Original Article

Association of apnea-hypopnea index during rapid eye movement sleep with insulin resistance in patients with suspected obstructive sleep apnea: a cross-sectional study

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Background: Obstructive sleep apnea (OSA) is associated with insulin resistance. However, the association between special stages of OSA [rapid eye movement (REM) sleep] and insulin resistance is not clear. This study was designed to assess the association of the frequency of respiratory events during REM sleep with insulin resistance in adults with suspected OSA.

Methods: In this cross-sectional study, 4,062 adult participants with suspected OSA who underwent polysomnography in our sleep center between 2009 and 2016 were screened. Polysomnographic variables, biochemical indicators, and physical measurements were collected. Logistic regression analyses were conducted to determine the odds ratios (ORs) and 95% confidence intervals (95% CIs) for insulin resistance as assessed by the presence of hyperinsulinemia, the homeostasis model assessment of insulin resistance (HOMA-IR) index, the fasting insulin resistance index (FIRI), and Bennett's insulin sensitivity index (ISI).

Results: The final analyses included 2,899 adults with suspected OSA. Multivariate adjustments, including the apnea-hypopnea index (AHI) during non-REM sleep (AHI_{NREM}), were performed. The AHI during REM sleep (AHI_{REM}) was found to be independently associated with insulin resistance across increasing AHI_{REM} quartiles. For hyperinsulinemia the ORs (95% CIs) followed the order of 1.340 (1.022, 1.757), 1.210 (0.882, 1.660), and 1.632 (1.103, 2.416). For abnormal HOMA-IR, ORs (95% CIs) were 1.287 (0.998, 1.661), 1.263 (0.933, 1.711), and 1.556 (1.056, 2.293). For abnormal FIRI, ORs (95% CIs) were 1.386 (1.048, 1.835), 1.317 (0.954, 1.818), and 1.888 (1.269, 2.807). For abnormal Bennett's ISI, ORs (95% CIs) were 1.297 (1.003, 1.678), 1.287 (0.949, 1.747), and 1.663 (1.127, 2.452). All linear trends were statistically significant ($P<0.01$). Additionally, the results showed that REM sleep duration was independently associated with hyperinsulinemia (OR =0.777, 95% CI: 0.615–0.982; $P<0.05$).

Conclusions: AHI_{REM} was independently associated with hyperinsulinemia and an abnormal HOMA-IR, FIRI, and Bennett's ISI in adults with suspected OSA. Additionally, REM sleep duration was independently associated with hyperinsulinemia.

Keywords: Obstructive sleep apnea (OSA); rapid eye movement sleep (REM sleep); sleep duration; insulin resistance

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Introduction

Obstructive sleep apnea (OSA) is a common chronic disease that is characterized by recurrent complete or partial upper airway obstruction during sleep resulting in intermittent hypoxia, hypercapnia, and cortical microarousals (1). Accumulating evidence indicates that OSA is related to various clinical sequelae, including diabetes, hypertension, dyslipidemia, stroke, and cardiovascular events (2,3). Insulin resistance has been suggested as an important shared risk factor for these sequelae (4,5).

OSA can occur during rapid eye movement (REM) sleep as well as non-REM (NREM) sleep. Although REM sleep accounts for only approximately 25% of a person's total sleep period, the propensity for upper airway collapse during REM sleep is greater due to the cholinergic mediation of genioglossus muscle suppression during this stage (6). Additionally, during REM sleep, the duration of respiratory events is longer, oxygen desaturation is greater, and respiratory effort is lower (7,8). Despite previous studies having uncovered an independent relationship between OSA and insulin resistance (9,10), the REM sleep stage is a unique stage, and the associations of insulin resistance with respiratory events and sleep duration during this stage have not been illuminated.

OSA during REM sleep is independently associated with increased carotid intima thickness (11), poor glycemic control (12) and recurrent cardiovascular events (13); however, little is known about its association with insulin resistance. A recent study (14) found that the apnea-hypopnea index (AHI) during REM sleep (AHI_{REM}) was associated with the homeostasis model assessment of insulin resistance (HOMA-IR) index. However, that study's findings were limited because only middle-aged and elderly participants were included, attended in-laboratory polysomnography (PSG) data were lacking, the risk of insulin resistance was not evaluated, and confounding factors were not fully adjusted for, including blood pressure (BP), which is closely associated with insulin resistance (15,16). Studies have also shown that repeated arousal during REM sleep can lead to a decrease in REM sleep duration, which in turn influences the levels of various adipokines and the activity of the hypothalamic-pituitary-adrenal axis (17,18). Thus, we speculate that REM sleep duration is related to insulin resistance.

Therefore, the primary objective of this large cross-sectional study was to investigate the association between AHI_{REM} and insulin resistance in adults of all ages using laboratory PSG data.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-3165).

Methods

Study population

The data reported in this cross-sectional study were obtained from the Shanghai Sleep Health Study (SSHS) cohort, which has been previously described (19). Initially, 4,062 consecutive participants aged 18 to 88 who underwent overnight PSG for suspected OSA in the sleep center of Shanghai Jiao Tong University Affiliated Sixth People's Hospital between 2009 and 2016 were recruited. The exclusion criteria were as follows: (I) a history of treatment for OSA; (II) use of lipid-lowering drugs; (III) presence of chronic diseases, such as chronic kidney disease, psychiatric disorders, malignancy, or hyperparathyroidism; (IV) <18 years of age; (V) treatment with insulin or hypoglycemic agents; (VI) REM sleep duration <30 min, which would reduce the precision of AHI_{REM} estimates (13); and (VII) missing clinical data. Finally, a total of 2,899 participants were included in this study (*Figure 1*). Written informed consent was obtained from all participants. This study was approved by the Internal Review Board of the Institutional Ethics Committee of Shanghai Jiao Tong University Affiliated Sixth People's Hospital [2018-KY-021(K)] and was conducted in accordance with the tenets of the Declaration of Helsinki (as revised in 2013).

