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

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Abstract

Objectives: Slow wave sleep (SWS) and obstructive sleep apnea (OSA) have attracted more and more attention. Their joint effect on insulin resistance (IR) remains to be further studied. This study explored whether less 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 gauged the IR status. SWS was derived from polysomnography data. Logistic regression analyses were 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 increases 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 those with SWS > 21.3%. OSA was an independent risk factor for IR after adjusting for all potential confounding factors. In stratified analyses according to the percentage of SWS, patients with OSA with SWS < 6.5% had 38.2% higher odds of IR than the PS group after adjusting for all potential confounders.

Conclusions: Less SWS is associated with higher odds for IR in OSA patients but not in PS patients. OSA is independently correlated 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.

Introduction

Sleep-disordered breathing has attracted more and more attention nowadays due to the abnormal ventilation during sleep. Obstructive sleep apnea (OSA) is one of the sleep breathing disorders with a prevalence of 3.5–4.6% in adults and 2–8% in children. 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. In addition, sleep fragmentation can cause daytime sleepiness, which then increases the incidence of related traffic accidents. In children, OSA can cause cognitive deficits, abnormal craniofacial development, and slowed growth. Therefore, OSA has become an important public health problem.

As we all know, the sleep period consists of rapid eye movement (REM) and non-rapid eye movement (NREM), which alternate during sleep. Slow wave sleep (SWS or N3) stages is one of the NREM sleep apart from N1 and N2 stage. Circadian rhythm and homeostatic processes regulate our sleep. 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 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.

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, cognitive, and cardiovascular problems.

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, energy conservation, clearance of metabolites, and immunity. Other
neuroendocrine changes that occur during SWS include increased release of growth hormone, higher insulin sensitivity, and decreased corticotropic and sympathetic nervous system activity.\textsuperscript{19,20} 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.\textsuperscript{21}

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.\textsuperscript{22} IR is associated with sleep apnea\textsuperscript{23} and SWS deprivation.\textsuperscript{19} An experimental SWS deprivation model predicted a decrease in insulin sensitivity.\textsuperscript{19} 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 β-cell reactivity but young healthy-weight adults showed a decline of 25% from baseline insulin sensitivity after SWS suppression for 3 days.\textsuperscript{24}

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

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 used 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.

\textbf{Methods}

Study subjects were enrolled during the period from 2007 to 2019 at our sleep center. This study performed in accordance with the Declaration of Helsinki. The study plan was approved by the Ethics Committee of our hospital and was registered in Chinese Clinical Trial Registry (No. ChiCTR1900025714). We obtained informed consent from all subjects.

\textbf{Subjects}

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).\textsuperscript{27} Those who scored an ESS value > 10 were considered to have excessive daytime sleepiness (EDS).\textsuperscript{28}

\textbf{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.\textsuperscript{29} 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 (kg/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 (μU/mL) multiplied by fasting glucose (mmol/L) and the result divided by 22.5.\(^{30}\) Subjects with HOMA-IR ≥ 2.5 were classified into the IR group.\(^{31}\) 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.\(^{32}\)

**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). They familiarized themselves with the sleep environment and followed their routine sleep time. A skilled technician manually checked the data and PSG output reports according to the AASM 2007 guidelines.\(^{33}\) SWS was expressed as a percentage of TST and categorized into quartiles (for patients with OSA: > 21.3%, 13.1–21.3%, 6.5–13% and <6.5%; for primary snorers: >24.7%, 17.1–24.7%, 10.6–17%, <10.6%). Patients with an AHI ≥ 5 events/h were included in the OSA group, while subjects with an AHI < 5 events/h were considered primary snoring (PS) subjects. Then OSA was classified into mild (AHI ≤ 5 to < 15 /h), moderate (AHI ≥ 15 to < 30 /h), and severe OSA (AHI ≥ 30 /h).

