

# Effect of Interaction Between Slow Wave Sleep and Obstructive Sleep Apnea on Insulin Resistance: A Large-Scale Study

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**Objective:** Slow-wave sleep (SWS) and obstructive sleep apnea (OSA) have attracted recent research attention. However, their joint effects on insulin resistance (IR) remain unclear. This study explored whether SWS influences the relationship between OSA and IR.

**Methods:** We enrolled potential participants in our sleep center from 2007 to 2019. We collected demographic and clinical characteristics and determined IR status. SWS was derived from polysomnography data. Logistic regression analysis was used to reveal the associations between SWS and IR.

**Results:** In all, 6966 participants (5709 OSA and 1257 primary snoring [PS] subjects) were enrolled. Less SWS increased the risk of IR in OSA patients but not in PS patients. OSA patients with SWS <6.5% were more likely to have IR than were those with SWS >21.3%. OSA was an independent risk factor for IR after adjusting for potential confounding factors. In stratified analyses according to the percentage of SWS, OSA patients with SWS <6.5% had an odds ratio for IR of 2.461 (95% CI, 2.018–3.002) compared to the PS group after adjusting for potential confounders.

**Conclusion:** Less SWS is associated with higher odds for IR in OSA patients but not in PS patients. OSA is independently associated with IR. In addition, OSA combined with an extreme lack of SWS has a more harmful effect on the status of IR than OSA itself.

**Keywords:** obstructive sleep apnea, slow-wave sleep, insulin resistance

## Introduction

Sleep-disordered breathing has attracted research attention, especially in terms of abnormal ventilation during sleep. Obstructive sleep apnea (OSA) is a sleep breathing disorder with a prevalence of 3.5–4.6% in adults and 2–8% in children.<sup>1,2</sup> In OSA subjects, repeated upper airway obstruction during sleep can lead to decreased blood oxygen saturation and sleep disorders. OSA increases the risk of cardiovascular, cerebrovascular, and metabolic diseases, leading to loss of work and death among middle-aged and elderly people.<sup>3</sup> In addition, sleep fragmentation can cause daytime sleepiness, which then increases the incidence of related traffic accidents. Therefore, OSA has become an important public health problem.<sup>4</sup>

As we all know, the sleep period consists of rapid eye movement (REM) and non-rapid eye movement (NREM), which alternate during sleep.<sup>5,6</sup> Slow-wave sleep (SWS or N3) stages is one of the NREM sleep apart from N1 and N2 stage.<sup>7</sup> Circadian rhythms and homeostatic processes regulate sleep.<sup>5,8,9</sup> The circadian rhythm is driven by the internal biological clock and is synchronized with the

light/dark cycle, which can regulate sleep tendency throughout the entire day (24 h). Homeostatic processes express the sleep pressure that accumulates during wakefulness and determine the duration of sleep, and more specifically the percentage of SWS. SWS, or deep sleep, is thus a homeostatic process thought to reflect the restorative role of sleep.<sup>10</sup>

A growing number of people experience poor sleep quality due to sleep fragmentation and other factors, and sleep deprivation is becoming a major problem. We should be paying more attention to OSA and SWS suppression, which are common globally, and are thought to be independent risk factors for metabolic,<sup>11,12</sup> cognitive,<sup>13,14</sup> and cardiovascular problems.<sup>15</sup>

The significance of SWS is not restricted to neurophysiological restoration but encompasses a broad range of functions. Increasing evidence supports a crucial role for SWS in modulating a multitude of physiological processes, including memory consolidation,<sup>16</sup> energy conservation,<sup>10</sup> clearance of metabolites,<sup>17</sup> and immunity.<sup>18</sup> Other neuroendocrine changes that occur during SWS include increased release of growth hormone, higher insulin sensitivity, and decreased corticotropin and sympathetic nervous system activity.<sup>19,20</sup> During SWS sleep, the upper airway appears to be less susceptible in OSA patients compared to their REM and NREM sleep stages. The apnea-hypopnea index (AHI) and lowest oxygen saturation clearly improve in most patients once they have achieved the SWS stage.<sup>21</sup>

Insulin resistance (IR) leads to various adverse clinical outcomes and increases the risk for the diseases mentioned above because of the decreased cellular response to insulin.<sup>22</sup> IR is associated with sleep apnea<sup>23</sup> and SWS deprivation.<sup>19</sup> An experimental SWS deprivation model predicted a decrease in insulin sensitivity.<sup>19</sup> In another study, SWS was not related to fasting blood glucose, insulin, or C-peptide levels when adolescents had mixed meals, nor did it impair insulin sensitivity or  $\beta$ -cell reactivity but young healthy-weight adults showed a decline of 25% from baseline insulin sensitivity after SWS suppression for 3 days.<sup>24</sup>

Other studies have had different outcomes. In one, less REM sleep led to higher cortisol concentrations and a higher homeostatic model assessment of insulin resistance (HOMA-IR) index, with no correlation between SWS and the index.<sup>25</sup> In another, variation in SWS was related to variation in glucose metabolism but not insulin sensitivity.<sup>26</sup>

Despite such studies, the severity and medical implications of sleep disorders are seldom considered. Many sleep-related breathing disorders can lead to significant suppression of SWS. Little is known of the effects of less SWS in OSA, particularly with regard to IR. Whether OSA and decreased SWS are independently correlated with IR has not been determined. Moreover, these associations in Han Chinese populations have not yet been explored.