PSG parameters

Overnight PSG, including electroencephalogram (EEG), electrooculogram (EOG), genioglossus electromyogram (EMG), electrocardiogram (ECG), pulse oxygen saturation (SpO_2), airflow, thoracic-abdominal movement, and body position measurements, was performed in the sleep center using the Respironics Alice 4 or 5 machine (Respironics Inc., Pittsburgh, USA). All sleep stages and respiratory events were evaluated according to the criteria of the American Academic Sleep Medicine (AASM) 2007 guidelines.

Apnea was defined as the complete cessation of airflow lasting for at least 10 s. Hypopnea was defined as either a ≥50% reduction in airflow for 10 s or more or a <50% but discernible reduction in airflow accompanied by either a

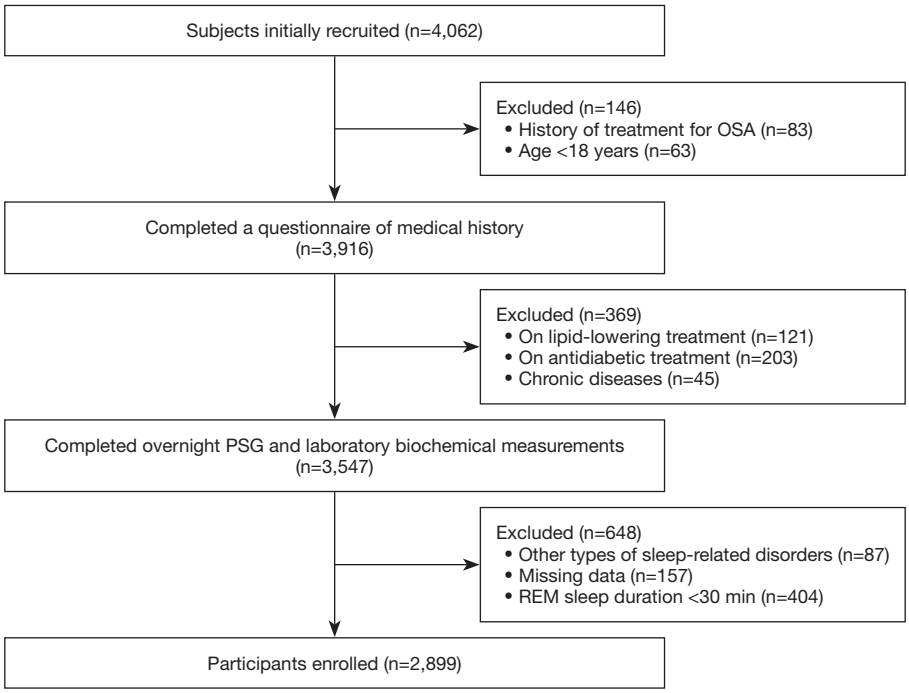

Figure 1 Flow diagram of recruitment and exclusion of participants. PSG, polysomnography.

decrease in oxyhemoglobin saturation of ≥4% or an arousal. The AHI was defined as the number of apnea and hypopnea events per hour during sleep. The AHI_{REM} and AHI during NREM sleep (AHI_{NREM}) were defined as the number of apnea and hypopnea events per hour during REM and NREM sleep, respectively. The arousal index was defined as the number of arousals per hour during recording. The oxygen desaturation index (ODI) was defined as the number of times the blood oxygen level decreased by ≥4% from baseline per hour.

Biochemical measurements

Fasting blood samples were obtained from all participants on the morning after the PSG procedure. Fasting blood glucose (FBG) levels were measured with an H-7600 autoanalyzer (Hitachi; Tokyo, Japan), and fasting insulin (FINS) levels were measured using an immunoradiology method. Four measures were used to quantify insulin resistance: (I) hyperinsulinemia; (II) HOMA-IR measured as FINS (mIU/L) × FBG (mmol/L)/22.5 (20); (III) fasting insulin resistance index (FIRI) measured as FINS (mIU/L) × FBG (mmol/L)/25 (21); and (IV) Bennett's insulin sensitivity index (ISI) measured as 1/(ln FBG × ln FINS) (22). FINS levels of 12.2 μU/mL or greater were defined as hyperinsulinemia. A HOMA index of 2.5 or greater, FIRI of 2.7 or greater, and Bennett's ISI of 1.34 or greater were considered to indicate insulin resistance (21,23,24).

Physical measurements

Participants' height and weight were measured according to standard procedures, with all participants wearing light clothes and barefoot. Body mass index (BMI) was calculated as the weight (kg) divided by the height squared (m^2), and waist circumference (WC) was measured midway between the lower costal margin and iliac crest. According to the recommendations of the International Diabetes Federation (IDF) for Chinese adults, a WC of ≥90 cm in men, or ≥80 cm in women was defined as abdominal obesity (25). BP was recorded as the average value of three sequential measurements using standard procedures and mean arterial pressure (MAP) was calculated as (systolic BP + 2 × diastolic BP)/3.

Statistical analysis

Descriptive statistics were expressed according to AHI_{REM} quartiles with continuous variables being presented as means ± standard deviations (SDs) and categorical variables being

presented as percentages. Linear trends across the AHI_{REM} quartiles were assessed using polynomial linear trend tests for continuous variables and linear-by-linear association tests for dichotomous variables. Collinearity diagnostics were carried out to eliminate possible multicollinearity among variables. The two steps of the collinearity analyses were: (I) a preliminary analysis using Spearman's correlation; and (II) collinearity diagnostics to determine the selected covariates in the multivariate regression analyses. The detailed results are shown in Tables S1-S9. Additionally, a correlation heat map was constructed using the corrplot package in R software. Binary logistic regression analyses were performed to assess odds ratios (ORs) and 95% confidence intervals (95% CIs) for hyperinsulinemia and abnormal HOMA-IR, FIRI, and Bennet's ISI values. Several factors, including age, sex, BMI, abdominal obesity, smoking status, alcohol consumption, and MAP, were incorporated into the multivariate regression model, while AHI_{NREM} was included when necessary. Linear trends across the four groups were computed by examining the median AHI_{REM} values for each quartile and conducting an overall F-test. Confirmatory analysis restricted to the subgroup with AHI_{NREM} values of ≤55.8 (the highest quartile) was performed to further exclude the influence of AHI_{NREM}.

All statistical analyses were performed with SPSS 19.0 software (SPSS, Inc.; Chicago, IL, USA) and R software. Two-tailed P values of <0.05 were considered to indicate statistical significance.

Results

Baseline characteristics

A total of 2,899 adults with suspected OSA were included in this study (*Figure 1*). Participant characteristics across the AHI_{REM} quartiles (≤8.1; >8.1, ≤34.3; >34.3, ≤56.5; and >56.5) are presented in *Table 1*. On average, participants in higher AHI_{REM} quartiles were more likely to be older, obese, and current smokers, and to have higher MAP (P<0.01 for all linear trends). There were also linear trends between AHI_{REM} quartiles and mean SpO_2, lowest SpO_2, AHI, sleep efficiency, and sleep time spent with SpO_2 <90% (P<0.001 for all linear trends). Additionally, AHI_{REM} showed positive dose-response relationships with FBG, FINS, HOMA-IR, FIRI, and ISI (P<0.001 for all linear trends). The percentages of patients with hyperinsulinemia, HOMA-IR ≥2.5, FIRI ≥2.7, and Bennett's ISI ≤1.34 rose with increasing AHI_{REM} quartile: from 20.8% to 64.6%, from 27.4% to 72.8%, from 18.1% to 63.6%, and from 26.1% to 72.4%, respectively (P<0.001 for all linear trends).

Association between AHI_{REM} and insulin resistance

Figure 2 presents a heatmap based on the Spearman correlation matrix. In the heatmap, numerical values are displayed by colors, with weaker correlations between variables displayed in light colors and stronger correlations displayed in darker colors, such as red or violet. AHI_{REM} was found to be weakly correlated with Bennett's ISI (r=–0.15), and mildly correlated with FINS (r=0.31), HOMA-IR (r=0.31), FIRI (r=0.31), hyperinsulinemia (r=0.33), abnormal HOMA-IR (r=0.34), abnormal FIRI (r=0.35), and abnormal Bennett's ISI (r=0.35) (all P values <0.01).

After adjustment for age, sex, BMI, WC, MAP, smoking status, and alcohol consumption in Model 1 and accounting for AHI_{NREM} in Model 2, the association between AHI_{REM} and insulin resistance (as measured by hyperinsulinemia and abnormal HOMA-IR, FIRI, and Bennett's ISI; *Table 2*) was estimated using logistic regression models. In Model 1, significant positive linear trends were observed in the ORs for insulin resistance as the AHI_{REM} quartile increased (P<0.001 for all linear trends). After the incorporation of AHI_{NREM} into Model 2, the linear relationship was slightly attenuated but remained significant (P<0.01 for all linear trends; *Table 2* & *Figure 3A,B,C,D*).

Analysis with OSA's severities was also performed, and similar results were observed (Table S10).

Subgroup verification

Table 3 displays the characteristics of participants after exclusion of the highest AHI_{NREM} quartile. Similar to the results of the analyses performed with all participants, on average, participants in the higher AHI_{REM} quartiles were more obese, had higher BP and were more likely to be smokers than those in the lower quartiles (P<0.01 for all linear trends). The sleep parameters, arousal index, ODI, and AHI all exhibited a linear increase across the AHI_{REM} groups, whereas the average SpO_2 and minimum SpO_2 showed linear decreases (P<0.001 for all linear trends). AHI_{REM} showed positive dose-response relationships with FINS, HOMA-IR, FIRI, and Bennett's ISI (P<0.001 for all linear trends). The percentage of individuals with hyperinsulinemia and abnormal HOMA-IR, FIRI, and Bennett's ISI increased across the AHI_{REM} quartiles from 18.5% to 46.4%, from 24.8% to 56.7%, from 15.6% to

Table 1 Characteristics, sleep parameters, and biochemical indicators of patients by AHI_{REM} quartile

Variables	AHI_{REM} ≤8.1 (N=725)	8.1< AHI_{REM} ≤34.3 (N=726)	34.3< AHI_{REM} ≤56.5 (N=730)	AHI_{REM} >56.5 (N=718)	P value for trend[a]
Characteristics					
Age, years	41.69±11.00	43.30±12.45	45.18±11.50	41.69±11.00	<0.001
Female, %	242, 33.4	155, 21.3	111, 15.2	98, 13.6	<0.001
BMI, kg/m^2	24.37±3.47	25.86±3.61	26.88±3.43	29.06±3.79	<0.001
WC, cm	88.20±10.44	93.60±9.69	96.67±9.49	101.95±10.32	<0.001
MAP, mmHg	91.42±10.32	93.31±11.29	96.49±12.42	98.24±11.76	<0.001
Current-smoker, %	128, 17.7	162, 22.3	191, 26.2	165, 23.0	0.004
Current-drinker, %	132, 18.2	160, 22.0	139, 19.0	144, 20.1	0.701
Abdominal obesity, %	427, 58.9	554, 76.3	614, 84.1	675, 94.0	<0.001
Sleep parameters					
Sleep efficiency, %	90.39±9.94	90.80±10.87	92.24±10.12	92.99±10.49	<0.001
Time spent on SpO_2 <90%, min	3.10±12.73	16.15±38.89	60.00±73.01	121.80±96.11	<0.001
AHI, events/h	5.68±7.74	19.45±14.09	41.95±17.04	66.08±18.01	<0.001
Mean SPO_2, %	96.20±1.45	95.05±2.14	93.27±3.21	90.78±4.50	<0.001
Lowest SPO_2, %	90.18±6.31	83.36±8.53	72.47±11.91	66.17±12.91	<0.001
ODI, events/h	6.23±9.15	20.43±16.40	42.97±20.20	66.99±20.96	<0.001
Arousal index, events/h	16.51±13.24	20.54±16.84	30.44±21.40	39.91±26.57	<0.001
REM sleep duration, h	0.99±0.38	0.97±0.37	0.94±0.36	0.96±0.40	0.044
Total sleep time, h	6.58±1.06	6.70±1.05	6.87±0.97	6.96±0.97	<0.001
Glucometabolism					
FBG, mmol/L	5.19±0.87	5.35±0.96	5.50±0.92	5.73±1.15	<0.001
FINS, μU/mL	9.36±6.78	11.54±8.01	13.13±9.05	16.65±10.64	<0.001
HOMA-IR	2.23±1.96	2.83±2.23	3.33±2.90	4.34±3.18	<0.001
FIRI	2.00±1.77	2.55±2.01	3.00±2.61	3.91±2.86	<0.001
Bennet's ISI	1.77±1.88	1.60±0.76	1.43±0.59	1.30±1.37	<0.001
Hyperinsulinemia, %	151, 20.8	243, 33.5	297, 40.7	464, 64.6	<0.001
HOMA-IR ≥2.5, %	199, 27.4	307, 42.3	382, 52.3	523, 72.8	<0.001
FIRI ≥2.7, %	131, 18.1	226, 31.1	287, 39.3	457, 63.6	<0.001
Bennet's ISI ≤1.34, %	189, 26.1	296, 40.8	372, 51.0	520, 72.4	<0.001

