Fasting Glycemia in Sleep Disordered Breathing: Lowering the Threshold on Oxyhemoglobin Desaturation

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Study Objectives: Commonly used definitions of sleep-disordered breathing (SDB) are based on identifying discrete events of breathing abnormalities during sleep that are accompanied by an oxyhemoglobin desaturation (ΔSaO_2) of at least 4%. However, it is not known whether disordered breathing events with oxyhemoglobin desaturation less than 4% are associated with clinical sequelae such as abnormalities in fasting glycemia.

Design: Cross-sectional study.

Subjects and Setting: Participants from the Sleep Heart Health Study (SHHS) with a fasting glucose measurement made within a year of the baseline polysomnogram.

Measurements and Results: SDB severity was defined using the apnea-hypopnea index (AHI) and the hypopnea index (HI) by counting events with different levels of oxyhemoglobin desaturation (0.0%–1.9%, 2.0%–2.9%, 3.0%–3.9%, ≥4.0%). Fasting glucose levels were used to classify individuals into normal (<100 mg/dL), impaired (100–125 mg/dL), and diabetic (≥126 mg/dL) groups. Ordinal logistic regression was used to determine the adjusted relative odds of an abnormal glucose value across quartiles of the hypopnea index, independent of factors such as age, body mass index, waist circumference, and usual sleep duration. The prevalence of impaired and diabetic fasting glucose in the analytical sample was 32.9% and 5.8%, respectively. The covariate-adjusted relative odds of impaired or diabetic fasting glucose in the highest versus the lowest AHI quartile was 1.35 (95% CI: 1.04–1.76) for events with a $\Delta SaO_2 \geq 4.0\%$, 1.72 (95% CI: 1.20–2.48) for events with a ΔSaO_2 between 3.0%-3.9%, 1.41 (95% CI: 1.07–1.86) for events with a ΔSaO_2 between 2.0%–2.9%, and 1.07 (95% CI: 0.84–1.37) for events with a ΔSaO_2 between 0.0%–1.9%. The corresponding odds ratios for the HI were 1.47 (95% CI: 1.13–1.92), 2.25 (95% CI: 1.59–3.19), 1.44 (95% CI: 1.09–1.90), and 1.15 (95% CI: 0.90–1.47), respectively.

Conclusions: The results of this study indicate that SDB events accompanied by oxyhemoglobin desaturation of between 2% to 4% are associated with fasting hyperglycemia. These findings suggest that milder degrees of SDB may predispose to adverse metabolic outcomes.

Keywords: Sleep-disordered breathing, glucose metabolism

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SLEEP DISORDERED BREATHING (SDB) IS A PREVALENT AND CHRONIC CONDITION THAT IS CHARACTERIZED BY RECURRENT EPISODES OF UPPER AIRWAY collapse during sleep. It is estimated that approximately 7% of adults in the general population have SDB of at least moderate severity.[1] Several epidemiological and clinic-based studies have shown that the prevalence of altered glucose metabolism and type 2 diabetes increases with severity and frequency of self-reported and objective measures of SDB, independent of age and central obesity.[2,3] Of the prospective observational studies, two have shown a higher incidence of type 2 diabetes mellitus among habitual snorers,[4,5] and one has shown a higher prevalence of type 2 diabetes among those with polysomnographically defined SDB.[6] Previous work from the Sleep Heart Health Study (SHHS) has also demonstrated a higher prevalence of impaired fasting glucose, glucose intolerance, and type 2 diabetes mellitus in individuals with SDB independent of body mass index and waist circumference.[7]

SDB is associated with a number of physiological derangements, including intermittent hypoxemia and sleep fragmentation. Experimental and observational studies that have attempted to uncouple these pathognomonic components of SDB have shown that both hypoxia and disrupted sleep can trigger a cascade of physiological events that may eventually result in altered glucose homeostasis. Increases in autonomic activity[8,9] and circulating neuroendocrine hormones such as cortisol[10,11] can be elicited by hypoxia and sleep disruption and thus may impair glucose metabolism in SDB. Epidemiologic observations from the SHHS cohort indicate that average oxyhemoglobin saturation during sleep independently correlates with impaired glucose tolerance and type 2 diabetes.[7] Thus, measures beside the conventional apnea-hypopnea index may provide a more nuanced understanding of the specific components of SDB that play a role in subsequent pathologies. In order to determine whether disordered breathing events with milder reductions in oxyhemoglobin saturation that are excluded from conventional measures are clinically relevant, it is important to examine the full spectrum of SDB-related events in the context of specific health-related outcomes.

The currently recommended criteria for defining a hypopnea include a reduction of airflow that is accompanied by an oxyhe-

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This was not an industry supported study. Dr. Sanders is a scientific consultant to and is on the speaker's bureau of Respironics. He is co-inventor of BiPAP® and has financial interest in this brand and related technologies by Respironics. He has also served on the advisory panel for Sanofi. The other authors have indicated no financial conflicts of interest.

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moglobin desaturation of at least 4%.[12] An alternative definition includes a decrease in airflow with an oxyhemoglobin desaturation of at least 3% or an arousal from sleep.[12] Whether SDB events characterized by less stringent criteria for sleep related hypoxemia (e.g., 2% or 3% oxyhemoglobin desaturation) are important for predicting the risk of adverse events is not known. To delineate the potential consequences of SDB events with lesser degrees of oxyhemoglobin desaturation during sleep, the current study examined the association between events at varying thresholds of SDB-related oxygen desaturation and glucose metabolism. Specifically, the primary objective was to determine whether events, in particular hypopneas, based on an oxyhemoglobin desaturation criterion below the 4% threshold for defining the disorder correlate with fasting glucose levels in a community-based sample of middle-aged and older adults.

METHODS

Study Sample

The specific aims and design of the SHHS have been previously described.[13] Briefly, the SHHS is a cohort study of the cardiovascular consequences of SDB. The baseline cohort for the SHHS study was recruited from ongoing epidemiologic studies of cardiovascular and respiratory disease. The recruited cohort was assessed for SDB with a full montage in-home polysomnogram. Participants were considered eligible if they were at least 40 years of age and were not being treated for SDB with positive airway pressure, oxygen, or a tracheostomy. The baseline SHHS cohort consisted of 6,441 subjects that underwent the overnight polysomnogram and completed a battery of interview-administered questionnaires. Informed consent was obtained from all participants and the study protocol was approved by the institutional review board of each participating institution.

The study sample for the current analysis consisted of a subset of the SHHS participants with a fasting glucose measurement performed using standardized methods in accordance with the parent study protocols. Three parent studies had collected data on fasting glucose levels including the Atherosclerosis Risk in Communities Study, the Cardiovascular Health Study, and the Framingham Heart Study. Because measurements of metabolic function were measured in accordance with the parent study timeline, only those measurements that were within a year of the SHHS baseline polysomnogram were included in the current analyses (N = 2,656). Participants were excluded if they were on insulin therapy or using an oral hypoglycemic agent. Covariate data on age, sex, race, smoking status (current, former, never smoker), weight, height, waist circumference, and self-reported sleep duration during workdays was ascertained as part of the SHHS baseline exam.

Polysomnography

An unattended polysomnogram was conducted in the participant's home and consisted of continuous recordings of the following physiologic channels: C_3-A_2 and C_4-A_1 electroencephalogram (EEG), right and left electrooculogram, a single bipolar electrocardiogram, chin electromyogram (EMG), oxyhemoglobin saturation by pulse oximetry, chest and abdominal excursion by inductance plethysmography, airflow by an oronasal thermocouple, and body position by a mercury gauge. The Nonin oximeter that was used as part of the recording montage calculated the oxyhemoglobin saturation once per second using a collection of valid pulse wave forms and an exponentially weighted averaging window based on heart rate. Using the exponentially weighted averaging function, the once-per-second oxyhemoglobin saturation values for a heart rate of 60 beats per minute are determined by the set of 4 recent pulse waves and an averaging window length of approximately 4 seconds. With increasing heart rate, the averaging window decreases. Thus, at a heart rate of 90 beats per minute the averaging widow length is approximately 2.5 sec. Additional details of polysomnographic equipment, hook-up procedures, failure rates, scoring, and quality assurance and control have been previously described.[14]

SDB severity was quantified with the following parameters: the apnea-hypopnea index (AHI), the apnea index (AI), and the hypopnea index (HI). Apneas were identified if airflow was absent or nearly absent for ≥10 sec. Hypopneas were identified if discernible, discrete reductions in airflow or thoracoabdominal movement (≥30% below baseline values) occurred for at least 10 sec. For each of the above parameters, apneas and hypopneas associated with an oxyhemoglobin desaturation of 0.0%–1.9%, 2.0%–2.9%, 3.0%–3.9% were tabulated separately to construct a panel of predictor variables representing SDB events based on less stringent desaturation criteria than typically used to define an event (i.e., ≥4.0%). For example, the frequencies of hypopneas associated with oxyhemoglobin desaturation less than 2.0% ($HI_{0.0–1.9\%}$), 2.0% to 2.9% ($HI_{2.0–2.9\%}$) and 3.0% to 3.9% ($HI_{3.0–3.9\%}$) were determined. Arousals were identified as abrupt shifts ≥3 sec in the EEG frequency.[15] In REM sleep, scoring of arousals also required concurrent increases in chin EMG amplitude. The arousal index was defined as the average number of arousals per hour of sleep.

Metabolic Assessment

After an overnight fast, a venipuncture was performed to obtain a blood sample. Extracted serum was stored at –70°C for further analyses. Serum glucose in all participants was measured by the hexokinase method. Based on the fasting serum glucose levels, glycemic status was categorized using the American Diabetes Association criteria[16] as follows: normal (<100 mg/dL), impaired (100 to 125 mg/dL), or diabetic (≥126 mg/dL).

Statistical Analysis

Pearson correlation coefficients were computed to examine the strength of association between variously defined measures of SDB across desaturation thresholds. The prevalence of normal, impaired, and diabetic fasting glucose levels was determined as a function of SDB severity using the AHI, AI, and HI at different thresholds of oxyhemoglobin desaturation. Because fasting glucose levels were represented as normal, impaired, or diabetic, ordinal logistic regression was used to characterize the associations between glycemic status and parameters of SDB severity. Analyses were conducted with the study sample categorized in quartiles for each predictor of interest (e.g., AHI) across the different oxyhemoglobin desaturation thresh-

olds (e.g., 3.0%–3.9%). Multivariable models were developed to adjust for confounding variables which included age, sex, body mass index, waist circumference, neck circumference, usual sleep duration, smoking status, alcohol use, and prevalent hypertension. The decision to include several obesity related measures (e.g., BMI, waist circumference, neck circumference) was driven by the need to adjust for not only the amount of body weight but also to account for the potential effects of central adiposity. Moreover, adjustments for usual sleep duration,[17] smoking history,[18,19] and alcohol use[20-22] were necessary, as these factors have been related to altered glucose metabolism. Finally, to test the metabolic implications of lower thresholds of oxyhemoglobin desaturation, each multivariable model for a specific desaturation threshold included terms that would account and adjust for SDB events with oxyhemoglobin desaturation above the threshold being examined. For example, in a multivariable model with the $AHI_{3.0–3.9\%}$ as the primary independent variable, $AHI_{\geq 4.0\%}$ was included as a covariate to account for the confounding effects of apneas and hypopneas associated with oxyhemoglobin desaturation of 4% or more. All statistical analyses were performed using SAS statistical software (SAS Institute Inc., Carey, NC, version 9.0).

RESULTS

The study sample of 2,656 subjects consisted of 54.3% women and 93.4% white subjects. The median age was 68.0 years (interquartile range: 60–75) and the median BMI was 27.6 kg/m^2 (interquartile range: 24.9–30.8). The prevalence of normal, impaired, and diabetic fasting glucose values was 61.3%, 32.9%, and 5.8%, respectively. As expected, the median AHI and HI progressively increased with less stringent oxyhemoglobin desaturation criteria. The median values of $AHI_{\geq 4.0\%}$, $AHI_{3.0–3.9\%}$, $AHI_{2.0–2.9\%}$, and $AHI_{0.0–1.9\%}$ were 4.61, 4.38, 7.27, and 9.03 events per hour, respectively. The median values of $HI_{\geq 4.0\%}$, $HI_{3.0–3.9\%}$, $HI_{2.0–2.9\%}$, and $HI_{0.0–1.9\%}$ were 3.28, 3.86, 6.79, and 8.66 events per hour, respectively. Finally, the median values of $AI_{\geq 4.0\%}$, $AI_{3.0–3.9\%}$, $AI_{2.0–2.9\%}$, and $AI_{0.0–1.9\%}$ were 0.52, 0.17, 0.16, and 0.16 events per hour, respectively. As expected, measures based on more stringent oxyhemoglobin desaturation criteria were more correlated with each other than with the other measures based on less stringent desaturation criteria, indicating the co-occurrence of events within adjacent bins of oxyhemoglobin desaturation (Table 1). While correlations between AHI and HI ranged from high to low, correlations between AI and AHI, as well as AI and HI were generally low. Thus, there was sufficient variation in these measures to allow independent examination of their association with glycemic status.

Table 2 shows the cumulative adjusted relative odds for impaired or diabetic fasting glucose levels across quartiles of AHI using different oxyhemoglobin desaturation criteria (0.0%–1.9%, 2.0%–2.9%, 3.0%–3.9%, and ≥ 4.0%) in separate multivariable models. Because the oxyhemoglobin desaturation criterion alters the distribution of SDB indices, comparisons of the adjusted relative odds for quartiles across separate models cannot be made. As shown in Table 2, impaired glucose metabolism was associated with $AHI_{\geq 4.0\%}$, $AHI_{3.0–3.9\%}$, and $AHI_{2.0–2.9\%}$ Compared to the first quartile of $AHI_{\geq 4.0\%}$, the multivariable adjusted relative odds for the fourth and third quartiles were 1.35 (95% CI: 1.04–1.76) and 1.32 (95% CI: 1.02–1.71), respectively. The adjusted relative odds of impaired or diabetic fasting glucose for the fourth, third, and second quartiles of $AHI_{3.0–3.9\%}$ were 1.72 (95% CI: 1.20–2.48), 1.53 (95% CI: 1.10–2.15), and 1.53 (95% CI: 1.13–2.06), respectively. The adjusted relative odds of impaired or diabetic fasting glucose values was also statistically significant for the fourth versus first quartile of $AHI_{2.0–2.9\%}$ (odds ratio [OR] = 1.41, 95% CI: 1.07–1.86). However, no association was observed between $AHI_{0.0-1.9\%}$ and fasting glycemia even when comparing the fourth and first quartiles (OR = 1.07, 95% CI: 0.84–1.37).

Given the relatively low burden of apneas in the study sample and lack of association between the AI and glycemic status (data not shown), analyses were then conducted to focus on the association between the HI at varying thresholds of oxyhemoglobin desaturation and metabolic impairment. Table 3 shows the relative adjusted odds for impaired or diabetic fasting glucose levels across quartiles of HI for the following oxyhemoglobin definitions: 0.0%–1.9%, 2.0%–2.9%, 3.0%–3.9%, and ≥ 4.0%. As before, each multivariable model included terms to reflect the frequency of hypopneas (and apneas) associated with oxyhemoglobin desaturation above the threshold being examined. Thus, the independent association between hypopneas within specific limits of oxyhemoglobin desaturation was delineated. Compared to the first quartile of $HI_{\geq 4.0\%}$, the adjusted relative odds of impaired or diabetic fasting glucose were higher for the fourth quartile (OR = 1.47, 95% CI: 1.13–1.92) and third quartile (OR = 1.25, 95% CI: 0.96–1.61). The adjusted relative odds of impaired or diabetic fasting glucose across quartiles

Table 1—Pearson Correlation Coefficients Between Sleep-Disordered Breathing Indices Defined According to Type of Event (Apnea, Hypopnea, or Both) and Level of Oxyhemoglobin Desaturation (0.0%–1.9%, 2.0%–2.9%, 3.0%–3.9%, ≥4.0%)

	$AHI_{0.0-1.9\%}$	$AHI_{2.0-2.9\%}$	$AHI_{3.0-3.9\%}$	$AHI_{\geq 4.0\%}$
$AHI_{0.0-1.9\%}$	1.00	0.53	0.11	−0.16
$AHI_{2.0-2.9\%}$		1.00	0.73	0.15
$AHI_{3.0-3.9\%}$			1.00	0.51
$AHI_{\geq 4.0\%}$				1.00
$HI_{0.0-1.9\%}$	0.99	0.51	0.07	−0.19
$HI_{2.0-2.9\%}$	0.53	0.98	0.68	0.11
$HI_{3.0-3.9\%}$	0.08	0.70	0.95	0.47
$HI_{\geq 4.0\%}$	−0.16	0.18	0.52	0.85
$AI_{0.0-1.9\%}$	0.23	0.27	0.29	0.26
$AI_{2.0-2.9\%}$	0.19	0.43	0.43	0.19
$AI_{3.0-3.9\%}$	0.11	0.38	0.57	0.33
$AI_{\geq 4.0\%}$	−0.11	0.06	0.32	0.82
	$HI_{0.0-1.9\%}$	$HI_{2.0-2.9\%}$	$HI_{3.0-3.9\%}$	$HI_{\geq 4.0\%}$
$HI_{0.0-1.9\%}$	1.00	0.52	0.07	−0.17
$HI_{2.0-2.9\%}$		1.00	0.71	0.19
$HI_{3.0-3.9\%}$			1.00	0.57
$HI_{\geq 4.0\%}$				1.00
$AI_{0.0-1.9\%}$	0.11	0.12	0.11	0.07
$AI_{2.0-2.9\%}$	0.11	0.23	0.19	0.03
$AI_{3.0-3.9\%}$	0.04	0.23	0.27	0.10
$AI_{\geq 4.0\%}$	−0.15	0.00	0.20	0.40

AHI = apnea-hypopnea index, AI = apnea index, HI = hypopnea index

Table 2—Adjusted Cumulative Odds Ratios* and Associated 95% Confidence Intervals (CI) for Impaired Fasting Glucose or Diabetes Across Quartiles of the Apnea-Hypopnea Index (AHI) Using Three Definitions of AHI Based on Associated Level of Oxyhemoglobin Desaturation (ΔSaO_2)

AHI (ΔSaO_2 criteria)	AHI cut-points (events/hr)	Impaired fasting glucose (%)	Diabetic fasting glucose (%)	Adjusted cumulative odds ratio (95% CI)*
AHI (ΔSaO_2: ≥4.0%)				
Model 1				
I	<1.44	22.6	4.4	Reference
II	1.44–4.60	31.5	3.5	1.06 (0.82–1.37)
III	4.61–11.37	35.5	7.1	1.32 (1.02–1.71)
IV	≥11.38	42.0	8.3	1.35 (1.04–1.76)
AHI (ΔSaO_2: 3.0%–3.9%)				
Model 2				
I	<2.25	21.8	3.2	Reference
II	2.25–4.37	32.3	5.3	1.53 (1.13–2.06)
III	4.38–7.33	35.2	6.3	1.53 (1.10–2.15)
IV	≥7.34	42.2	8.4	1.72 (1.20–2.48)
AHI (ΔSaO_2: 2.0%–2.9%)				
Model 3				
I	<4.69	25.4	3.8	Reference
II	4.69–7.27	30.0	4.5	0.93 (0.71–1.20)
III	7.27–10.92	34.2	6.2	1.18 (0.90–1.54)
IV	≥10.93	42.0	8.7	1.41 (1.07–1.86)
AHI (ΔSaO_2: 0.0%–1.9%)				
Model 4				
I	<5.48	33.2	5.0	Reference
II	5.48–9.04	33.3	5.3	1.00 (0.79–1.27)
III	9.04–14.69	31.3	6.5	1.06 (0.83–1.34)
IV	≥14.70	33.8	6.5	1.07 (0.84–1.37)

*Odds ratio are adjusted for sex, age (quartiles), race (categories), smoking status (former, current, or never), alcohol consumption (none, moderate, heavy), usual sleep duration categories (≤6, 7, 8, ≥9), prevalent hypertension, neck circumference (quartiles), waist circumference (quartiles), body mass index (quartiles), and AHI (quartiles) based on apneas and hypopneas that are associated with more severe desaturation than the upper cut-point of predictor variable.

of $HI_{3.0–3.9\%}$ were 2.25 (95% CI: 1.59–3.19), 1.46 (95% CI: 1.05–2.01), and 1.70 (95% CI: 1.27–2.27) for the fourth, third, and second quartiles, respectively. The adjusted relative odds of impaired or diabetic fasting glucose values were also higher in the fourth (OR = 1.44, 95% CI: 1.09–1.90) and third (OR = 1.29, 95% CI: 0.99–1.68) quartiles of $HI_{2.0–2.9\%}$ compared to the first quartile. However, no association was observed between $HI_{0.0–1.9\%}$ and fasting glycemia even when comparing the fourth and first quartiles (OR = 1.15, 95% CI: 0.90–1.47).