We performed a large-scale, hospital-based study to explore whether an objectively measured decrease in SWS% and OSA are independently associated with IR, and whether SWS influences the relationship between OSA and IR.

## Methods

Study subjects were enrolled from 2007 to 2019 at our sleep center. This study was performed in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Shanghai Jiao Tong University Affiliated Sixth People's Hospital (Approval No: 2019-KY-050[K]) and was registered at the Chinese Clinical Trial Registry (No. ChiCTR1900025714). We obtained informed consent from all subjects.

## Subject Recruitment

Subjects were enrolled according to the following inclusion and exclusion criteria. All participants were adults (aged  $\geq 18$  years) and underwent standard polysomnography (PSG). OSA patients had not previously been treated. Subjects with chronic diseases such as pulmonary, hepatic, and cardiac disease, or other comorbid sleep disorders (insomnia, upper airway resistance syndrome, narcolepsy and restless legs syndrome) were excluded. The participants did not take anxiolytics, antidepressants, hypnotics, antipsychotics, or anti-diabetes drugs. We learned about their general health status including habits such as smoking, alcohol consumption, and medication use through a comprehensive questionnaire. Participants completed the Epworth Sleepiness Scale (ESS).<sup>27</sup> Those who scored an ESS value  $> 10$  were considered to have excessive daytime sleepiness (EDS).<sup>28</sup>

## Clinical and Biochemical Measurements

We used the mean values of two consecutive measurements to assess the physical condition of subjects including height (m), weight (kg), circumferences of neck, waist, and hip (cm), and blood pressure (mmHg), before PSG.<sup>29</sup> Blood pressure was measured by a standard mercury

sphygmomanometer after resting for 15 min. Body mass index (BMI) was the weight divided by the height squared ( $\text{kg}/\text{m}^2$ ). At 07:00 the next morning, fasting blood samples were taken from each participant. The glycolipid metabolism index was measured in our laboratory. The HOMA-IR index was calculated as fasting insulin ( $\mu\text{U}/\text{mL}$ ) multiplied by fasting glucose ( $\text{mmol}/\text{L}$ ) and the result divided by 22.5.<sup>30</sup> Subjects with  $\text{HOMA-IR} \geq 2.5$  were classified into the IR group.<sup>31</sup> Subjects diagnosed by their physician and using antihypertensive medications were considered to have hypertension. The diagnoses of diabetes and hyperlipidemia relied on their past history and the lipid index according to the 2016 ESC/EAS guidelines for the management of dyslipidemias.<sup>32</sup>

## Polysomnography

All enrolled participants underwent full-night standard PSG at our sleep center using Alice 4, 5 or 6 devices (Respironics Inc, Pittsburgh, PA, USA). A skilled technician manually checked the data and PSG output reports according to the AASM 2007 guidelines.<sup>33</sup> SWS was expressed as a percentage of TST and categorized into quartiles (for patients with OSA:  $> 21.3\%$ ,  $13.1\text{--}21.3\%$ ,  $6.5\text{--}13\%$  and  $< 6.5\%$ ; for primary snorers:  $> 24.7\%$ ,  $17.1\text{--}24.7\%$ ,  $10.6\text{--}17\%$ ,  $< 10.6\%$ ). Patients with an  $\text{AHI} \geq 5$  events/h were included in the OSA group, while subjects with an  $\text{AHI} < 5$  events/h were considered primary snoring (PS) subjects. Then OSA was classified into mild ( $\text{AHI} \geq 5$ ,  $< 15/\text{h}$ ), moderate ( $\text{AHI} \geq 15$ ,  $< 30/\text{h}$ ), and severe OSA ( $\text{AHI} \geq 30/\text{h}$ ).

## Statistical Analyses

The sample size was determined based on power analysis. According to our data, 27.53% of primary snorers have IR, compared to 57.3% of those with OSA. With a power of 90% and  $\alpha$  of 0.05, 228 participants were required. Assuming an attrition rate of 15%, a minimum of 263 participants were required. Continuous variables are shown as means  $\pm$  SD. Skewed data are presented as the median (IQR). Categorical data are presented as percentages. We used ANOVA, *t* test, the Kruskal–Wallis tests, and the  $\chi^2$  test to further analyze the data. OSA and non-OSA (primary snorers with an  $\text{AHI} < 5$ ) groups were compared. For SWS, quartile reference groups were established and we used the highest SWS quartile as reference group. We used the polynomial linear trend test to calculate *p*-values for linear trends across groups. Logistic regression was used to analyze the associations between

SWS and IR. Sex, age, BMI, alcohol consumption, smoking, hypertension, hyperlipidemia, TST, sleep efficiency (SE), ESS, and AHI (or SWS%) were considered covariates. A *p*-value  $< 0.05$  indicated statistical significance. All statistical analyses were performed using SPSS software version 22.0 (IBM SPSS Statistics, IBM Corp., Armonk, NY, USA).