Data are presented as means ± SD or percentage. [a], tested by the polynomial linear trend test for continuous variables and the linear-by-linear association test for dichotomous variables. REM, rapid eye movement; AHI_{REM}, apnea-hypopnea index during REM sleep; BMI, body mass index; WC, waist circumference; MAP, mean arterial pressure; AHI, apnea hypopnea index; ODI, oxygen desaturation index; FBG, fasting blood glucose; FINS, fasting insulin; HOMA-IR, homeostasis model assessment of insulin resistance; FIRI, fasting insulin resistance index; ISI, insulin sensitivity index.

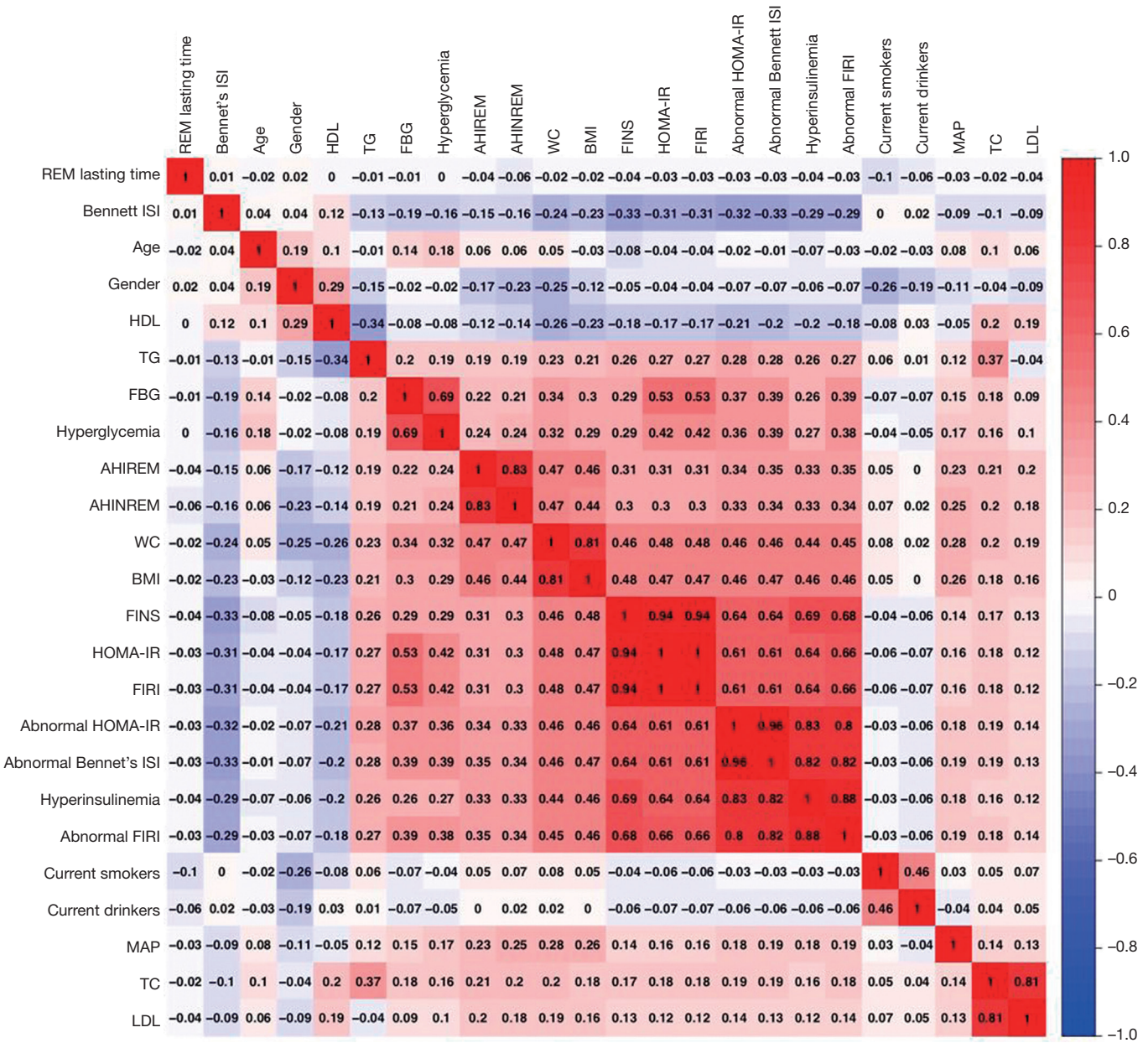

Figure 2 Heatmap based on the Spearman correlation matrix of the 24 metrics. REM, rapid eye movement; NREM, non-rapid eye movement; ISI, insulin sensitivity index; HDL, high-density lipoprotein; TG, triglyceride; FBG, fasting blood glucose; AHI, apnea-hypopnea index; AHIREM, AHI during REM sleep; AHINREM, AHI during NREM sleep; WC, waist circumference; BMI, body mass index; FINS, fasting insulin; HOMA-IR, homeostasis model assessment of insulin resistance; FIRI, fasting insulin resistance index; MAP, mean arterial pressure; TC, total cholesterol; LDL, low-density lipoprotein.

44.9%, and from 23.7% to 54.9%, respectively (P<0.001 for all linear trends).

Logistic regression analyses adjusted for age, sex, BMI, WC, MAP, smoking status, and alcohol consumption showed that AHI_{REM} was independently correlated with hyperinsulinemia and abnormal HOMA-IR, FIRI, and Bennett's ISI. These correlations persisted after AHI_{NREM} was incorporated in Model 2 (*Table 4* & *Figure 3E,F,G,H*).

Table 2 Adjusted odds ratios for characteristics of insulin resistance by AHI_{REM} quartile in Models 1 and 2

Model	Hyperinsulinemia	HOMA-IR ≥2.5	FIRI ≥2.7	Bennet's ISI ≤1.34
Model 1 adjusted OR (95% CI)				
AHI_{REM} ≤8.1	1	1	1	1
8.2< AHI_{REM} ≤34.3	1.455 (1.116, 1.897)	1.388 (1.082, 1.781)	1.495 (1.136, 1.967)	1.397 (1.086, 1.796)
34.3< AHI_{REM} ≤56.5	1.545 (1.181, 2.023)	1.587 (1.230, 2.048)	1.641 (1.245, 2.162)	1.608 (1.244, 2.079)
AHI_{REM} >56.5	2.466 (1.870, 3.252)	2.282 (1.738, 2.996)	2.736 (2.064, 3.625)	2.415 (1.838, 3.174)
P for trend	<0.001	<0.001	<0.001	<0.001
Model 2 adjusted OR (95% CI)				
AHI_{REM} ≤8.1	1	1	1	1
8.2< AHI_{REM} ≤34.3	1.340 (1.022, 1.757)	1.287 (0.998, 1.661)	1.386 (1.048, 1.835)	1.297 (1.003, 1.678)
34.3< AHI_{REM} ≤56.5	1.210 (0.882, 1.660)	1.263 (0.933, 1.711)	1.317 (0.954, 1.818)	1.287 (0.949, 1.747)
AHI_{REM} >56.5	1.632 (1.103, 2.416)	1.556 (1.056, 2.293)	1.888 (1.269, 2.807)	1.663 (1.127, 2.452)
P for trend	0.006	0.003	0.001	0.001

Model 1: to observe the risks of insulin resistance across AHI_{REM} quartile, the age, gender, BMI, WC, MAP, smoking status, and alcohol consumption were adjusted. Model 2: to consider the influence of AHI_{NREM}, we adjusted the factors in model 1 as well as AHI_{NREM}. REM, rapid eye movement; NREM, non-rapid eye movement; AHI_{REM}, apnea-hypopnea index during REM sleep; AHI_{NREM}, apnea-hypopnea index during NREM sleep; HOMA-IR, homeostasis model assessment of insulin resistance; FIRI, fasting insulin resistance index; ISI, insulin sensitivity index; OR, odds ratio; CI, confidence interval; BMI, body mass index; WC, waist circumference; MAP, mean arterial pressure.

Association between REM sleep duration and insulin resistance

After adjustment for age, sex, BMI, WC, MAP, AHI, smoking status, alcohol consumption, and NREM sleep duration, REM sleep duration was found to be associated with hyperinsulinemia (OR: 0.777, 95% CI: 0.615, 0.982; *Table 5*). Furthermore, for every 1-hour increase in REM sleep duration, the risk of hyperinsulinemia decreased by 22.3% (P=0.035).

To further confirm the results, logistic analysis was performed with adjustment for age, sex, BMI, abdominal obesity, smoking status, alcohol consumption, MAP, NREM sleep duration, AHI_{REM}, and AHI_{NREM}. REM sleep duration was found to be associated with hyperinsulinemia (OR: 0.764, 95% CI: 0.604, 0.966; Table S11) and abnormal FIRI (OR: 0.786, 95% CI: 0.619, 0.997; Table S11).

Discussion

This large cross-sectional study demonstrated an independent association between AHI_{REM} and insulin resistance in adults of all ages based on laboratory PSG data and multivariate adjustments. Furthermore, a positive linear trend for the risk of insulin resistance across AHI_{REM} quartiles was observed after adjustment for multiple variables, including AHI_{NREM}. Additionally, REM sleep duration was independently associated with the risk of hyperinsulinemia.

Several previous studies have evaluated the associations of AHI_{REM} with various clinical sequelae, including lipid metabolism, hypertension, peripheral arterial stiffness, and cardiovascular events (11-13,26,27); however, the association between AHI_{REM} and insulin resistance, which is a common and important risk factor, has rarely been investigated. While a recent study (14) reported that AHI_{REM} was associated with insulin resistance, this study was limited by the inclusion of only middle-aged and elderly participants; lack of in-laboratory PSG data; lack of adjustment for BP, which is closely associated with insulin resistance (15,16); and lack of risk assessment of insulin resistance. The present study accounted for the above-mentioned limitations, and found that, after adjustment for age, sex, BMI, WC, MAP, smoking status, alcohol consumption, and AHI_{NREM}, patients with higher AHI_{REM} had an increased risk of insulin resistance. The potential mechanisms involved in this association may include increased sympathetic nerve activity