**Statistical analyses**

Continuous variables are shown as means±SD. Skewed data are presented as means with 95% confidence intervals (CIs). Categorical data are presented as percentages. We used ANOVA, t test, Wilcoxon's signed-rank test, and χ\(^2\) test to further analyze the data. 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. Tables 2 and 3 summarize the demographics and clinical characteristics of OSA and PS patients 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. As shown in Table 4, SWS was significantly associated with IR in OSA patients. Taking the highest quartile of percentages of SWS (>21.3%) as the reference, those with lower percentages of SWS exhibited higher odds of IR. After adjustment for all potential confounders, OSA patients with SWS < 6.5% were 32.8% (odds ratio [OR], 1.328 [95% CI, 1.118–1.578]) more likely to have IR relative to those with SWS > 21.3%. No significant relationship between SWS and IR was found in the PS group.

In the whole cohort, OSA was independently correlated with IR compared to primary snorers after adjustment for all potential confounding factors (OR, 1.827 [95% CI, 1.554–2.149]) (Table 5). Table 5 shows the joint effect of OSA and SWS on IR. 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, hyperlipidemia, TST, SE, ESS, and AHI, OSA patients with SWS < 6.5% had a 38.2% (OR, 1.382 [95% CI, 1.100–1.736]) increased odds of IR compared to the PS group. Logistic regression was used to analyze the associations between SWS and IR in different categories of OSA severity. SWS was independently associated with IR in each subgroup in a dose-dependent manner after adjusting for the confounding factors (Table 6) using PS subjects as the reference. There were no significant differences in each subgroup when we performed subgroup analyses by sex, age, and BMI.

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 had higher odds of IR than primary snorers with SWS < 6.5%. AHI has been reported to increase the risk of IR after adjusting for confounding factors, and intermittent hypoxia might lead to hyperglycemia, hyperinsulinemia, and IR. 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 this relationship was modified by SWS. Further studies are needed on oxidative stress, excitability of the sympathetic nervous system, inflammation and the dysfunction of hypothalamic-pituitary-adrenal (HPA) axis 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. Benedict theorized that the reduced risk for new-onset type 2 diabetes mellitus in patients with hypertension observed with bedtime ingestion of 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, accompanied by low expression of circadian clock genes. 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. Zhu 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 β-cell function, and higher insulin sensitivity. 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. 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. OSA was independently correlated with IR and may modulate the effects of SWS 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 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. We might rely on the 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, 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 correlated with IR after adjusting for all potential confounding factors. SWS is independently associated with IR in OSA patients in a dose-dependent manner. OSA severity may modulate the effects of SWS on IR. 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.

List Of 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; CIs, confidence intervals; SE, sleep efficiency; OR, odds ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; LSpO2, lowest oxygen saturation; ODI, oxygen desaturation index; SaO2, oxygen saturation.

Declarations

Ethics approval and consent to participate: This study performed in accordance with the Declaration of Helsinki. The study plan was approved by the Ethics Committee of our hospital and was registered in Chinese Clinical Trial Registry (No. ChiCTR1900025714). We obtained informed consent from all subjects.

Availability of data and materials: The datasets used and analyzed in this study are available from the corresponding author on reasonable request.

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

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Authors’ contributions: The corresponding authors are responsible for the authenticity of the data. Under reasonable requirements, all study data can be obtained from the corresponding authors. Study design: WH, HX and HY; Data collection: WH, XW, YL, XL, JZ and YL; Statistical analysis: WH, XW, XL and YL; Manuscript draft: WH, XW, HX, HZ and HY; Manuscript revision: HY, JG and SY. All authors have read and agreed to submit the manuscript.

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Tables

Table 1. Clinical and sleep characteristics of subjects stratified by OSA severity categories
| Characteristics | PS (n = 1257) | OSA (n = 5709) | Mild OSA (n = 1115) | Moderate OSA (n = 1133) | Severe OSA (n = 3461) | p-value |
|----------------|--------------|----------------|--------------------|-------------------------|----------------------|--------|
| Demographic and clinical characteristics | | | | | | |
| Men, n (%) | 788 (62.69) | 4777 (83.67) | 829 (74.30) | 893 (78.80) | 3055 (88.30) | <0.001 |
| Age, y | 39.55±12.02 | 44.57±12.21 | 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 | 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 | 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 | 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 | 0.93±0.06 | 0.94±0.06 | 0.96±0.06 | <0.001 |
| Body mass index, kg/m² | 24.25±3.72 | 27.31±3.87 | 25.72±3.49 | 26.48±3.56 | 28.07±3.87 | <0.001 |
| Hypertension, n (%) | 132 (10.50) | 1508 (26.41) | 197 (17.70) | 276 (24.40) | 1035 (29.90) | <0.001 |
| SBP (mmHg) | 120.49±14.80 | 127.81±16.06 | 124.47±14.95 | 126.22±16.36 | 129.37±16.09 | <0.001 |
| DBP (mmHg) | 77.40±10.21 | 82.01±11.79 | 79.01±11.21 | 80.03±11.24 | 83.58±11.86 | <0.001 |
| Diabetes mellitus, n (%) | 65 (5.17) | 450 (7.88) | 83 (7.40) | 106 (9.40) | 261 (7.50) | 0.12 |
| Hyperlipidemia, n (%) | 164 (13.05) | 1892 (33.14) | 306 (27.40) | 345 (30.50) | 1241 (35.90) | <0.001 |
| Tobacco use, n (%) | 235 (18.70) | 1137 (19.92) | 218 (19.60) | 219 (19.30) | 700 (20.20) | 0.761 |
| Alcohol consumption, n (%) | 599 (47.65) | 2972 (52.06) | 567 (50.90) | 588 (51.90) | 1817 (52.50) | 0.628 |
| Fasting glucose (mmol/L) | 5.14±1.11 | 5.61±1.34 | 5.39±1.29 | 5.52±1.27 | 5.71±1.37 | <0.001 |
| Fasting insulin (µU/mL) | 9.51±9.65 | 14.80±23.57 | 11.89±11.75 | 13.16±13.32 | 16.28±28.43 | <0.001 |
| IR | 346 (27.53) | 3271 (57.30) | 465 (41.70) | 569 (50.20) | 2237 (64.60) | <0.001 |
| HOMA-IR | 2.28±2.80 | 3.83±6.03 | 3.02±3.85 | 3.34±3.69 | 4.26±7.10 | <0.001 |
| Cholesterol (mmol/L) | 4.44±0.99 | 4.93±6.10 | 4.70±0.98 | 4.78±0.91 | 4.92±1.32 | <0.001 |
| Triglyceride (mmol/L) | 1.49±1.36 | 2.12±1.83 | 1.74±1.53 | 1.98±1.49 | 2.29±2.00 | <0.001 |
|                          | Mean ± SD       | Mean ± SD       | Mean ± SD       | Mean ± SD       | Mean ± SD       | p-Value     |
|--------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-------------|
| **High density Lipoprotein (mmol/L)** | 1.14±0.28       | 1.07±1.65       | 1.10±0.27       | 1.07±0.25       | 1.03±0.24       | <0.001      |
| **Low density Lipoprotein (mmol/L)** | 2.68±0.79       | 3.08±4.33       | 2.97±1.27       | 3.00±0.81       | 3.06±0.83       | 0.013       |
| **Apolipoprotein A-1 (g/L)** | 1.10±0.22       | 1.08±0.25       | 1.10±0.27       | 1.09±0.36       | 1.07±0.19       | 0.007       |
| **Apolipoprotein B (g/L)** | 0.76±0.19       | 0.87±0.20       | 0.83±0.19       | 0.86±0.19       | 0.89±0.21       | <0.001      |
| **Apolipoprotein E (mg/dL)** | 4.11±1.59       | 4.79±2.40       | 4.34±1.62       | 4.69±2.75       | 4.96±2.47       | <0.001      |
| **Lipoprotein-α (mg/dL)** | 14.72±18.29     | 12.62±15.39     | 14.47±18.44     | 12.71±14.88     | 12.00±14.41     | <0.001      |
| **ESS**                  | 5.50±5.14       | 8.56±6.13       | 7.00±5.12       | 6.88±5.55       | 9.57±6.35       | <0.001      |
| **ESS > 10, n (%)**      | 193 (15.35)     | 2066 (36.19)    | 248 (22.2)      | 288 (25.4)      | 1530 (44.2)     | <0.001      |
| **Polysomnography**      |                 |                 |                 |                 |                 |             |
| **Total sleep time, min**| 379.89±81.89    | 397.34±77.46    | 384.94±80.30    | 388.07±78.24    | 404.37±75.45    | <0.001      |
| **Sleep efficiency, %**  | 89.44±13.51     | 90.57±13.02     | 89.49±12.76     | 90.18±12.32     | 91.05±13.29     | 0.001       |
| **N1, % TST**            | 18.84±12.82     | 21.32±14.30     | 20.31±13.54     | 20.58±13.76     | 21.89±14.68     | 0.001       |
| **N2, % TST**            | 49.62±14.99     | 51.16±16.15     | 49.03±15.81     | 49.99±16.11     | 52.23±16.18     | <0.001      |
| **SWS, % TST**           | 18.74±12.19     | 15.78±13.01     | 18.46±12.48     | 17.51±12.18     | 14.34±13.23     | <0.001      |
| **REM, % TST**           | 12.59±7.03      | 11.26±6.63      | 11.83±7.21      | 11.51±6.85      | 11.00±6.35      | <0.001      |
| **AHI, events/h**        | 1.99±1.46       | 41.39±24.96     | 9.61±2.92       | 22.00±4.24      | 57.98±17.17     | <0.001      |
| **Lowest SpO2, %**       | 92.13±4.60      | 75.31±12.81     | 86.39±6.35      | 81.58±7.70      | 69.69±12.42     | <0.001      |
| **ODI, events/h**        | 4.20±12.70      | 41.59±26.44     | 10.42±7.05      | 23.16±9.19      | 57.66±20.66     | <0.001      |
| **Mean SaO2**            | 96.39±1.39      | 93.30±3.53      | 95.55±1.63      | 94.93±1.75      | 92.04±3.82      | <0.001      |
| **Micro arousal index, events/h** | 16.86±13.83    | 31.39±22.03     | 20.88±18.27     | 24.16±17.06     | 37.14±22.64     | <0.001      |

The data are presented as means and standard deviation (SD) and categorical data are given as the number (percentage). Acronyms: PS, primary snorers; OSA, obstructive sleep apnea; BMI, body mass index; IR, insulin resistance; HOMA-IR, homeostasis model assessment of insulin resistance; SBP, systolic blood pressure; DBP, diastolic blood pressure; ESS, Epworth Sleepiness Scale; AHI, apnea-hypopnea index; TST, total sleep time; SWS, slow wave sleep; REM, rapid eye movement; LSpO2, lowest oxygen saturation, ODI, oxygen desaturation index; SaO2, oxygen saturation.
Table 2. Clinical and sleep characteristics of OSA patients (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/m²    | 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)   | 14.55±27.79         | 13.20±9.56             | 15.19±31.21        | 16.28±19.69    | 0.638    |
| IR                        | 795 (55.7)          | 771 (53.8)             | 783 (55.5)         | 922 (64.2)     | <0.001   |
| HOMA-IR                   | 3.66±4.87           | 3.46±3.37              | 3.91±8.21          | 4.30±6.57      | 0.001    |
| Cholesterol (mmol/L)      | 4.82±0.95           | 4.83±0.96              | 4.84±1.02          | 4.90±1.68      | 0.218    |
| Triglyceride (mmol/L)     | 2.07±1.73           | 2.07±1.70              | 2.15±2.02          | 2.21±1.87      | 0.093    |
| High density lipoprotein (mmol/L) | 1.05±0.24        | 1.06±0.24              | 1.05±0.25          | 1.04±0.25      | 0.072    |
| Low density lipoprotein (mmol/L) | 2.96±0.81         | 3.03±0.83              | 3.04±0.81          | 3.09±1.21      | 0.003    |
| ApolipoproteinA-1 (g/L)   | 1.08±0.36           | 1.06±0.19              | 1.07±0.20          | 1.10±0.21      | 0.003    |
| Apolipoprotein-B (g/L)    | 0.87±0.19           | 0.86±0.19              | 0.87±0.20          | 0.89±0.21      | 0.025    |
| Apolipoprotein-E (mg/dL)  | 4.81±2.87           | 4.68±1.92              | 4.72±2.09          | 4.94±2.59      | 0.023    |
| Lipoprotein-a (mg/dL)     | 13.12±15.69         | 12.75±15.19            | 11.76±13.26        | 12.84±17.13    | 0.104    |
| ESS                       | 7.94±6.09           | 8.34±5.63              | 8.75±6.21          | 9.22±6.50      | <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 |
| N1, % TST                                                                        | 17.87±12.77  | 17.94±10.96  | 20.64±12.63  | 28.80±17.17  | <0.001 |
| 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                                                                    | 36.62±24.07  | 35.45±23.11  | 41.66±24.64  | 51.79±24.59  | <0.001 |
| Lowest SpO2, %                                                                   | 74.95±12.86  | 77.50±11.92  | 75.75±12.89  | 73.06±13.14  | <0.001 |
| ODI                                                                             | 35.97±26.11  | 36.21±24.69  | 42.36±26.24  | 51.79±25.53  | <0.001 |
| Mean SaO2                                                                        | 93.24±3.70   | 94.10±3.02   | 93.37±3.29   | 92.50±3.86   | <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                                                     | 25.45±21.94   | 27.44±18.52   | 32.28±20.80  | 40.34±23.51   | <0.001 |

The data are presented as means and standard deviation (SD) and categorical data are given as the number (percentage). Acronyms: OSA, obstructive sleep apnea; BMI, body mass index; IR, insulin resistance; HOMA-IR, homeostasis model assessment of insulin resistance; SBP, systolic blood pressure; DBP, diastolic blood pressure; ESS, Epworth Sleepiness Scale; AHI, apnea-hypopnea index; TST, total sleep time; SWS, slow wave sleep; REM, rapid eye movement; LSpO2, lowest oxygen saturation, ODI, oxygen desaturation index; SaO2, oxygen saturation.

Table 3 Clinical and sleep characteristics of primary snoring subjects (n = 1257) stratified by SWS categories
| Characteristics                      | > 24.7% (n = 310) | 17.1–24.7% (n = 319) | 10.6–17% (n = 312) | < 10.5% (n = 316) | p-value |
|-------------------------------------|-------------------|----------------------|--------------------|------------------|---------|
| **Demographic and clinical characteristics** |                   |                      |                    |                  |         |
| Men, n (%)                          | 194 (62.6)        | 190 (59.6)           | 203 (65.1)         | 201 (63.6)       | 0.531   |
| Age, y                               | 38.62±12.00       | 37.65±11.98          | 39.33±11.59        | 42.59±11.98      | <0.001  |
| Neck circumference (cm)              | 36.52±3.47        | 36.39±3.63           | 36.70±3.67         | 36.80±4.92       | 0.588   |
| Waist circumference (cm)             | 87.24±11.55       | 86.79±10.44          | 86.50±9.73         | 87.35±10.97      | 0.746   |
| Hip circumference (cm)               | 96.65±8.04        | 96.72±6.90           | 96.64±6.54         | 97.29±7.67       | 0.649   |
| Waist hip ratio                      | 0.90±0.07         | 0.90±0.07            | 0.89±0.06          | 0.90±0.07        | 0.656   |
| Body mass index, kg/m²               | 24.37±3.68        | 24.02±3.80           | 24.02±3.50         | 24.57±3.86       | 0.173   |
| Hypertension, n (%)                  | 35 (11.3)         | 32 (10.0)            | 26 (8.3)           | 39 (12.3)        | 0.395   |
| SBP (mmHg)                           | 119.23±16.32      | 118.99±13.95         | 121.60±14.92       | 122.19±13.61     | 0.016   |
| DBP (mmHg)                           | 76.84±10.28       | 76.86±10.48          | 78.04±10.52        | 77.87±9.52       | 0.336   |
| Diabetes mellitus, n (%)             | 24 (7.7)          | 9 (2.8)              | 5 (1.6)            | 27 (8.5)         | <0.001  |
| Hyperlipidemia, n (%)                | 61 (19.7)         | 54 (16.9)            | 58 (18.6)          | 59 (18.7)        | 0.846   |
| Tobacco use, n (%)                   | 47 (15.2)         | 58 (18.2)            | 60 (19.2)          | 70 (22.2)        | 0.161   |
| Alcohol consumption, n (%)           | 139 (44.8)        | 172 (53.9)           | 144 (46.2)         | 144 (45.6)       | 0.077   |
| Fasting glucose (mmol/L)             | 5.22±1.41         | 5.08±0.95            | 5.01±0.72          | 5.24±1.23        | 0.028   |
| Fasting insulin (µU/mL)              | 9.73±7.66         | 9.42±6.97            | 8.93±5.72          | 9.94±15.22       | 0.584   |
| IR                                   | 85 (27.4)         | 87 (27.3)            | 84 (26.9)          | 90 (28.5)        | 0.975   |
| HOMA-IR                              | 2.41±2.76         | 2.19±1.82            | 2.04±1.53          | 2.49±4.24        | 0.164   |
| Cholesterol (mmol/L)                 | 4.43±0.96         | 4.41±0.85            | 4.46±1.09          | 4.45±1.03        | 0.936   |
| Triglyceride (mmol/L)                | 1.50±1.46         | 1.38±0.98            | 1.47±1.51          | 1.60±1.41        | 0.251   |
| High density lipoprotein (mmol/L)    | 1.10±0.24         | 1.17±0.30            | 1.16±0.30          | 1.12±0.29        | 0.007   |
| Low density lipoprotein (mmol/L)     | 2.67±0.72         | 2.69±0.74            | 2.73±0.94          | 2.62±0.76        | 0.336   |
| ApolipoproteinA-1 (g/L)              | 1.07±0.25         | 1.10±0.21            | 1.10±0.20          | 1.14±0.22        | 0.005   |
| Apolipoprotein-B (g/L)               | 0.77±0.20         | 0.76±0.19            | 0.77±0.21          | 0.75±0.18        | 0.693   |
| Apolipoprotein-E (mg/dL)             | 4.14±1.84         | 4.00±1.26            | 4.06±1.51          | 4.23±1.71        | 0.337   |
| Lipoprotein-a (mg/dL)                | 11.96±14.63       | 16.23±20.33          | 16.07±19.22        | 14.51±18.11      | 0.013   |
| ESS                                  | 5.77±5.23         | 6.26±5.40            | 4.83±4.78          | 5.14±5.03        | 0.004   |
| ESS > 10, n (%)                      | 52 (16.8)         | 60 (18.8)            | 37 (11.9)          | 44 (13.9)        | 0.077   |
| Polysomnography                      |                   |                      |                    |                  |         |
| Total sleep time, min               | 384.20±85.53      | 375.63±80.50         | 387.07±70.75       | 372.85±89.15     | 0.092   |
| Predictors                        | n    | OR (95% CI)      | Model 1          | Model 2          | Model 3          |
|----------------------------------|------|------------------|------------------|------------------|------------------|
|                                  |      |                  |                  |                  |                  |
|                                  |      |                  |                  |                  |                  |
| **OSA**                          |      |                  |                  |                  |                  |
| > 21.3%                          | 1427 | Reference        | Reference        | Reference        | Reference        |
| 13.1–21.3%                       | 1434 | 0.966 (0.822–1.137) | 0.976 (0.829–1.150) | 0.980 (0.830–1.157) |
| 6.5–13%                          | 1412 | 0.946 (0.803–1.114) | 0.954 (0.809–1.125) | 0.949 (0.803–1.123) |
| < 6.5%                           | 1436 | *1.389 (1.175–1.641) | *1.373 (1.161–1.625) | *1.328 (1.118–1.578) |
| p for linear trend               | <0.001 | 0.001 | 0.004 |
| **Primary snoring**              |      |                  |                  |                  |                  |
| > 24.7%                          | 310  | Reference        | Reference        | Reference        | Reference        |
| 17.1–24.7%                       | 319  | 1.069 (0.728–1.57) | 1.035 (0.701–1.528) | 1.150 (0.765–1.729) |
| 10.6–17%                         | 312  | 1.066 (0.727–1.563) | 1.090 (0.739–1.607) | 1.128 (0.750–1.697) |
| < 10.6%                          | 316  | 1 (0.68–1.47)    | 1.025 (0.693–1.518) | 1.163 (0.770–1.757) |
| p for linear trend               | 0.999 | 0.839 | 0.515 |

The data are presented as means and standard deviation (SD), and categorical data are given as the number (percentage). Acronyms: OSA, obstructive sleep apnea; BMI, body mass index; IR, insulin resistance; HOMA-IR, homeostasis model assessment for insulin resistance; SBP, systolic blood pressure; DBP, diastolic blood pressure; ESS, Epworth Sleepiness Scale; AHI, apnea-hypopnea index; TST, total sleep time; SWS, slow wave sleep; REM, rapid eye movement; LSpO2, lowest oxygen saturation, ODI, oxygen desaturation index; SaO2, oxygen saturation.

Table 4 Adjusted ORs and 95% CIs for the association between SWS and IR in OSA and primary snoring subjects
Model 1 was adjusted for age, BMI, and sex; Model 2 was adjusted for variables included in Model 1 and alcohol consumption, smoking, hypertension, and hyperlipidemia; Model 3 was adjusted for variables included in Model 2 and TST, SE, ESS, and AHI. Acronyms: OSA, obstructive sleep apnea; OR, odds ratio; CI, confidence interval; SWS, slow wave sleep; BMI, body mass index; TST, total sleep time; SE, sleep efficiency; ESS, Epworth Sleepiness Scale; AHI, apnea-hypopnea index. *p indicates a significant difference

Table 5 Adjusted ORs and 95% CIs for the joint effects of OSA and SWS on IR

| Predictors | n    | OR (95% CI)   |
|------------|------|---------------|
|            |      | Model 1       | Model 2       | Model 3       |
| Primary snoring | 1257 | Reference     | Reference     | Reference     |
| OSA        | 5709 | *2.009 (1.721–2.346) | *1.899 (1.624–2.220) | *1.827 (1.554–2.149) |
| OSA-SWS > 21.3% | 1427 | *1.927 (1.605–2.314) | *1.814 (1.509–2.181) | 1.221 (0.994–1.501) |
| 13.1–21.3% | 1434 | *1.858 (1.549–2.230) | *1.763 (1.467–2.119) | 1.214 (0.991–1.489) |
| 6.5–13%    | 1412 | *1.817 (1.510–2.187) | *1.727 (1.434–2.082) | 1.096 (0.886–1.357) |
| < 6.5%     | 1436 | *2.662 (2.203–3.217) | *2.497 (2.064–3.023) | *1.382 (1.100–1.736) |
| p for linear trend | <0.001 | <0.001 | 0.081 |

Model 1 was adjusted for age, BMI, and sex; Model 2 was adjusted for variables included in Model 1 and alcohol consumption, smoking, hypertension, and hyperlipidemia; Model 3 was adjusted for variables included in Model 2 and TST, SE, ESS, and SWS% (or AHI). Acronyms: OSA, obstructive sleep apnea; OR, odds ratio; CI, confidence interval; SWS, slow wave sleep; BMI, body mass index; TST, total sleep time; SE, sleep efficiency; ESS, Epworth Sleepiness Scale; AHI, apnea-hypopnea index. *p indicates a significant difference