## Results

The sample included 6966 subjects, of which 5709 were OSA patients (Table 1). An overwhelming majority of OSA patients were male, heavier, and older, with poorer metabolic profiles compared to simple snorers. Table 2 and Table S1 summarized the demographics and clinical characteristics of OSA and PS subjects stratified according to the percentage of SWS, respectively. In the OSA group, patients with a lower percentage of SWS were older, and had a higher BMI, higher prevalence of IR, higher AHI, and lower nocturnal oxygen saturation. On the contrary, no instructive significant difference in PS subjects was found (Table S1). In the whole cohort, OSA was independently correlated with IR after adjustment for potential confounding factors (OR, 1.876 [95% CI, 1.592–2.211]) (Table 3). As shown in Table 3, subjects with  $\text{SWS} < 6.9\%$  were 37.1% (odds ratio [OR], 1.371 [95% CI, 1.175–1.600]) more likely to have IR compared to those with  $\text{SWS} > 22.1\%$  after adjusting for age, BMI, sex, alcohol consumption, smoking, hypertension, diabetes mellitus, and hyperlipidemia. However, significance disappeared after further adjusting for TST, SE, ESS, and AHI. Hence, SWS was not independently associated with IR in the whole cohort. The joint effect of OSA and SWS on IR were also presented in Table 3. Significantly increased odds of IR were found among OSA patients with a lower percentage of SWS. After adjusting for age, BMI, sex, alcohol consumption, smoking, hypertension, diabetes mellitus, hyperlipidemia, TST, SE and ESS, OSA patients with  $\text{SWS} < 6.5\%$  had an odds ratio for IR of 2.461 (95% CI, 2.018–3.002) compared to the PS group (Table 3).

SWS was significantly associated with IR in OSA patients (Table 4). A low percentage of SWS was associated with an increased risk of IR when OSA was present. After adjusting for potential confounders, OSA patients with  $\text{SWS} < 6.5\%$  were 34.8% (odds ratio [OR], 1.348 [95% CI, 1.133–1.603]) more likely to have IR than those with  $\text{SWS} > 21.3\%$  (Table 4). No significant relationship

**Table 1** Clinical and Sleep Characteristics of Subjects Stratified by OSA Severity Categories

Characteristics	Whole Cohort			OSA			
	PS (n = 1257)	Total OSA (n = 5709)	p-value 1	Mild OSA (n = 1115)	Moderate OSA (n = 1133)	Severe OSA (n = 3461)	p-value 2
Demographic and clinical characteristics							
Men, n (%)	788 (62.69)	4777 (83.67)	<0.001	829 (74.3)	893 (78.8)	3055 (88.3)	<0.001
Age, y	39.55±12.02	44.57±12.21	<0.001	43.15±12.67	45.74±12.80	44.64±11.82	<0.001
Neck circumference (cm)	36.60±3.96	39.87±3.53	<0.001	38.19±3.31	38.97±3.31	40.70±3.40	<0.001
Waist circumference (cm)	86.97±10.68	97.44±10.55	<0.001	92.25±9.73	95.02±9.79	99.89±10.27	<0.001
Hip circumference (cm)	96.82±7.31	102.22±7.89	<0.001	99.53±7.46	100.80±7.38	103.55±7.89	<0.001
Waist hip ratio	0.90±0.07	0.95±0.06	<0.001	0.93±0.06	0.94±0.06	0.96±0.06	<0.001
Body mass index, kg/m <sup>2</sup>	24.25±3.72	27.31±3.87	<0.001	25.72±3.49	26.48±3.56	28.07±3.87	<0.001
Hypertension, n (%)	132 (10.50)	1508 (26.41)	<0.001	197 (17.7)	276 (24.4)	1035 (29.9)	<0.001
SBP (mmHg)	120.49±14.80	127.81±16.06	<0.001	124.47±14.95	126.22±16.36	129.37±16.09	<0.001
DBP (mmHg)	77.40±10.21	82.01±11.79	<0.001	79.01±11.21	80.03±11.24	83.58±11.86	<0.001
Diabetes mellitus, n (%)	65 (5.17)	450 (7.88)	<0.001	83 (7.4)	106 (9.4)	261 (7.5)	0.12
Hyperlipidemia, n (%)	164 (13.05)	1892 (33.14)	<0.001	306 (27.4)	345 (30.5)	1241 (35.9)	<0.001
Tobacco use, n (%)	235 (18.70)	1137 (19.92)	0.172	218 (19.6)	219 (19.3)	700 (20.2)	0.761
Alcohol consumption, n (%)	599 (47.65)	2972 (52.06)	0.003	567 (50.9)	588 (51.9)	1817 (52.5)	0.628
Fasting glucose (mmol/L)	5.14±1.11	5.61±1.34	<0.001	5.39±1.29	5.52±1.27	5.71±1.37	<0.001
Fasting insulin (µU/mL)	7.69(5.91)	11.72(9.47)	<0.001	9.25(7.56)	10.46(7.72)	12.87(10.05)	<0.001
IR	346 (27.53)	3271 (57.30)	<0.001	465 (41.7)	569 (50.2)	2237 (64.6)	<0.001
HOMA-IR	1.73(1.47)	2.82(2.58)	<0.001	2.10(1.92)	2.47(1.96)	3.14(2.80)	<0.001
Cholesterol (mmol/L)	4.36(1.15)	4.77(1.21)	<0.001	4.59(1.20)	4.72(1.18)	4.83(1.21)	<0.001
Triglyceride (mmol/L)	1.19(0.96)	1.67(1.25)	<0.001	1.41(1.00)	1.63(1.19)	1.78(1.31)	<0.001
High density Lipoprotein (mmol/L)	1.10(0.34)	1.02(0.28)	<0.001	1.06(0.33)	1.04(0.30)	1.00(0.26)	<0.001
Low density Lipoprotein (mmol/L)	2.62(1.00)	2.99(1.04)	<0.001	2.91(1.03)	2.96(1.00)	3.03(1.05)	0.013
Apolipoprotein-A-I (g/L)	1.07(0.26)	1.05(0.24)	<0.001	1.06(0.26)	1.05(0.24)	1.05(0.23)	0.007
Apolipoprotein-B (g/L)	0.74(0.25)	0.85(0.25)	<0.001	0.82(0.24)	0.84(0.24)	0.88(0.24)	<0.001
Apolipoprotein-E (mg/dL)	3.79(1.55)	4.31(1.89)	<0.001	4.01(1.60)	4.28(1.77)	4.43(2.03)	<0.001
Lipoprotein-α (mg/dL)	7.80(13.73)	7.30(11.50)	<0.001	8.10(13.10)	7.40(11.20)	7.10(11.00)	<0.001
ESS	5.00(9.00)	8.00(9.00)	<0.001	7.00(8.00)	6.00(9.00)	9.00(9.00)	<0.001
ESS > 10, n (%)	193 (15.35)	2066 (36.19)	<0.001	248 (22.2)	288 (25.4)	1530 (44.2)	<0.001

(Continued)

Table 1 (Continued).

Characteristics	Whole Cohort			OSA			
	PS (n = 1257)	Total OSA (n = 5709)	p-value 1	Mild OSA (n = 1115)	Moderate OSA (n = 1133)	Severe OSA (n = 3461)	p-value 2
Polysomnography							
Total sleep time, min	379.89±81.89	397.34±77.46	<0.001	384.94±80.30	388.07±78.24	404.37±75.45	<0.001
Sleep efficiency, %	89.44±13.51	90.57±13.02	0.007	89.49±12.76	90.18±12.32	91.05±13.29	0.001
N1, % TST	18.84±12.82	21.32±14.30	<0.001	20.31±13.54	20.58±13.76	21.89±14.68	0.001
N2, % TST	49.62±14.99	51.16±16.15	0.001	49.03±15.81	49.99±16.11	52.23±16.18	<0.001
SWS, % TST	18.74±12.19	15.78±13.01	<0.001	18.46±12.48	17.51±12.18	14.34±13.23	<0.001
REM, % TST	12.59±7.03	11.26±6.63	<0.001	11.83±7.21	11.51±6.85	11.00±6.35	<0.001
AHI, events/h	1.80(2.60)	39.50(43.20)	<0.001	9.40(5.10)	21.70(7.20)	57.4(25.70)	<0.001
Lowest SaO <sub>2</sub> , %	93.00(5.00)	78.00(17.00)	<0.001	88.00(7.00)	83.00(9.00)	71.50(16.00)	<0.001
ODI, events/h	1.90(2.90)	39.00(43.85)	<0.001	9.40(6.00)	21.90(9.55)	57.10(28.50)	<0.001
Mean SaO <sub>2</sub>	97.00(1.00)	94.00(4.00)	<0.001	96.00(2.00)	95.00(2.00)	93.00(4.00)	<0.001
Micro arousal index, events/h	13.10(12.05)	26.10(29.70)	<0.001	17.10(14.60)	20.60(17.95)	34.60(34.10)	<0.001

**Notes:** Continuous variables were shown as the mean ± SD. Skewed data were presented as median (IQR). Categorical data were presented as the number (percentage). ANOVA, the Kruskal–Wallis tests, and the  $\chi^2$  test were used to further analyze the data. P-value 1: significant difference between PS and total OSA groups. P-value 2: significant difference among all groups (mild OSA, moderate OSA and severe OSA).

**Abbreviations:** OSA, obstructive sleep apnea; PS, primary snorers; SBP, systolic blood pressure; DBP, diastolic blood pressure; IR, insulin resistance; HOMA-IR, homeostasis model assessment of insulin resistance; ESS, Epworth Sleepiness Scale; SWS, slow wave sleep; REM, rapid eye movement; AHI, apnea-hypopnea index; SaO<sub>2</sub>, oxygen saturation, ODI, oxygen desaturation index.

between SWS and IR was found in the PS group. Furthermore, SWS was significantly associated with IR in OSA patients varying in severity (Table 5). Using PS subjects as the reference, subjects with the lowest percentage of SWS showed the highest likelihood of IR, especially in moderate to severe OSA patients (Table 5).

Besides, we performed a subgroup analysis by sex (male, female), age (< 60 years, ≥ 60 years) and BMI (< 28 kg/m<sup>2</sup>, ≥ 28 kg/m<sup>2</sup>), SWS was correlated with IR in thinner subjects especially with SWS < 6.5% (OR, 1.583; 95% CI, 1.223–2.050) (Table S2). We also performed multivariable linear regression to explore the interaction of AHI and SWS. AHI, SWS and AHI\*SWS were significantly associated with HOMA-IR in the model (Table S3).

## Discussion

We explored the association between SWS and the development of IR with a large sample of OSA and PS subjects. We found a significant interaction between SWS and OSA in patients with IR. OSA patients with

SWS < 6.5% had higher odds of IR than primary snorers. AHI has been reported to increase the risk of IR after adjusting for confounding factors,<sup>34</sup> and intermittent hypoxia might lead to hyperglycemia, hyperinsulinemia, and IR.<sup>35</sup> Our study reaffirmed that patients with OSA are more likely to have IR than primary snorers. Greater odds of developing IR were evident only in OSA patients with a low percentage of SWS, indicating that OSA and SWS interacted and had a joint effect on IR. Further studies are needed on oxidative stress, excitability of the sympathetic nervous system, inflammation, and the dysfunction of hypothalamic-pituitary-adrenal (HPA) axis<sup>36</sup> to reveal the potential mechanisms between OSA and IR.

Less SWS is becoming recognized as a marker for an increased risk for IR. In a previous study, as SWS increased, the HOMA-IR index significantly decreased, suggesting that it has a significant effect on improving IR.<sup>37</sup> Benedict<sup>38</sup> and Hermida<sup>39</sup> theorized that the reduced risk for new-onset type 2 diabetes mellitus in patients with hypertension observed with bedtime ingestion of

**Table 2** Clinical and Sleep Characteristics of OSA Patients (n=5709) Stratified by SWS Categories

Characteristics	>21.3% (n = 1427)	13.1–21.3% (n = 1434)	6.5–13% (n = 1412)	<6.5% (n = 1436)	p-value
Demographic and clinical characteristics					
Men, n (%)	1123 (78.7)	1174 (81.9)	1206 (85.4)	1274 (88.7)	<0.001
Age, y	43.56±12.32	43.85±12.36	44.38±11.97	46.47±11.99	<0.001
Neck circumference (cm)	39.43±3.54	39.49±3.48	40.15±3.45	40.45±3.53	<0.001
Waist circumference (cm)	97.04±10.70	96.30±10.60	97.66±10.35	98.84±10.41	<0.001
Hip circumference (cm)	102.01±8.11	101.57±7.87	102.67±7.65	102.68±7.89	<0.001
Waist hip ratio	0.95±0.06	0.95±0.06	0.95±0.06	0.96±0.06	<0.001
Body mass index, kg/m <sup>2</sup>	27.24±4.01	27.00±3.78	27.36±3.73	27.66±3.91	<0.001
Hypertension, n (%)	374 (26.2)	334 (23.3)	368 (26.1)	432 (30.1)	0.001
SBP (mmHg)	127.86±16.56	126.91±15.80	128.10±15.82	128.43±16.02	0.088
DBP (mmHg)	81.78±12.41	81.23±11.38	82.19±11.66	92.93±11.61	0.003
Diabetes mellitus, n (%)	116 (8.1)	105 (7.3)	111 (7.9)	118 (8.2)	0.810
Hyperlipidemia, n (%)	469 (23.9)	475 (33.1)	445 (31.5)	503 (35.0)	0.257
Tobacco use, n (%)	301 (21.1)	254 (17.7)	288 (20.4)	294 (20.5)	0.107
Alcohol consumption, n (%)	755 (52.9)	805 (56.1)	744 (52.7)	668 (46.5)	<0.001
Fasting glucose (mmol/L)	5.56±1.25	5.61±1.43	5.58±1.30	5.70±1.38	0.032
Fasting insulin (μU/mL)	11.53(9.20)	11.06(8.55)	11.49(9.24)	12.77(10.08)	0.638
IR	795 (55.7)	771 (53.8)	783 (55.5)	922 (64.2)	<0.001
HOMA-IR	2.72(2.48)	2.65(2.29)	2.72(2.48)	3.12(2.79)	0.001
Cholesterol (mmol/L)	4.76(1.25)	4.77(1.19)	4.75(1.17)	4.79(1.24)	0.218
Triglyceride (mmol/L)	1.62(1.22)	1.66(1.25)	1.69(1.19)	1.75(1.33)	0.093
High density lipoprotein (mmol/L)	1.01(0.27)	1.03(0.29)	1.02(0.27)	1.01(0.28)	0.072
Low density lipoprotein (mmol/L)	2.94(1.02)	2.98(1.04)	3.01(1.01)	3.04(1.11)	0.003
ApolipoproteinA-I (g/L)	1.05(0.23)	1.04(0.23)	1.04(0.23)	1.07(0.24)	0.003
Apolipoprotein-B (g/L)	0.85(0.24)	0.85(0.26)	0.85(0.24)	0.88(0.26)	0.025
Apolipoprotein-E (mg/dL)	4.31(1.95)	4.23(1.84)	4.26(1.76)	4.44(1.99)	0.023
Lipoprotein-α (mg/dL)	7.60(12.60)	7.80(11.95)	6.90(10.50)	7.20(10.80)	0.104
ESS	8.00(9.00)	8.00(8.00)	8.00(9.00)	9.00(10.00)	<0.001
ESS > 10, n (%)	438 (30.7)	505 (35.2)	519 (36.8)	604 (42.1)	<0.001
Polysomnography					
Total sleep time, min	403.91±77.74	401.68±71.05	399.09±73.71	384.72±85.18	<0.001
Sleep efficiency, %	92.36±11.83	91.54±10.45	91.19±10.70	87.21±17.24	<0.001
NI, % TST	17.87±12.77	17.94±10.96	20.64±12.63	28.80±17.17	<0.001