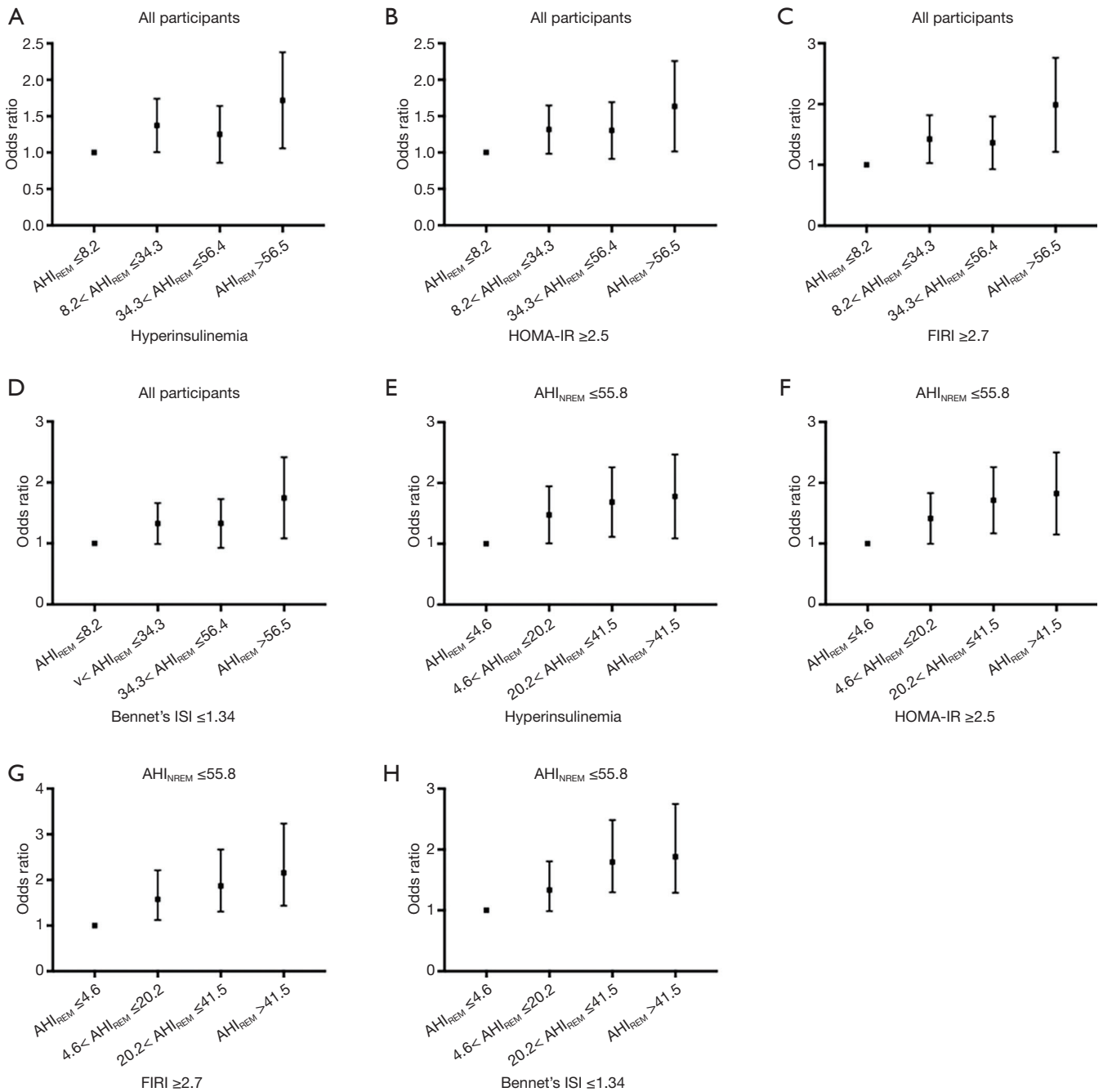

Figure 3 ORs and 95% CIs for insulin resistance across AHI_{REM} quartiles among all participants (A,B,C,D) and subgroups (E,F,G,H). The estimates were adjusted for age, sex, BMI, WC, MAP, smoking status, alcohol consumption and AHI_{NREM}. REM, rapid eye movement; NREM, non-rapid eye movement; AHI_{REM}, apnea-hypopnea index during REM sleep; AHI_{NREM}, apnea-hypopnea index during NREM sleep; HOMA-IR, homeostasis model assessment of insulin resistance; FIRI, fasting insulin resistance index; ISI, insulin sensitivity index.

during REM sleep, decreased genioglossus muscle tone due to hypoglossal nerve inhibition and prolonged apnea and hypopnea (7,8,28).

As the first-line treatment for OSA, continuous positive airway pressure (CPAP) therapy can enlarge the airway, alleviate somnolence, and improve health status (29).

Table 3 Characteristics of subjects with AHI_{NREM} ≤55.8 further stratified by AHI_{REM} quartiles and with AHI_{NREM} >55.8 events/hour

