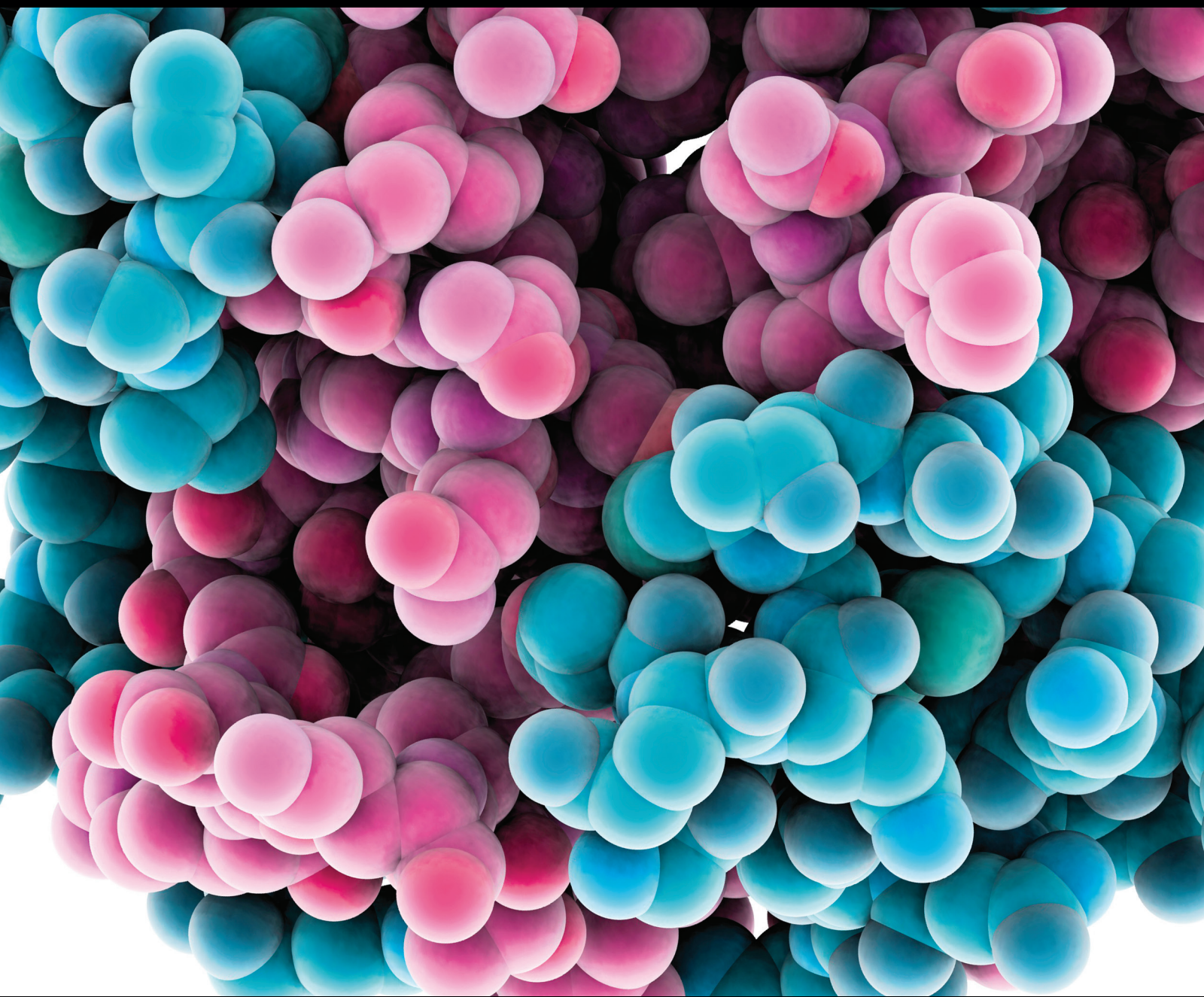
Journal of Diabetes Research

The Relationship between Disturbed Sleep, OSAS, and Metabolic Diseases

Special Issue Editor in Chief: Patrizio Tatti
Guest Editors: Sirimon Reutrakul, Abd Tahrani, Carlos Zamarron, Desiderio Passàli, and Thirumagal Kanagasabai



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Editorial

The Relationship between Disturbed Sleep, OSAS, and Metabolic Diseases

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The relationship among sleep quality, duration, regularity and metabolic disorders is an unknown territory. We know that sleep has its own architecture, made of progressive stages, recurring throughout the night, but we largely ignore the meaning of this, and which consequences the disruption of this architecture may cause. We do not even know what the optimal duration of sleep is, a topic that has been debated since the Epic of Gilgamesh. It is only in the final years of the last century that we could gain some insight into the medical meaning of sleep and the consequences of its disruption. Being the most obvious marker and cause of disturbed sleep, OSAS has come in the crosshair of most researchers.

We know that OSAS/disturbed sleep has a causative role in most metabolic and cardiovascular disorders and possibly even in cancer.

This issue of the journal has the merit of bringing together the best answers available to, at least, some of the mysteries surrounding sleep.

The paper from W. Martorina and A. Tavares, "Real-World Data in Support of Short Sleep Duration with Poor Glycemic Control, in People with Type 2 Diabetes Mellitus," on 140 50- to 61-year-old patients examines the effect of the "sum up sleep," thus encompassing both night- and daytime sleep segments. This aspect is of special interest because before the advent of artificial light people used to sleep in two segments, interrupted by two or three hours of wakefulness, during which they attended religious practices or social events. This paper supports the idea that the final outcome on the HbA1c level does not dramatically change if we add this "catch up sleep." In most countries, people used to nap in the afternoon, and we had previously no insight on the effect of this practice.

The paper from K. Neumann et al., "Sleep-Disordered Breathing Is Associated with Metabolic Syndrome in Outpatients with Diabetes Mellitus Type 2," uses the severity of OSAS to assess the relationship with the metabolic syndrome in subjects with type 2 diabetes mellitus. One of the merits of this study is the demonstration of a "dose-dependent effect," one of the most relevant of the Bradford-Hill criteria used to accept statistical results.

The study from Y. Zhang et al. adds an in-depth study of glucose metabolism. Using the HOMA Index and the overnight metabolic profile, the authors could demonstrate a change in the indexes of insulin resistance, a deep involvement of the hypothalamic-endocrine axis and an increase of the inflammatory cytokines in the most severe OSAS patients.

Conflicts of Interest

The editors declare that they have no conflicts of interest regarding the publication of this special issue.

Patrizio Tatti
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Desiderio Passali
Sirimon Reutrakul
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Research Article

Real-World Data in Support of Short Sleep Duration with Poor Glycemic Control, in People with Type 2 Diabetes Mellitus

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Aims. Sleep duration (SD) has been associated with metabolic outcomes. Is there an independent association between short/long SD and glycemic control (GC) in type 2 diabetes mellitus (T2DM) outpatients, compared to intermediate SD? Employing up-to-date definitions of SD, we comprehensively considered, simultaneously, all known confounding/mediating factors that recently emerged in the literature: age, gender, diet, physical activity, obesity, night pain, nocturnal diuresis, sleep quality, chronotype, sleep apnea, depressive symptoms, alcohol, caffeine, tobacco, number of endocrinologist appointments, T2DM family history, and sleep medication. *Methods*. A cross-sectional study of 140 consecutive T2DM outpatients, ages 40-65, *glycohemoglobin* (HbA_{1c}) *goal* ