasting glucose, 2-hour post-prandial glucose, and HOMA-IR index differed significantly the main analyses were repeated restricting the sample to participants with available HOMA-IR.

We also performed secondary confirmatory analyses that excluded participants in the highest quartile of AHI_{NREM} distribution ($AHI_{NREM} \geq 8.3$ events/h) (rather than including both AHI_{REM} and AHI_{NREM} in the same model) to select a subset of the cohort with a predominance of REM-related SDB. Alternate sensitivity analyses excluded subjects with AHI_{NREM} greater than or equal to five events per hour.

For ease of interpretation, we also assessed the association of fasting glucose, 2-hour post-prandial glucose, and log (HOMA-IR) to REM-SDB defined as a categorical variable along quartiles of AHI_{REM} using analysis of covariance, excluding participants in the highest quartile of AHI_{NREM} ($AHI_{NREM} \geq 8.3$). In

an alternate analysis REM-SDB was also defined using a proposed clinical definition by categorizing SDB as non-REM-SDB ($AHI_{NREM} \geq 5$) REM-SDB ($AHI_{NREM} < 5$, $AHI_{REM} \geq 5$, and REM duration > 30 min), and no SDB ($AHI_{NREM} < 5$ and $AHI_{REM} < 5$).

Effect modification by BMI was evaluated by stratifying the main analysis by BMI group (above/below median) and by adding an interaction term to the regression model.

In all analyses, the demographic model adjusted for age, sex, race, and study site. The demographic + BMI model further adjusted for BMI, an important correlate of REM-SDB and impaired glucose metabolism. The multivariable model further adjusted for waist circumference (a measure of central adiposity) and for self-reported usual sleep duration, which is another known determinant of glucose intolerance and insulin resistance. The sample sizes of 2,224 and 3,007, respectively, provided more than 95% power to detect an association between AHI_{REM} and post-prandial glucose with an effect size as small as 0.013 mg/dl and between AHI_{REM} and fasting glucose with an effect size as small as 0.01 mg/dl while adjusting for 15 covariates in the linear regression model with a type I error rate of 5%.

Results

Characteristics of participants in the fasting glucose, glucose tolerance, and insulin resistance analyses are presented in Table 1. Participants in the insulin resistance

analysis were somewhat younger, but the remaining characteristics were not different among the three samples. Characteristics of participants included and excluded from the glucose tolerance and insulin resistance analyses are provided in Table E1 of the online supplement. The characteristics of the study subjects with AHI_{NREM} above and below the threshold of 8.3 events/h stratified by quartiles of AHI_{REM} are presented in Table 2. Subjects with more severe REM-related SDB (and $AHI_{NREM} < 8.3$) were on average older, more likely to be women, and had a larger BMI and waist circumference. Participants in the lowest to highest quartiles of AHI_{REM} ($AHI_{NREM} < 8.3$) had a median AHI_{REM} of 0, 2.9, 8.4, and 22.6 events/h (Table 1). The respective median values of AHI_{NREM} were 0.4, 0.8, 1.9, and 3.2 events/h, confirming the REM-predominant nature of SDB in the higher AHI_{REM} quartiles, whereas participants in the lower quartiles of AHI_{REM} distribution had no significant SDB.

Main Analysis

In the main analyses, which treated AHI_{REM} and AHI_{NREM} as continuous variables in separate models, both AHI_{REM} and AHI_{NREM} were associated with fasting and post-prandial glucose levels, and with HOMA-IR in unadjusted models and demographic adjusted models (Table 3). However, only AHI_{NREM} was associated with both fasting and post-prandial glucose levels in models further adjusting for BMI, waist circumference, and sleep duration,

Table 1. Characteristics of Participants in the Fasting Glucose, Glucose Tolerance, and Insulin Resistance (HOMA) Analyses

Characteristic	Fasting Glucose	Glucose Tolerance	Insulin Resistance (HOMA)
Number	3,086	2,264	1,531
Mean (SD) age, yr	66.4 (9.5)	67.7 (8.8)	62.8 (5.6)
Sex, % females	54%	54%	55%
Race, % white	95%	94%	99%
Mean (SD) BMI, kg/m ²	28.1 (4.8)	28.1 (4.8)	28.4 (4.9)
Mean (SD) waist circumference, cm	99.7 (13.1)	100.2 (13.1)	101.3 (12.8)
Mean (SD) usual sleep time, h	7.2 (1.2)	7.2 (1.1)	7.2 (1.1)
Mean (SD) REM time, min	74.5 (26.7)	73.8 (26.7)	77.2 (26.2)
Median (IQR) AHI, events/h	4.4 (1.4–11.0)	4.5 (1.4–11.3)	3.9 (1.2–10.4)
Median (IQR) AHI_{REM} , events/h	7.8 (2.1–21.1)	8.3 (2.3–22.1)	7.4 (2.1–20.6)
Median (IQR) AHI_{NREM} , events/h	2.5 (0.7–8.3)	2.7 (0.7–8.6)	2.2 (0.6–7.4)
No SDB (AHI_{NREM} and $AHI_{REM} < 5$), %	35	34	36
REM SDB ($AHI_{NREM} < 5$, $AHI_{REM} > 5$), %	29	30	31
Non-REM SDB ($AHI_{NREM} > 5$), %	36	36	33
$AHI_{REM}/AHI_{NREM} > 2$, %	51.3	52	53
SDB ($AHI > 5$), %	46	47	44

Definition of abbreviations: AHI = apnea-hypopnea index; BMI = body mass index; HOMA = homeostatic model assessment index; IQR = interquartile range; SDB = sleep-disordered breathing.

Table 2. Characteristics of Subjects with $AHI_{NREM} \geq 8.3$ and with $AHI_{NREM} < 8.3$ (Events/h) Further Stratified by AHI_{REM} Quartiles ($n = 3,086$)

Characteristic	$AHI_{NREM} < 8.3$				$AHI_{NREM} \geq 8.3$
	$AHI_{REM} < 1.3$	$AHI_{REM} 1.3-5.2$	$AHI_{REM} 5.2-13.3$	$AHI_{REM} \geq 13.3$	
Number	578	577	579	580	772
Mean (SD) age, yr	64.4 (10.1)	64.9 (9.5)	66.1 (9.3)	67.0 (9.2)	68.6 (9.1)
Sex, % females	66	61	59	57	32.8
Race, % white	96	96	96	94	93
Mean (SD) BMI, kg/m ²	25.5 (3.6)	26.6 (3.9)	28.0 (4.3)	30.1 (5.0)	29.7 (5.2)
Mean (SD) waist circumference, cm	93.1 (11.4)	95.9 (11.7)	99.5 (11.7)	104.1 (13.4)	104.4 (13.2)
Mean (SD) usual sleep time, h	7.1 (1.1)	7.2 (1.2)	7.1 (1.2)	7.0 (1.2)	7.2 (1.2)
Mean (SD) REM time, min	78.4 (28.1)	81.9 (26.2)	78.4 (25.1)	71.6 (25.5)	65.4 (25.4)
Median (IQR) AHI, events/h	0.5 (0.2–1.2)	1.4 (0.8–2.3)	3.4 (2.5–5.0)	7.6 (5.4–10.0)	18.4 (13.1–29.5)
Median (IQR) AHI_{REM} , events/h	0 (0–0.8)	2.9 (2.1–3.9)	8.4 (6.6–10.6)	22.6 (17.3–32.3)	25.1 (11.8–42.2)
Median (IQR) AHI_{NREM} , events/h	0.4 (0–1.4)	0.8 (0.3–2.0)	1.9 (0.8–3.9)	3.2 (1.8–5.5)	16.7 (11.2–27.1)

Definition of abbreviations: AHI = apnea–hypopnea index; BMI = body mass index; IQR = interquartile range.

whereas AHI_{REM} was not (Table 3). In contrast, AHI_{REM} was associated with HOMA-IR in demographic- and BMI-adjusted models, whereas AHI_{NREM} was not (Table 3). The association of AHI_{REM} with HOMA-IR remained significant despite adjustments for waist circumference and sleep duration (Table 3). With additional adjustments for AHI_{NREM} by including both AHI_{REM} and AHI_{NREM} in

the same model (Table 4), or by excluding participants in the highest quartile of AHI_{NREM} (Table 5), the results were similar. The findings were similar in analyses using SDB events scored based on 3% rather than 4% desaturation (see Tables E2 and E3).

When the main analysis was stratified by median BMI, the association of AHI_{REM} with HOMA-IR was observed only in individuals

heavier than the median BMI of 27.6 (see Tables E4 and E5). Formal tests of interaction between BMI and $\log AHI_{REM}$ were significant in the HOMA-IR analysis ($\beta = 0.05$; 95% confidence interval, 0.03–0.01; $P = 0.04$), but not in the fasting glucose ($\beta = 0.042$; 95% confidence interval, –1.09 to 1.17; $P = 0.95$) or glucose tolerance analyses ($\beta = 1.34$; 95% confidence interval, –2.26 to 4.94; $P = 0.46$).

Table 3. Association of AHI_{REM} and AHI_{NREM} with Fasting Glucose ($n = 3,086$), Glucose Intolerance ($n = 2,264$), and Insulin Resistance ($n = 1,531$) (AHI_{REM} and AHI_{NREM} Analyzed in Separate Regression Models)

	Demographic Adjusted	Demographic + BMI Adjusted	Multivariable Adjusted
Fasting glucose, mg/dl	$n = 3,086$	$n = 3,073$	$n = 3,007$
$\log(AHI_{NREM} + 1)$			
β (95% CI)	2.05 (1.42 to 2.68)	0.85 (0.19 to 1.50)	0.87 (0.21 to 1.53)
P value	<0.0001	0.01	0.01
$\log(AHI_{REM} + 1)$			
β (95% CI)	1.70 (1.16 to 2.23)	0.25 (–0.32 to 0.83)	0.33 (–0.25 to 0.93)
P value	<0.0001	0.4	0.3
Post-prandial glucose, mg/dl	$n = 2,264$	$n = 2,261$	$n = 2,224$
$\log(AHI_{NREM} + 1)$			
β (95% CI)	5.4 (3.40 to 7.40)	2.64 (0.57 to 4.72)	2.84 (0.75 to 4.94)
P value	<0.0001	0.01	0.008
$\log(AHI_{REM} + 1)$			
β (95% CI)	4.49 (2.78 to 6.20)	1.10 (–0.76 to 2.96)	1.19 (–0.68 to 3.07)
P value	0.0001	0.2	0.2
$\log$ HOMA, U	$n = 1,531$	$n = 1,529$	$n = 1,517$
$\log(AHI_{NREM} + 1)$			
β (95% CI)	0.12 (0.09 to 0.15)	0.02 (–0.01 to 0.04)	0.01 (–0.01 to 0.04)
P value	0.0001	0.3	0.3
$\log(AHI_{REM} + 1)$			
β (95% CI)	0.14 (0.12 to 0.17)	0.04 (0.01 to 0.06)	0.03 (0.009 to 0.06)
P value	0.0001	0.005	0.007

Definition of abbreviations: AHI = apnea–hypopnea index; BMI = body mass index; CI = confidence interval; HOMA = homeostatic model assessment index.

Demographic: age, sex, race, and study site. Multivariable: adjusted for demographic variables, BMI, usual sleep duration, and waist circumference.

Table 4. Association of AHI_{REM} and AHI_{NREM} with Fasting Glucose (n = 3,086), Glucose Tolerance (n = 2,264), and Insulin Resistance (n = 1,531) (AHI_{REM} and AHI_{NREM} Analyzed in the Same Regression Model)

	Demographic Adjusted	Demographic + BMI Adjusted	Multivariable Adjusted
Fasting glucose, mg/dl	n = 3,086	n = 3,073	n = 3,007
log(AHI _{NREM} + 1)			
β (95% CI)	1.31 (0.53 to 2.1)	0.97 (0.20 to 1.75)	0.93 (0.14 to 1.72)
P value	0.001	0.01	0.02
log(AHI _{REM} + 1)			
β (95% CI)	1.03 (0.37 to 1.70)	−0.21 (−0.91 to 0.47)	−0.11 (−0.82 to 0.58)
P value	0.002	0.5	0.7
Post-prandial glucose, mg/dl	n = 2,264	n = 2,261	n = 2,224
log(AHI _{NREM} + 1)			
β (95% CI)	3.5 (1.00 to 5.99)	2.8 (0.30 to 5.2)	3.0 (0.50 to 5.5)
P value	0.006	0.03	0.02
log(AHI _{REM} + 1)			
β (95% CI)	2.7 (0.6 to 4.8)	−0.23 (−2.4 to 2.0)	−0.24 (−2.5 to 2.0)
P value	0.01	0.8	0.8
log HOMA, U	n = 1,531	n = 1,529	n = 1,517
log(AHI _{NREM} + 1)			
β (95% CI)	0.03 (−0.01 to 0.07)	−0.01 (−0.04 to 0.03)	−0.009 (−0.04 to 0.03)
P value	0.13	0.6	0.6
log(AHI _{REM} + 1)			
β (95% CI)	0.13 (0.1 to 0.16)	0.04 (0.01 to 0.07)	0.04 (0.009 to 0.07)
P value	<0.0001	0.01	0.01

Definition of abbreviations: AHI = apnea–hypopnea index; BMI = body mass index; CI = confidence interval; HOMA = homeostatic model assessment index.

Demographic: age, sex, race, and study site. Multivariable: adjusted for demographic variables, BMI, usual sleep duration, and waist circumference.

Secondary Analyses

In secondary analyses restricting the fasting glucose and glucose tolerance samples to participants with available HOMA-IR data (n = 1,531), the association of AHI_{REM} with fasting and post-prandial glucose levels remained significant in unadjusted and demographic adjusted models, and nonsignificant in BMI and multivariable adjusted models (see Tables E6 and E7). No material differences were observed in

analyses that excluded participants with REM sleep duration of less than 10 minutes and in analyses restricted to participants who had their metabolic assessments within 6 months of polysomnography (results not shown).

In secondary analyses treating AHI_{REM} as a categorical variable, and excluding participants in the highest quartile of AHI_{NREM} (≥ 8.3 events/h), AHI_{REM} was associated with fasting or post-prandial

glucose levels and with HOMA-IR in demographics-adjusted model (Figure 1). Only the association of AHI_{REM} with HOMA-IR persisted in BMI-adjusted models, and in the multivariable-adjusted models further adjusting for waist circumference and sleep duration (Figure 1). Results were similar in sensitivity analyses excluding participants with AHI_{NREM} greater than or equal to five events/h instead of excluding participants

Table 5. Association of REM-SDB [log(AHI_{REM} + 1)] with Fasting Glucose, Glucose Tolerance (2-h Post-Prandial Glucose), and Insulin Resistance in Samples Excluding AHI_{NREM} ≥ 8.3

	Demographic Adjusted	Demographic + BMI Adjusted	Multivariable Adjusted
Fasting glucose, mg/dl	n = 2,314	n = 2,304	n = 2,259
β (95% CI)	1.43 (0.80 to 2.05)	0.08 (−0.59 to 0.75)	0.16 (−0.51 to 0.84)
P value	<0.0001	0.8	0.6
Post-prandial glucose, mg/dl	n = 1,684	n = 1,681	n = 1,660
β (95% CI)	3.92 (1.83 to 6.01)	0.89 (−1.34 to 3.12)	0.74 (−1.50 to 2.98)
P value	0.0002	0.4	0.5
log HOMA, U	n = 1,238	n = 1,236	n = 1,228
β (95% CI)	0.14 (0.11 to 0.17)	0.04 (0.01 to 0.07)	0.04 (0.01 to 0.07)
P value	<0.0001	0.02	0.01

Definition of abbreviations: AHI = apnea–hypopnea index; BMI = body mass index; CI = confidence interval; HOMA = homeostatic model assessment index; SDB = sleep-disordered breathing.

Demographic: age, sex, race, and study site. Multivariable: adjusted for demographic variables, BMI, usual sleep duration, and waist circumference.