(Continued)

Table 2 (Continued).

Characteristics	>21.3% (n = 1427)	13.1–21.3% (n = 1434)	6.5–13% (n = 1412)	<6.5% (n = 1436)	p-value
N2, % TST	38.09±16.22	52.84±10.96	57.16±12.44	56.57±16.31	<0.001
SWS, % TST	33.96±10.88	16.87±2.35	9.77±1.91	2.52±2.21	<0.001
REM, % TST	9.95±6.82	11.86±6.34	11.75±6.45	11.48±6.75	<0.001
AHI, events/h	33.90(39.40)	31.60(37.70)	42.30(41.35)	57.20(36.30)	<0.001
Lowest SpO <sub>2</sub> , %	78.00(17.00)	80.00(15.00)	78.00(17.00)	75.00(18.00)	<0.001
ODI	31.70(39.60)	32.70(38.60)	41.40(41.90)	56.30(37.60)	<0.001
Mean SaO <sub>2</sub>	94.00(4.00)	95.00(3.00)	94.00(3.90)	93.00(4.00)	<0.001
Mild OSA, n (%)	350 (24.5)	352 (24.5)	254 (18)	159 (11.1)	<0.001
Moderate OSA, n (%)	322 (22.6)	345 (24.1)	291 (20.6)	175 (12.2)	<0.001
Severe OSA, n (%)	755 (52.9)	737 (51.4)	867 (61.4)	1102 (76.7)	<0.001
Micro arousal index, events/h	19.50(22.80)	22.80(22.70)	28.20(28.25)	39.00(36.80)	<0.001

**Notes:** Continuous variables were shown as the mean ± SD. Skewed data were presented as median (IQR). Categorical data were presented as the number (percentage). ANOVA, the Kruskal–Wallis tests, and the  $\chi^2$  test were used to further analyze the data. P-value: significant difference among all four groups.

**Abbreviations:** OSA, obstructive sleep apnea; SWS, slow wave sleep; SBP, systolic blood pressure; DBP, diastolic blood pressure; IR, insulin resistance; HOMA-IR, homeostasis model assessment of insulin resistance; ESS, Epworth Sleepiness Scale; REM, rapid eye movement; AHI, apnea-hypopnea index; SpO<sub>2</sub>, oxygen saturation; ODI, oxygen desaturation index.

angiotensin-converting enzyme inhibitors was partially mediated by improvement in SWS.

Endocrine metabolism is regulated by sleep and the circadian rhythm. Insufficient sleep, and circadian rhythm or sleep structure disorders, lead to the imbalance of metabolic homeostasis, and further, cause hypertension, diabetes mellitus, and multiple organ injury. The mechanism is related to systemic inflammation and IR,<sup>40</sup> accompanied by low expression of circadian clock genes.<sup>41,42</sup> The circadian clock input signal related to chronic sleep deprivation directly reduces the expression of CRY proteins, which in turn activates the cAMP/PKA inflammation signaling pathway and leads to the synthesis of a series of inflammatory factors, resulting in a chronic low inflammatory state of the body. Inflammatory factors directly inhibit the PI3K/AKT signaling pathway, leading to IR and higher blood levels of glucose.<sup>37</sup> Zhu<sup>43</sup> analyzed the bivariate correlation between sleep structure and glucose and insulin levels. Subjects with higher TS and SE and SWS phases (%TST) had lower 2 h blood glucose, better islet  $\beta$ -cell function, and higher insulin sensitivity. For the thinner people, the metabolic status is less affected by obesity than the obese people, so the risk of IR caused by the reduction of SWS is greater. Meanwhile, higher N1 and

N2 were related to poorer glucose tolerance and insulin sensitivity. The SWS stage still had the same effect on glucose and insulin metabolism indicators after adjusting for age, sex, BMI, puberty status and AHI. Therefore, overactivity of the sympathetic nervous system and SWS reduction might eventually lead to IR.<sup>44,45</sup> Our study corroborates these previous findings, showing a graded relationship between less SWS and increased odds of IR. SWS may provide a reliable indicator of the biological and medical significance of OSA, although the percentage of SWS is not generally recommended as a criterion of severity in OSA. Meanwhile, OSA severity may modulate the effects of SWS on the odds of IR as the results above showed. Our main finding is that less SWS is associated with higher odds for IR in OSA but not in PS. It was more likely to be a threshold effect such that the odds of IR were significantly higher in the OSA patients with the lowest SWS quartile. OSA was independently associated with IR. OSA and SWS also have an interaction effect on IR.