Although the primary results of this study have been reported in terms of the relative odds of being in a clinically defined risk category (i.e., impaired fasting glucose, overt diabetes) for ease of clinical interpretation, analysis of the data entirely precluding clinical cut-points found that mean fasting glucose levels significantly increased across quartiles of $HI_{3.0–3.9\%}$ and $HI_{2.0–2.9\%}$ even after full covariate adjustment (results not shown), indicating that these findings are not model-dependent. Finally, inclusion of arousal frequency in each of the constructed multivariable models did not alter the strength of association between the HI at various hypoxemia thresholds and glycemic status.

DISCUSSION

The results of the current study provide evidence that breathing abnormalities during sleep indexed by events (i.e., hypopneas) with accompanying oxyhemoglobin desaturation less than 4% are associated with impaired and diabetic fasting glucose levels. Using data from the multicenter Sleep Heart Health Study, the results of this study demonstrate that the prevalence of impaired glucose metabolism increased with the frequency of hypopneas that were defined using alternative and less stringent oxyhemoglobin desaturation criteria, even after adjusting for measures of body composition, as well as demographic and other health-related factors such as age, sex, race, education, usual sleep duration, smoking status, alcohol consumption, and hypertension. Our results also suggest that sleep-related breathing events with lesser degrees of hypoxemia are associated with metabolic impairment at higher event frequencies while a similar level of metabolic impairment is found at lower event frequencies of more severe hypoxemia (Table 2). While not conclusive, the results reported herein raise the possibility that the impact of SDB events may be cumulative and that the adverse effects may accumulate even over less severe insults if they are recurrent and sustained.

The health-related consequences of intermittent and sustained hypoxemia are now being increasingly recognized. Elevations in fasting insulin levels have been demonstrated after continuous hypoxic exposure in several animal models with as little as 2 hours of exposure.[23-25] Additional evidence from experiments using murine models indicates that the derangements

Table 3—Adjusted Cumulative Odds Ratios* and Associated 95% Confidence Intervals (CI) for Impaired Fasting Glucose or Diabetes Across Quartiles of the Hypopnea Index (HI) Using 3 Definitions of HI Based on Associated Level of Oxyhemoglobin Desaturation (ΔSaO_2)

HI (ΔSaO_2 criteria)	HI cut-points (events/hr)	Impaired fasting glucose (%)	Diabetic fasting glucose (%)	Adjusted cumulative odds ratio (95% CI)*
HI (ΔSaO_2: ≥4.0%) (Model 1)				
I	<1.08	22.7	4.2	Reference
II	1.08–3.27	28.2	4.1	1.01 (0.78–1.30)
III	3.28–7.56	35.9	6.2	1.25 (0.96–1.61)
IV	≥7.57	44.8	8.7	1.47 (1.13–1.92)
HI (ΔSaO_2: 3.0%–3.9%) (Model 2)				
I	<1.99	20.7	3.2	Reference
II	1.99–3.85	32.3	5.3	1.70 (1.27–2.27)
III	3.86–6.43	32.7	5.6	1.46 (1.05–2.01)
IV	≥6.44	45.9	9.2	2.25 (1.59–3.19)
HI (ΔSaO_2: 2.0%–2.9%) (Model 3)				
I	<4.46	25.2	3.3	Reference
II	4.46–6.78	28.8	4.9	0.94 (0.72–1.22)
III	6.79–10.32	35.4	6.5	1.29 (0.99–1.68)
IV	≥10.33	42.2	8.4	1.44 (1.09–1.90)
HI (ΔSaO_2: 0.0%–1.9%) (Model 4)				
I	<5.21	33.5	4.7	Reference
II	5.21–8.65	32.9	5.9	1.09 (0.85–1.38)
III	8.66–13.99	31.9	6.0	1.09 (0.86–1.39)
IV	≥14.00	33.3	6.6	1.15 (0.90–1.47)

*Odds ratio are adjusted for sex, age(quartiles), race (categories), smoking status (former, current, or never), alcohol consumption (none, moderate, heavy), usual sleep duration categories (≤6, 7, 8, ≥9), prevalent hypertension, neck circumference (quartiles), waist circumference (quartiles), body mass index (quartiles), and AHI (quartiles) based on apneas and hypopneas that are associated with more severe desaturation than the upper cut-point of predictor variable.

in glucose homeostasis with intermittent hypoxia may be most significant in the presence of obesity.[26] Although experimental work on the sequelae associated with hypoxia in humans is limited, several investigators have shown that even brief periods of hypoxic exposure can have detrimental effects on glucose metabolism. Conditions of altitude and hypobaric or normobaric hypoxia have been shown to consistently increase insulin levels, decrease insulin sensitivity, and worsen glucose tolerance.[27-29] Furthermore, patients with hypoxic pulmonary disease exhibit impaired glucose tolerance [30] that improves with supplemental oxygen therapy.[31] Thus, there is sufficient experimental and observational evidence to implicate SDB related intermittent hypoxemia as one of the putative intermediates for altered glucose metabolism. The findings of the current study indicate that the even milder degrees of sleep related hypoxemia, if recurrent, may have an important role in the pathogenesis of metabolic dysfunction.