Figure 1. Homeostatic model assessment (HOMA) index by AHI_{REM} category, in participants with AHI_{NREM} <8.3 events/h, n = 1,177. Demographic variables: age, sex, race, study site. AHI = apnea-hypopnea index; BMI = body mass index; sleep time = self-reported usual sleep time; waist = waist circumference.

in the highest quartile of AHI_{NREM} (≥ 8.3 events/h). In analyses that categorized SDB as REM-SDB, non-REM-SDB, and no SDB (Figure 2; see Table E8), the mean adjusted HOMA-IR was highest in individuals with REM-SDB (Figure 2A) in all models. The mean adjusted fasting glucose was significantly higher in the non-REM-SDB group compared with REM-SDB and no SDB in all models (Figure 2B). The increased post-prandial glucose level in the non-REM-SDB group noted in the demographic-adjusted model was not statistically significant in the BMI-adjusted and multivariable-adjusted models (Figure 2C). Finally, there was no association between HOMA-IR and the arousal index in REM and non-REM in any models (see Tables E8 and E9).

Discussion

In a community-based sample of middle-aged and older adults, increased AHI_{REM} was associated with increased insulin resistance as measured by HOMA-IR, but not with impaired fasting glucose and glucose intolerance after adjustment for multiple potential confounders, including age, sex, race, adiposity, and self-reported sleep duration and AHI_{NREM}. In contrast, increased AHI_{NREM} was associated with impaired fasting glucose and glucose intolerance after adjusting for adiposity, but AHI_{REM} was not.

Several previous studies evaluated and largely support the association of SDB with

glucose metabolism (1–12, 30). Two clinic-based studies support an association between increased AHI_{REM} and the risk of diabetes but neither study adjusted for AHI_{NREM} (31, 32). Furthermore, one community-based study supports an association between AHI_{REM} and glucose control in subjects with diabetes independent of AHI_{NREM} (33). However, to our knowledge, this is the first community-based study to evaluate the independent association of AHI_{REM} with insulin resistance and glucose intolerance. The finding of an independent association between AHI_{REM} and HOMA-IR, a measure of insulin resistance that correlates well with the gold standard hyperinsulinemic euglycemic clamp (26–29), is of potential clinical importance, because HOMA-IR predicts incident type 2 diabetes and cardiovascular disease (34). The difference in mean adjusted HOMA-IR between individuals in the highest and lowest AHI_{REM} category of 0.39 U was less than the previously reported average difference of 1.61 U, between individuals with incident type 2 diabetes and those who did not develop type 2 diabetes (34).

In contrast with AHI_{REM}, increased AHI_{NREM} was associated with impaired fasting glucose and glucose intolerance after adjusting for adiposity, but not with HOMA-IR. It is well established that both insulin resistance and pancreatic insufficiency are needed to impair glucose tolerance and increase the predisposition for type 2 diabetes (35). The differences in the metabolic impairments associated with

increased AHI_{REM} and AHI_{NREM} could reflect the influences of SDB across the spectrum of disease severity. REM-related SDB, which is an early manifestation of SDB, may be associated with mild metabolic disruption in the form of insulin resistance, whereas in the generally more severe non-REM-related SDB, insulin secretion may also be compromised, resulting in glucose intolerance and fasting hyperglycemia.

It is also possible that the observed differences in the metabolic impairments associated with AHI_{REM} versus AHI_{NREM} could reflect different pathogenic responses. REM-related SDB, which is characterized by an overall lower frequency of respiratory disturbances that are prolonged and associated with a higher level of hypoxemia and sympathetic nervous system activation (13, 18), may preferentially affect insulin resistance. Non-REM-related SDB, which is characterized by an overall higher frequency of respiratory disturbance, may preferentially affect glucose tolerance and fasting hyperglycemia. Animal models of SDB and experimental human studies support an adverse effect of SDB on insulin resistance and glucose tolerance (36); however, the effect of selective REM-SDB has not been specifically examined.

Several studies support a relationship between SDB during REM sleep and impaired glucose metabolism. SDB during REM sleep has been shown to abolish the decrease in glucose levels that occurs during REM sleep (37), whereas SDB during non-REM sleep had no significant impact on glucose levels during non-REM sleep. Furthermore, nocturnal hyperglycemia associated with SDB in patients with diabetes is especially accentuated during REM sleep (38). Finally, the association of hypoxemia with decreased glucose variability in patients with SDB was noted primarily during REM sleep (39).