Table 6 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 |
|------------------|-----|------------------------------|---------|---------|---------|
|                  |     |                              |         |         |         |
| Primary snoring  | 1257| Reference                     | Reference| Reference| Reference|
| Mild OSA         | 1115|                              |         |         |         |
| > 21.3%          | 332 | *1.560 (1.187–2.050)         | *1.470 (1.115–1.937) | *1.382 (1.029–1.858) |
| 13.1–21.3%       | 341 | 1.198 (0.910–1.577)          | 1.192 (0.904–1.572) | 1.212 (0.911–1.613) |
| 6.5–13%          | 233 | *1.419 (1.035–1.945)         | *1.432 (1.042–1.969) | *1.419 (1.012–1.991) |
| < 6.5%           | 209 | *1.865 (1.273–2.733)         | *1.725 (1.170–2.543) | *1.601 (1.067–2.401) |
| p for linear trend|     | 0.001                        | 0.002   | 0.005   |
| Moderate OSA     | 1133|                              |         |         |         |
| > 21.3%          | 316 | *1.898 (1.436–2.507)         | *1.804 (1.362–2.389) | *1.815 (1.365–2.414) |
| 13.1–21.3%       | 340 | *1.530 (1.162–2.016)         | *1.482 (1.123–1.955) | *1.484 (1.121–1.965) |
| 6.5–13%          | 289 | *1.788 (1.340–2.386)         | *1.748 (1.307–2.337) | *1.741 (1.298–2.334) |
| < 6.5%           | 188 | *2.507 (1.747–3.598)         | *2.442 (1.699–3.510) | *2.414 (1.673–3.484) |
| p for linear trend|     | <0.001                       | <0.001  | <0.001  |
| Severe OSA       | 3461|                              |         |         |         |
| > 21.3%          | 743 | *2.231 (1.789–2.781)         | *2.090 (1.673–2.611) | *2.001 (1.592–2.516) |
| 13.1–21.3%       | 729 | *2.615 (2.095–3.263)         | *2.399 (1.917–3.001) | *2.306 (1.833–2.901) |
| 6.5–13%          | 860 | *2.035 (1.643–2.521)         | *1.896 (1.528–2.354) | *1.803 (1.443–2.253) |
| < 6.5%           | 1129| *2.935 (2.383–3.615)         | *2.764 (2.239–3.411) | *2.573 (2.072–3.196) |
| p for linear trend|     | <0.001                       | <0.001  | <0.001  |

Model 1 was adjusted for age, BMI, and sex; Model 2 was adjusted for variables included in Model 1 and alcohol consumption, smoking, hypertension, and hyperlipidemia; Model 3 was adjusted for variables included in Model 2 and TST, SE, and ESS. Acronyms: OSA, obstructive sleep apnea; OR, odds ratio; CI, confidence interval; SWS, slow wave sleep; BMI, body mass index; TST, total sleep time; SE, sleep efficiency; ESS, Epworth Sleepiness Scale. *p indicates a significant difference.

Table 7 Adjusted ORs and 95% CIs of IR associated with SWS in different subgroups.
| Predictors | Sex | Age | BMI |
|------------|-----|-----|-----|
|            | Men | Women | < 60 | ≥ 60 | < 28 kg/m² | ≥ 28 kg/m² |
|            | 5565 | 1401 | 6072 | 894 | 4637 | 2329 |
| Primary snoring | Reference | Reference | Reference | Reference | Reference | Reference |
| <21.3% | 1.133 (0.894–1.436) | 1.501 (0.974–2.313) | 1.165 (0.938–1.446) | 1.834 (0.869–3.870) | 1.250 (0.983–1.590) | 1.046 (0.681–1.607) |
| 13.1–21.3% | 1.083 (0.859–1.365) | *1.807 (1.157–2.823) | 1.168 (0.944–1.446) | 1.722 (0.825–3.597) | 1.138 (0.898–1.443) | 1.263 (0.820–1.946) |
| 6.5–13% | 0.958 (0.752–1.219) | *1.848 (1.147–2.978) | 1.059 (0.846–1.326) | 1.601 (0.753–3.407) | 0.992 (0.771–1.276) | 1.192 (0.766–1.855) |
| <6.5% | 1.277 (0.989–1.648) | 1.574 (0.903–2.745) | *1.382 (1.084–1.763) | 1.733 (0.810–3.711) | *1.357 (1.037–1.776) | 1.287 (0.806–2.057) |
| p for linear trend | 0.325 | 0.051 | 0.071 | 0.632 | 0.376 | 0.168 |

Model was adjusted for age, BMI, sex, alcohol consumption, smoking, hypertension, hyperlipidemia, TST, SE, ESS, and AHI. Acronyms: OSA, obstructive sleep apnea; OR, odds ratio; CI, confidence interval; BMI, body mass index; TST, total sleep time; SE, sleep efficiency; ESS, Epworth Sleepiness Scale; AHI, apnea-hypopnea index. *p indicates a significant difference.