An advantage of our study was the large sample size, which increases representativity. In addition, this is the first study to report that SWS moderates the association between OSA and IR. However, there were several limitations. First, hospital-based, full-night PSG did not truly

**Table 3** Adjusted ORs and 95% CIs for the Associations of IR with OSA (PS as the Reference), SWS (SWS > 22.1% as the Reference) and Their Joint Effects (PS as Reference)

Predictors	n	OR (95% CI)		
		Model 1	Model 2	Model 3
OSA				
PS	1257	Reference	Reference	Reference
OSA	5709	*2.009 (1.721–2.346)	*1.956 (1.670–2.292)	*1.876 (1.592–2.211)
SWS				
> 22.1%	1748	Reference	Reference	Reference
13.8–22.1%	1742	1.012 (0.872–1.175)	1.048 (0.901–1.219)	1.071 (0.917–1.252)
7–13.7%	1739	1.023 (0.881–1.189)	1.043 (0.896–1.214)	0.996 (0.851–1.166)
< 6.9%	1737	*1.345 (1.156–1.566)	*1.371 (1.175–1.600)	1.093 (0.927–1.287)
p for linear trend		<0.001	<0.001	0.565
OSA-SWS				
PS	1257	Reference	Reference	Reference
> 21.3%	1427	*1.927 (1.605–2.314)	*1.860 (1.543–2.241)	1.810 (1.493–2.193)
13.1–21.3%	1434	*1.858 (1.549–2.230)	*1.824 (1.514–2.197)	1.785 (1.474–2.160)
6.5–13%	1412	*1.817 (1.510–2.187)	*1.775 (1.470–2.143)	1.721 (1.417–2.090)
< 6.5%	1436	*2.662 (2.203–3.217)	*2.597 (2.140–3.150)	*2.461 (2.018–3.002)
p for linear trend		<0.001	<0.001	<0.001

**Notes:** Model 1 was adjusted for age, BMI, and sex; Model 2 was adjusted for variables included in Model 1 and alcohol consumption, smoking, hypertension, diabetes mellitus and hyperlipidemia; Model 3 was adjusted for variables included in Model 2 and TST, SE, ESS in analysis of the joint effects of OSA and SWS on IR. Model 3 was adjusted for variables included in Model 2 and TST, SE, ESS, SWS% (in analysis of OSA and IR) or AHI (in analysis of SWS and IR). Logistic regression was used to further analyze the data.

**Abbreviations:** OR, odds ratio; CI, confidence interval; IR, insulin resistance; OSA, obstructive sleep apnea; PS, primary snorers; SWS, slow wave sleep; BMI, body mass index; TST, total sleep time; SE, sleep efficiency; ESS, Epworth Sleepiness Scale; AHI, apnea-hypopnea index. \*p indicated a significant difference. PS group was the reference category for OSA and interaction of OSA and SWS. Group of subjects with SWS > 22.1% was the reference category for SWS categories to find the association of IR and SWS.

**Table 4** Adjusted ORs and 95% CIs for the Association Between SWS and IR in OSA (SWS > 21.3% as the Reference) and PS Groups (SWS > 24.7% as the Reference)

Predictors	n	OR (95% CI)		
		Model 1	Model 2	Model 3
OSA				
> 21.3%	1427	Reference	Reference	Reference
13.1–21.3%	1434	0.966 (0.822–1.137)	0.986 (0.836–1.163)	0.989 (0.837–1.169)
6.5–13%	1412	0.946 (0.803–1.114)	0.956 (0.810–1.128)	0.950 (0.802–1.125)
< 6.5%	1436	*1.389 (1.175–1.641)	*1.393 (1.176–1.651)	*1.348 (1.133–1.603)
p for linear trend		<0.001	<0.001	<0.001
PS				
> 24.7%	310	Reference	Reference	Reference
17.1–24.7%	319	1.069 (0.728–1.57)	1.093 (0.737–1.621)	1.150 (0.764–1.730)
10.6–17%	312	1.066 (0.727–1.563)	1.171 (0.791–1.733)	1.167 (0.775–1.756)
< 10.6%	316	1 (0.68–1.47)	1.041 (0.699–1.549)	1.119 (0.740–1.692)
p for linear trend		0.999	0.876	0.882

**Notes:** Model 1 was adjusted for age, BMI, and sex; Model 2 was adjusted for variables included in Model 1 and alcohol consumption, smoking, hypertension, diabetes mellitus and hyperlipidemia; Model 3 was adjusted for variables included in Model 2 and TST, SE, and ESS. Logistic regression was used to further analyze the data. \*p indicated a significant difference. Group of OSA subjects with SWS > 21.3% was the reference category for SWS categories to find the association of IR and SWS in OSA. Group of PS with SWS > 24.7% was the reference category for SWS categories to find the association of IR and SWS in primary snoring subjects.