Multiple mechanisms could mediate the association of AHI_{REM} and impaired glucose metabolism including intermittent hypoxemia (40, 41), recurrent arousal/sleep fragmentation (42, 43), sympathetic stimulation (44, 45), alteration in corticotrophic regulation (46, 47), and potentially other effects of selective REM-sleep deprivation. Hypoxemia is likely to be implicated because it is accentuated during REM-related SDB. Furthermore, the AHI includes events associated with oxyhemoglobin desaturation, thus the lack

Figure 2. (A) Fasting glucose, (B) post-prandial glucose, and (C) homeostatic model assessment (HOMA) in non-REM-SDB ($AHI_{NREM} \geq 5$), REM-SDB ($AHI_{NREM} < 5$, $AHI_{REM} \geq 5$), and no SDB ($AHI_{NREM} < 5$ and $AHI_{REM} < 5$). Demographic variables: age, sex, race, study site. Multivariable: demographic variables, BMI, waist circumference, and self-reported usual sleep time. BMI = body mass index; SDB = sleep-disordered breathing.

of association of impaired glucose metabolism with arousal index and the association with AHI suggest that intermittent hypoxia is more likely to be the culprit mechanism. In fact, both animal (48, 49) and experimental human studies (50, 51) support the hypothesis that acute sustained hypoxemia decreases insulin sensitivity. The association may also be mediated, in part, by inflammatory cytokines, such as IL-6 and tumor necrosis factor- α (52, 53). Short-term acute intermittent hypoxia was shown to acutely increase insulin resistance in mice (40) and humans (41). Chronic intermittent hypoxia, however, was associated with impaired glucose-stimulated insulin release suggesting pancreatic endocrine insufficiency that, when combined with insulin resistance, increases the predisposition for type 2 diabetes (54). Finally, given the observational study design, common underlying risk factors could explain the cooccurrence of REM-related SDB and insulin resistance.

The current study has several potential limitations. Although the association between increased AHI_{REM} and insulin resistance is biologically plausible, the cross-sectional design of this study does not permit definitive conclusions on whether this association is causal or on the direction of causation. Furthermore, insulin resistance is closely associated with visceral adiposity. Although we adjusted for two measures of adiposity (BMI and waist circumference), residual confounding by visceral adiposity cannot be ruled out, nor can confounding by unmeasured covariates be excluded. For more definitive inferences, a randomized controlled trial assessing the effect of treating REM-related SDB on glucose intolerance and insulin resistance is needed (27).

The moderate to strong correlation between AHI_{REM} and AHI_{NREM} raises concerns about collinearity in analysis that included both variables in the model. Yet, collinearity diagnostics using variance inflation measures and condition indices showed that collinearity did not affect the regression estimates in these models (see Table E10). Moreover, adjustment for the confounding effect of AHI_{NREM} on the association of AHI_{REM} with glucose metabolism by excluding subjects in the highest quartile of AHI_{NREM} instead of including AHI_{REM} and AHI_{NREM} in the same model led to the same conclusions.

The study sample consisted primarily of white subjects, which limits the generalizability of the findings to other ethnic groups. The large sample size provided plenty of power, thus it is unlikely that the lack of association between AHI_{REM} and fasting glucose or glucose tolerance was caused by type 2 error. Finally, glucose metabolism was not always assessed in close proximity to polysomnography. However, restricting the analysis to participants who had glucose metabolism assessed within 6 months from polysomnography did not materially impact the association. Furthermore, AHI_{REM} was associated with fasting and post-prandial glucose in the demographic-adjusted model; therefore, it is unlikely that the temporal difference is the cause of nonassociation in the BMI-adjusted model. Balancing these limitations are several strengths including the large, well-

characterized community-based sample selected independent of suspected SDB or metabolic syndrome and the standardized polysomnography and glucose metabolism assessments following strict protocols and rigorous quality control measures.

In summary, in this community-based sample selected independent of SDB symptoms or risk factors for type 2 diabetes, increased AHI_{REM} was associated with insulin resistance after adjustment for multiple potential confounders, but was not associated with fasting or post-prandial hyperglycemia. This finding suggests that REM-related SDB is likely to have an impact on glucose metabolism even in the absence of non-REM-SDB. Clinical trials and studies evaluating the effects of REM-related SDB on other health outcomes, such as cardiovascular disease and neurocognitive function, are needed to

clarify whether REM-SDB should be treated in the absence of non-REM-SDB. ■

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