Repetitive cycles of hypoxemia and re-oxygenation in SDB can induce the release of reactive oxygen species and trigger an inflammatory response. Compared to normal subjects, patients with SDB have higher levels of plasma IL-6 and TNF-α which improve with continuous positive pressure therapy.[32-35] IL-6 is a pleiotropic cytokine that is released by adipose tissue, endothelial cells, and immune cells as a glycosylated protein.[36] Higher serum levels of IL-6 positively correlate with insulin resistance and incident type 2 diabetes mellitus.[37-39] Administration of recombinant human IL-6 to healthy volunteers leads to higher fasting glucose levels in a dose dependent fashion.[40] While the role for TNF-α in the development of an insulin resistant state remains to be defined, neutralization of TNF-α has been associated with improvements in insulin sensitivity in obese rats.[41] Finally, hypoxemia can increase sympathetic neural traffic[42,43] and the release of glucoregulatory neuroendocrine hormones such as cortisol[44-46] that can result in hyperglycemia. Thus, the available evidence provides sound biologic plausibility for hypoxia as a modulator of glucose metabolism. Nonetheless, the putative causal pathways linking SDB, and in particular nocturnal hypoxemia, to altered glucose metabolism remains to be better defined.

A discussion of the mechanisms through which SDB may impair glucose metabolism must also consider the impact of SDB-related recurrent arousals form sleep. As previously noted, sleep fragmentation can elicit a set of pathophysiologic events that may play a role in the development and progression of impaired glucose metabolism. For example, increased sympathetic and corticotropic activity triggered by frequent arousals from sleep may provide the milieu for altering glucose homeostasis. Activation of the sympathetic nervous system, a hallmark of SDB, is known to increase catecholamines, pancreatic secretion of glucagon, release of cortisol from the adrenals, and lipolysis in adipose tissue, thus providing the resources for inducing a hyperglycemic state. Experimentally induced arousals from

sleep have been also shown to stimulate cortisol secretion,[10,11] thus providing support for the notion that independent of intermittent hypoxemia, sleep fragmentation can increase the predisposition for altered glucose metabolism. Interestingly, inclusion of the overall arousal frequency in our multivariable models relating measures of hypoxemia to glycemic status did not materially affect our findings. Nonetheless, further work is needed to elucidate the relative impact of intermittent arousals and hypoxemia on altered glucose metabolism in SDB.

A major strength of the current study was the careful consideration for the frequency of disordered breathing events associated with severe oxyhemoglobin desaturation. Such accounting was necessary to ensure that the results for a given desaturation threshold were not driven by events with greater degrees of desaturation. Statistical adjustments for such events showed that disordered breathing with milder degrees of hypoxemia may in fact be detrimental for glucose metabolism. Although the AHI based on the 4% threshold was correlated with hypopnea indices at thresholds below 4%, the correlation became weaker at lower thresholds. The decreasing concordance suggests that there was a fair amount of variation in the milder indices that was not explained by the more severe index, indicating that the results for milder events were not solely driven by the co-occurrence of the more severe events. Another unique aspect of this study is the availability of full-montage polysomnography and measurements of glycemic status on a large community-based sample. The diversity of the cohort enabled a thorough examination of dose-response relationships across a broad range of breathing abnormalities during sleep.

Despite these strengths, there are several limitations that need consideration. First, because the analyses were cross-sectional, definitive conclusions regarding the temporality of metabolic impairment in SDB cannot be delineated. However, a reverse-causation argument is somewhat weakened given the fact that the dependent variable (i.e., fasting glycemia) was based on preclinical categories with exclusion of clinically diagnosed and treated diabetics. Second, although measures of obesity and in particular central obesity were included in all multivariable models, the concern for residual confounding due to visceral obesity remains.[47,48] Availability of total body and visceral fat mass measurements would have minimized the well-established confounding effects of visceral obesity[49-53] in segregating the independent impact of SDB from that of obesity on glucose metabolism. Finally, the measurements of airflow in the SHHS cohort were based on the use of a thermistor device. Studies that have compared measurements of airflow with a thermistor and newer approaches, such as nasal pressure recordings, have found that the thermistor may not adequately identify disordered breathing abnormalities during sleep.[54-56]

The agenda of etiological research calls for an understanding of the pathogenic potential of SDB across a range of the disorder, which may extend beyond cutpoints currently used to diagnose cases that merit clinical treatment. The major implication of the current investigation is that milder forms of SDB may be important in predicting the risk of having impaired glucose metabolism and possibly other adverse health effects. Reliance on stringent criteria in defining SDB may overlook those with milder forms of the disorder who are nonetheless at risk of adverse consequences.

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REFERENCES

1. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med 2002;165:1217-39.
2. Punjabi NM, Ahmed MM, Polotsky VY, Beamer BA, O'Donnell CP. Sleep-disordered breathing, glucose intolerance, and insulin resistance. Respir Physiol Neurobiol 2003;136:167-78.
3. Punjabi NM, Polotsky VY. Disorders of glucose metabolism in sleep apnea. J Appl Physiol 2005;99:1998-2007.
4. Elmasry A, Janson C, Lindberg E, Gislason T, Tageldin MA, Boman G. The role of habitual snoring and obesity in the development of diabetes: a 10-year follow-up study in a male population. J Intern Med 2000;248:13-20.
5. Al Delaimy WK, Manson JE, Willett WC, Stampfer MJ, Hu FB. Snoring as a risk factor for type II diabetes mellitus: a prospective study. Am J Epidemiol 2002;155:387-93.
6. Reichmuth KJ, Austin D, Skatrud JB, Young T. Association of sleep apnea and type II diabetes: a population-based study. Am J Respir Crit Care Med 2005;172:1590-5.
7. Punjabi NM, Shahar E, Redline S, Gottlieb DJ, Givelber R, Resnick HE. Sleep-disordered breathing, glucose intolerance, and insulin resistance: the Sleep Heart Health Study. Am J Epidemiol 2004;160:521-30.
8. Xie A, Skatrud JB, Crabtree DC, Puleo DS, Goodman BM, Morgan BJ. Neurocirculatory consequences of intermittent asphyxia in humans. J Appl Physiol 2000;89:1333-9.
9. Xie A, Skatrud JB, Puleo DS, Morgan BJ. Exposure to hypoxia produces long-lasting sympathetic activation in humans. J Appl Physiol 2001;91:1555-62.
10. Spath-Schwalbe E, Gofferje M, Kern W, Born J, Fehm HL. Sleep disruption alters nocturnal ACTH and cortisol secretory patterns. Biol Psychiatry 1991;29:575-84.
11. Follenius M, Brandenberger G, Bandesapt JJ, Libert JP, Ehrhart J. Nocturnal cortisol release in relation to sleep structure. Sleep 1992; 15:21-27.
12. Iber C, Ancoli-Israel S, Chesson A, Quan SF. The AASM manual for scoring of sleep and associated events: rules, terminology and technical specifications. Westchester, IL: American Academy of Sleep Medicine; 2007.
13. Quan SF, Howard BV, Iber C, et al. The Sleep Heart Health Study: design, rationale, and methods. Sleep 1997;20:1077-85.
14. Redline S, Sanders MH, Lind BK, et al. Methods for obtaining and analyzing unattended polysomnography data for a multicenter study. Sleep Heart Health Research Group. Sleep 1998;21:759-67.
15. EEG arousals: scoring rules and examples: a preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. Sleep 1992;15:173-84.
16. Diagnosis and classification of diabetes mellitus. Diabetes Care 2007;30 Suppl 1:S42-7.

17. Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. Lancet 1999;354:1435-9.
18. Houston TK, Person SD, Pletcher MJ, Liu K, Iribarren C, Kiefe CI. Active and passive smoking and development of glucose intolerance among young adults in a prospective cohort: CARDIA study. BMJ 2006;332:1064-9.
19. Foy CG, Bell RA, Farmer DF, Goff DC Jr, Wagenknecht LE. Smoking and incidence of diabetes among U.S. adults: findings from the Insulin Resistance Atherosclerosis Study. Diabetes Care 2005;28:2501-7.
20. Lee KS, Park CY, Meng KH, et al. The association of cigarette smoking and alcohol consumption with other cardiovascular risk factors in men from Seoul, Korea. Ann Epidemiol 1998;8:31-8.
21. Bell RA, Mayer-Davis EJ, Martin MA, D'Agostino RB Jr, Haffner SM. Associations between alcohol consumption and insulin sensitivity and cardiovascular disease risk factors: the Insulin Resistance and Atherosclerosis Study. Diabetes Care 2000;23:1630-6.
22. Carlsson S, Hammar N, Efendic S, Persson PG, Ostenson CG, Grill V. Alcohol consumption, Type 2 diabetes mellitus and impaired glucose tolerance in middle-aged Swedish men. Diabet Med 2000;17:776-81.
23. Cheng N, Cai W, Jiang M, Wu S. Effect of hypoxia on blood glucose, hormones, and insulin receptor functions in newborn calves. Pediatr Res 1997; 41:852-856.
24. Raff H, Bruder ED, Jankowski BM, Colman RJ. Effect of neonatal hypoxia on leptin, insulin, growth hormone and body composition in the rat. Horm Metab Res 2001;33:151-5.
25. Raff H, Bruder ED, Jankowski BM. The effect of hypoxia on plasma leptin and insulin in newborn and juvenile rats. Endocrine 1999;11:37-9.
26. Polotsky VY, Li J, Punjabi NM, et al. Intermittent hypoxia increases insulin resistance in genetically obese mice. J Physiol 2003;552:253-64.
27. Larsen JJ, Hansen JM, Olsen NV, Galbo H, Dela F. The effect of altitude hypoxia on glucose homeostasis in men. J Physiol (Lond) 1997;504(Pt 1):241-9.
28. Braun B, Rock PB, Zamudio S, et al. Women at altitude: short-term exposure to hypoxia and/or alpha(1)-adrenergic blockade reduces insulin sensitivity. J Appl Physiol 2001;91:623-31.
29. Oltmanns KM, Gehring H, Rudolf S et al. Hypoxia causes glucose intolerance in humans. Am J Respir Crit Care Med 2004;169:1231-37.
30. Hjalmarsen A, Aasebo U, Birkeland K, Sager G, Jorde R. Impaired glucose tolerance in patients with chronic hypoxic pulmonary disease. Diabetes Metab 1996; 22:37-42.
31. Jakobsson P, Jorfeldt L. Oxygen supplementation increases glucose tolerance during euglycaemic hyperinsulinaemic glucose clamp procedure in patients with severe COPD and chronic hypoxaemia. Clin Physiol Funct Imaging 2006;26:271-4.
32. Vgontzas AN, Papanicolaou DA, Bixler EO, et al. Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia. J Clin Endocrinol Metab 2000;85:1151-8.
33. Liu H, Liu J, Xiong S, Shen G, Zhang Z, Xu Y. The change of interleukin-6 and tumor necrosis factor in patients with obstructive sleep apnea syndrome. J Tongji Med Univ 2000;20:200-2.
34. Yokoe T, Minoguchi K, Matsuo H, et al. Elevated levels of C-reactive protein and interleukin-6 in patients with obstructive sleep apnea syndrome are decreased by nasal continuous positive airway pressure. Circulation 2003;107:1129-34.
35. Ciftci TU, Kokturk O, Bukan N, Bilgihan A. The relationship between serum cytokine levels with obesity and obstructive sleep apnea syndrome. Cytokine 2004;28:87-91.
36. Mohamed-Ali V, Pinkney JH, Coppack SW. Adipose tissue as an endocrine and paracrine organ. Int J Obes Relat Metab Disord 1998;22:1145-58.
37. Fernandez-Real JM, Vayreda M, Richart C, et al. Circulating interleukin 6 levels, blood pressure, and insulin sensitivity in apparently healthy men and women. J Clin Endocrinol Metab 2001;86:1154-9.
38. Hak AE, Pols HA, Stehouwer CD, et al. Markers of inflammation and cellular adhesion molecules in relation to insulin resistance in nondiabetic elderly: the Rotterdam study. J Clin Endocrinol Metab 2001;86:4398-405.
39. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. JAMA 2001;286:327-34.
40. Tsigos C, Papanicolaou DA, Kyrou I, Defensor R, Mitsiadis CS, Chrousos GP. Dose-dependent effects of recombinant human interleukin-6 on glucose regulation. J Clin Endocrinol Metab 1997;82:4167-70.
41. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science 1993;259:87-91.
42. Leuenberger U, Jacob E, Sweer L, Waravdekar N, Zwillich C, Sinoway L. Surges of muscle sympathetic nerve activity during obstructive apnea are linked to hypoxemia. J Appl Physiol 1995;79:581-8.
43. Smith ML, Niedermaier ON, Hardy SM, Decker MJ, Strohl KP. Role of hypoxemia in sleep apnea-induced sympathoexcitation. J Auton Nerv Syst 1996; 56:184-190.
44. Anand IS, Chandrashekhar Y, Rao SK, et al. Body fluid compartments, renal blood flow, and hormones at 6,000 m in normal subjects. J Appl Physiol 1993;74:1234-9.
45. Obminski Z, Golec L, Stupnicki R, Hackney AC. Effects of hypobaric-hypoxia on the salivary cortisol levels of aircraft pilots. Aviat Space Environ Med 1997;68:183-6.
46. Barnholt KE, Hoffman AR, Rock PB, et al. Endocrine responses to acute and chronic high-altitude exposure (4,300 meters): modulating effects of caloric restriction. Am J Physiol Endocrinol Metab 2006;290:E1078-88.
47. Montague CT, O'Rahilly S. The perils of portliness: causes and consequences of visceral adiposity. Diabetes 2000;49:883-88.
48. Lafontan M, Berlan M. Do regional differences in adipocyte biology provide new pathophysiological insights? Trends Pharmacol Sci 2003;24:276-83.
49. Fujioka S, Matsuzawa Y, Tokunaga K, Tarui S. Contribution of intra-abdominal fat accumulation to the impairment of glucose and lipid metabolism in human obesity. Metabolism 1987;36:54-9.
50. Despres JP, Nadeau A, Tremblay A, et al. Role of deep abdominal fat in the association between regional adipose tissue distribution and glucose tolerance in obese women. Diabetes 1989;38:304-9.
51. Pouliot MC, Despres JP, Nadeau A, et al. Visceral obesity in men. Associations with glucose tolerance, plasma insulin, and lipoprotein levels. Diabetes 1992;41:826-34.
52. Park KS, Rhee BD, Lee KU, et al. Intra-abdominal fat is associated with decreased insulin sensitivity in healthy young men. Metabolism 1991;40:600-3.
53. Marin P, Andersson B, Ottosson M, et al. The morphology and metabolism of intraabdominal adipose tissue in men. Metabolism 1992;41:1242-8.
54. Norman RG, Ahmed MM, Walsleben JA, Rapoport DM. Detection of respiratory events during NPSG: nasal cannula/pressure sensor versus thermistor. Sleep 1997;20:1175-84.
55. Series F, Marc I. Nasal pressure recording in the diagnosis of sleep apnoea hypopnoea syndrome. Thorax 1999;54:506-10.
56. BaHammam A. Comparison of nasal prong pressure and thermistor measurements for detecting respiratory events during sleep. Respiration 2004;71:385-90.