**Abbreviations:** OR, odds ratio; CI, confidence interval; SWS, slow wave sleep; IR, insulin resistance; OSA, obstructive sleep apnea; PS, primary snorers; BMI, body mass index; TST, total sleep time; SE, sleep efficiency; ESS, Epworth Sleepiness Scale.



**Table 5** Adjusted ORs and 95% CIs of IR Associated with SWS in Analyses Stratified by OSA Severity

Predictors	n	OR (95% CI)		
		Model 1	Model 2	Model 3
PS	1257	Reference	Reference	Reference
Mild OSA	1115			
> 21.3%	332	*1.560 (1.187–2.050)	*1.496 (1.133–1.974)	*1.407 (1.045–1.894)
13.1–21.3%	341	1.198 (0.910–1.577)	1.209 (0.915–1.597)	1.222 (0.917–1.629)
6.5–13%	233	*1.419 (1.035–1.945)	*1.451 (1.054–1.997)	*1.431 (1.019–2.011)
< 6.5%	209	*1.865 (1.273–2.733)	*1.793 (1.212–2.653)	*1.652 (1.097–2.487)
p for linear trend		0.001	0.003	0.027
Moderate OSA	1133			
> 21.3%	316	*1.898 (1.436–2.507)	*1.889 (1.424–2.507)	*1.895 (1.422–2.525)
13.1–21.3%	340	*1.530 (1.162–2.016)	*1.545 (1.169–2.043)	*1.539 (1.160–2.043)
6.5–13%	289	*1.788 (1.340–2.386)	*1.769 (1.321–2.370)	*1.753 (1.305–2.356)
< 6.5%	188	*2.507 (1.747–3.598)	*2.450 (1.696–3.540)	*2.405 (1.658–3.489)
p for linear trend		<0.001	<0.001	<0.001
Severe OSA	3461			
> 21.3%	743	*2.231 (1.789–2.781)	*2.141 (1.710–2.681)	*2.044 (1.623–2.575)
13.1–21.3%	729	*2.615 (2.095–3.263)	*2.508 (2.000–3.146)	*2.405 (1.907–3.033)
6.5–13%	860	*2.035 (1.643–2.521)	*1.976 (1.588–2.458)	*1.875 (1.497–2.349)
< 6.5%	1129	*2.935 (2.383–3.615)	*2.899 (2.343–3.588)	*2.699 (2.168–3.360)
p for linear trend		<0.001	<0.001	<0.001

**Notes:** Model 1 was adjusted for age, BMI, and sex; Model 2 was adjusted for variables included in Model 1 and alcohol consumption, smoking, hypertension, diabetes mellitus and hyperlipidemia; Model 3 was adjusted for variables included in Model 2 and TST, SE, and ESS. Logistic regression was used to further analyze the data. \*p indicated a significant difference. Primary snoring group was the reference category for all groups.

**Abbreviations:** OR, odds ratio; CI, confidence interval; IR, insulin resistance; SWS, slow wave sleep; OSA, obstructive sleep apnea; PS, primary snorers; BMI, body mass index; TST, total sleep time; SE, sleep efficiency; ESS, Epworth Sleepiness Scale.

reflect routine sleep. PSG in the sleep center is the gold standard for examining sleep stages and detecting respiratory-related events; therefore, first-night effects and variation among nights could not be ruled out. Second, this study was cross-sectional and observational. Prospective longitudinal research to confirm the relationship between sleep structure and glucose tolerance. Third, because menopause was related to changes in sleep quality and glucose metabolism,<sup>46,47</sup> our findings may differ based on menopausal status.

## Conclusions

SWS and OSA interact to increase the odds of developing IR. Compared to PS subjects, OSA is independently associated with IR after adjusting for potential confounding factors. The odds of IR in OSA patients are significantly higher for those in the lowest SWS quartile. Further studies are needed to elucidate the pathophysiological mechanisms underlying this relationship and to test the hypothesis that SWS enhancement may ameliorate the risk for IR.

## Abbreviations

SWS, slow-wave sleep; OSA, obstructive sleep apnea; IR, insulin resistance; PS, primary snoring; REM, rapid eye movement; NREM, non-rapid eye movement; AHI, apnea hypopnea index; HOMA-IR, homeostasis model assessment for insulin resistance; PSG, polysomnography; ESS, Epworth Sleepiness Scale, EDS, excessive daytime sleepiness; BMI, body mass index; CI, confidence interval; SE, sleep efficiency; OR, odds ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; LSpO<sub>2</sub>, lowest oxygen saturation; ODI, oxygen desaturation index; SaO<sub>2</sub>, oxygen saturation.

## Data Sharing Statement

The datasets used and analyzed in this study are available from Huajun Xu, the corresponding author, on reasonable request.

## Ethics Approval and Consent to Participate

This study was performed in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Shanghai Jiao Tong University Affiliated Sixth People's Hospital (Approval No: 2019-KY-050[K]) and was registered at the Chinese Clinical Trial Registry (No. ChiCTR1900025714). We obtained informed consent from all subjects.

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## Author Contributions

The corresponding authors are responsible for the authenticity of the data. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare that there is no conflict of interest in the study.

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