Variables	AHI_{NREM} >55.8 (N=723)	AHI_{NREM} ≤55.8				
		AHI_{REM} ≤4.60 (N=545)	4.60< AHI_{REM} ≤20.20 (N=549)	20.20< AHI_{REM} ≤41.50 (N=539)	AHI_{REM} >41.50 (N=543)	P value for trend
Characteristics						
Age, years	42.16±10.86	39.01±11.97	42.03±12.11	44.36±12.35	44.33±11.74	<0.001
Female, %	68, 9.4	206, 37.8	121, 22.0	111, 20.6	101, 18.6	<0.001
BMI, kg/m^2	28.83±3.82	24.13±3.65	25.34±3.14	26.24±3.65	27.41±3.56	<0.001
WC, cm	101.81±10.13	87.48±10.80	91.78±9.37	94.56±9.61	97.64±9.74	<0.001
MAP, mmHg	98.44±11.83	91.18±10.44	92.44±10.62	94.63±12.43	96.44±11.75	<0.001
Current-smoker, %	184, 25.4	89, 16.3	131, 23.9	103, 19.1	139, 25.6	0.003
Current-drinker, %	145, 20.1	95, 17.4	124, 22.6	100, 18.6	111, 20.4	0.513
Abdominal obesity, %	678, 93.8	303, 55.6	389, 70.9	434, 80.5	468, 86.2	<0.001
Sleep parameters						
Sleep efficiency, %	92.90±10.37	89.97±10.30	91.07±10.47	91.11±10.38	92.53±10.27	<0.001
Time spent on SpO_2 <90%, min	137.73±94.98	2.68±12.81	8.00±24.72	22.96±42.43	50.52±58.75	<0.001
AHI, times/h	71.45±11.54	4.57±7.15	12.77±11.03	25.34±13.03	39.52±12.19	<0.001
Mean SpO_2, %	90.18±4.50	96.36±1.43	95.50±1.61	94.68±2.33	93.63±2.64	<0.001
Lowest SpO_2, %	64.63±12.71	90.86±5.99	86.48±7.46	79.40±9.83	73.30±10.95	<0.001
ODI, times/h	71.67±16.57	5.19±8.50	13.26±12.86	26.79±16.03	41.29±17.39	<0.001
MAI, times/h	43.74±25.63	16.44±13.14	18.47±15.31	22.32±17.46	27.57±20.84	<0.001
REM sleep duration, h	0.92±0.36	0.99±0.37	0.96±0.36	0.98±0.40	0.98±0.41	0.850
Total sleep time, h	6.96±0.92	6.55±1.08	6.63±1.06	6.80±0.98	6.90±1.03	<0.001
Glucometabolism						
FBG, mmol/L	5.73±1.10	5.15±0.77	5.27±0.88	5.41±0.98	5.56±1.07	<0.001
FINS, μU/mL	16.41±10.56	8.98±6.67	10.61±7.24	12.04±8.22	14.02±9.63	<0.001
HOMA-IR	4.28±3.13	2.11±1.87	2.56±2.03	2.99±2.44	3.61±3.11	<0.001
FIRI	3.85±2.82	1.90±1.68	2.30±1.83	2.69±2.20	3.25±2.80	<0.001
Bennet's ISI	1.27±0.73	1.83±2.13	1.65±0.79	1.53±0.72	1.43±1.42	<0.001
Hyperinsulinemia, %	450, 62.2	101, 18.5	155, 28.2	197, 36.5	252, 46.4	<0.001
HOMA-IR ≥2.5, %	516, 71.4	135, 24.8	200, 36.4	252, 46.8	308, 56.7	<0.001
FIRI ≥2.7, %	445, 61.5	85, 15.6	142, 25.9	185, 34.3	244, 44.9	<0.001
Bennet's ISI ≤1.34, %	516, 71.4	129, 23.7	187, 34.1	247, 45.8	298, 54.9	<0.001

Data are presented as means ± SD or percentage. REM, rapid eye movement; NREM, non-rapid eye movement; AHI_{REM}, apnea-hypopnea index during REM sleep; AHI_{NREM}, apnea-hypopnea index during NREM sleep; BMI, body mass index; WC, waist circumference; MAP, mean arterial pressure; ODI, oxygen desaturation index; MAI, microarousal index; FBG, fasting blood glucose; FINS, fasting insulin; HOMA-IR, homeostasis model assessment of insulin resistance; FIRI, fasting insulin resistance index; ISI, insulin sensitivity index.

Table 4 Adjusted odds ratios for characteristics of insulin resistance by AHI_{REM} quartile in Models 1 and 2 among subjects with AHI_{NREM} ≤55.8

Model	Hyperinsulinemia	HOMA-IR ≥2.5	FIRI ≥2.7	Bennet's ISI ≤1.34
Model 1 adjusted OR (95% CI)				
AHI_{REM} ≤4.60	1	1	1	1
4.60< AHI_{REM} ≤20.20	1.462 (1.062, 2.012)	1.389 (1.034, 1.865)	1.569 (1.123, 2.194)	1.322 (0.981, 1.783)
20.20< AHI_{REM} ≤41.50	1.733 (1.260, 2.385)	1.708 (1.270, 2.298)	1.845 (1.323, 2.574)	1.752 (1.299, 2.362)
AHI_{REM} >41.50	1.902 (1.378, 2.625)	1.838 (1.356, 2.492)	2.110 (1.512, 2.945)	1.803 (1.328, 2.448)
P for trend	<0.001	<0.001	<0.001	<0.001
Model 2 adjusted OR (95% CI)				
AHI_{REM} ≤4.60	1	1	1	1
4.60< AHI_{REM} ≤20.20	1.426 (1.032, 1.970)	1.373 (1.019, 1.850)	1.576 (1.123, 2.212)	1.334 (0.986, 1.805)
20.20< AHI_{REM} ≤41.50	1.621 (1.149, 2.288)	1.656 (1.199, 2.286)	1.867 (1.305, 2.670)	1.794 (1.297, 2.483)
AHI_{REM} >41.50	1.689 (1.138, 2.508)	1.740 (1.194, 2.536)	2.154 (1.434, 3.236)	1.881 (1.288, 2.748)
P for trend	0.006	0.001	<0.001	<0.001

Model 1: to observe the risks for insulin resistance across AHI_{REM} quartile, the age, gender, BMI, WC, MAP, smoking status, and alcohol consumption were adjusted. Model 2: to consider the influence of AHI_{NREM}, we adjusted the factors in model 1 as well as AHI_{NREM}. REM, rapid eye movement; NREM, non-rapid eye movement; AHI_{REM}, apnea-hypopnea index during REM sleep; AHI_{NREM}, apnea-hypopnea index during NREM sleep; HOMA-IR, homeostasis model assessment of insulin resistance; FIRI, fasting insulin resistance index; ISI, insulin sensitivity index; OR, odds ratio; CI, confidence interval; BMI, body mass index; WC, waist circumference; MAP, mean arterial pressure.

However, no consensus has been reached as to whether this therapy can improve insulin resistance. Martinez and colleagues (30) reviewed related research and found that CPAP improved insulin levels and insulin resistance, whereas Jullian and colleagues (31) failed to find these beneficial effects. As REM sleep occurs mainly during the latter half of sleep, 4 hours of CPAP therapy per night may not cover all periods of REM sleep. Additionally, in the present study, AHI_{REM} was independently associated with insulin resistance. Therefore, it is plausible that untreated OSA during REM sleep could weaken the effects of CPAP on insulin resistance. In contrast, 7 hours of CPAP therapy per night covers more than 85% of REM sleep (12). Therefore, insufficient CPAP use may be the reason for the poor treatment effects, suggesting that more attention should be paid to verifying whether nightly CPAP treatment should be extended beyond 4 hours. In addition, higher CPAP pressure during REM sleep may be effective in thoroughly eliminating respiratory events.

In terms of sleep duration, short sleep duration is reported to be significantly associated with decreased insulin sensitivity (32), as well as increased subclinical atherosclerosis risk (33). However, to date, no studies have investigated the association between REM sleep duration and insulin resistance in OSA patients. The results of the current study showed that after multivariate adjustments, the risk of hyperinsulinemia decreased by 22.3% for every 1-hour increase in REM sleep duration. To the best of our knowledge, this is the first clinical research study to investigate the association between REM sleep duration and insulin resistance among OSA adults. Several factors may be involved in the mechanisms that mediate the association between REM sleep duration and hyperinsulinemia. Firstly, decreased REM sleep duration is related to changes in adipokine levels, which can disrupt insulin levels (34). Visfatin, for instance, competitively inhibits the binding of insulin to the insulin receptor (35). Secondly, decreased REM sleep duration results in uncontrolled negative hypothalamic-pituitary-adrenal axis feedback, and excessive levels of cortisol induce pancreatic islet β cells to produce more insulin (17,18). Thus, the present results indicate that improved sleep quality may contribute to lowering the risk of hyperinsulinemia.

The present study has several strengths, including its large sample size, assessments of standard in-laboratory PSG data, employment of multivariate adjustments, and inclusion of adults of all ages. However, there are several limitations that should be noted. Firstly, this was a cross-

Table 5 Adjusted odds ratios for characteristics of insulin resistance

Characteristics	Hyperinsulinemia		HOMA-IR ≥2.5		FIRI ≥2.7		Bennet's ISI ≤1.34	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Sex, %	1.532 (1.187, 1.978)	0.001	1.426 (1.111, 1.829)	0.005	1.348 (1.039, 1.748)	0.024	1.454 (1.131, 1.868)	0.003
Age, years	0.978 (0.970, 0.986)	<0.001	0.989 (0.981, 0.997)	0.005	0.987 (0.979, 0.995)	0.002	0.989 (0.982, 0.997)	0.008
BMI, kg/m^2	1.189 (1.140, 1.241)	<0.001	1.186 (1.137, 1.238)	<0.001	1.182 (1.133, 1.234)	<0.001	1.189 (1.139, 1.241)	<0.001
WC, cm	1.055 (1.038,1.071)	<0.001	1.065 (1.049, 1.082)	<0.001	1.058 (1.041, 1.075)	<0.001	1.064 (1.047, 1.081)	<0.001
MAP, mmHg	1.008 (1.000, 1.016)	0.053	1.006 (0.998,1.013)	0.160	1.009 (1.001, 1.017)	0.029	1.008 (1.000, 1.016)	0.045
Current-smoker, %	0.744 (0.584, 0.947)	0.016	0.736 (0.581,0.932)	0.011	0.698 (0.546, 0.892)	0.004	0.702 (0.553, 0.891)	0.004
Current-drinker, %	0.779 (0.607, 1.000)	0.050	0.773 (0.607,0.986)	0.038	0.785 (0.609, 1.013)	0.062	0.805 (0.631, 1.028)	0.082
AHI, events/h	1.012 (1.009, 1.016)	<0.001	1.012 (1.008,1.016)	<0.001	1.013 (1.010, 1.017)	<0.001	1.013 (1.009, 1.016)	0.045
NREM sleep duration, h (every 1 hour)	1.002 (1.000, 1.004)	0.121	1.002 (1.000,1.004)	0.097	1.003 (1.001, 1.005)	0.003	1.003 (1.000, 1.005)	0.016
REM sleep duration, h (every 1 hour)	0.777 (0.615,0.982)	0.035	0.823 (0.653,1.037)	0.099	0.808 (0.637, 1.025)	0.078	0.835 (0.662, 1.053)	0.128

The data were adjusted for age, gender, BMI, WC, MAP, AHI, smoking status, alcohol consumption and NREM sleep duration. HOMA-IR, homeostasis model assessment of insulin resistance; FIRI, fasting insulin resistance index; ISI, insulin sensitivity index; OR, odds ratio; CI, confidence interval; BMI, body mass index; WC, waist circumference; MAP, mean arterial pressure; AHI, apnea hypopnea index.

sectional study, so causality could not be assessed. Secondly, this was a hospital-based observational study rather than a community-based, prospective study. Thirdly, the participants' dietary, lifestyle, and physical exercise habits, all of which may affect insulin resistance, were not assessed. Thus, not all potentially confounding factors were fully controlled. Finally, certain data, such as the hemogloblinA1c (HbA1c) levels, were unavailable, meaning the level of insulin resistance could not be fully evaluated.

The independent associations of AHI_{REM} or REM sleep duration with insulin resistance evidenced by this study are of great clinical significance. For instance, reducing respiratory events during REM sleep and improving sleep architecture may be beneficial for reducing the risk of insulin resistance. In other words, more attention should be devoted to increasing CPAP pressure during REM sleep or extending the nightly duration of CPAP treatment. Drugs that improve sleep quality may also be useful, especially for individuals with insulin resistance.

Conclusions

In summary, the present study demonstrated an independent association between the frequency of respiratory events during REM sleep and insulin resistance, as assessed by the presence of hyperinsulinemia, abnormal HOMA-IR, FIRI, and Bennett's ISI, in adults with suspected OSA. Additionally, REM sleep duration was found to be associated with hyperinsulinemia. These findings suggest that improvement of sleep architecture and sleep quality may be beneficial in reducing the risk of insulin resistance.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the tenets of the Declaration of Helsinki (as revised in 2013) and was approved by the Internal Review Board of the Institutional Ethics Committee of Shanghai Jiao Tong University Affiliated Sixth People's Hospital [2018-KY-021(K)] and informed consent was taken from all the patients.

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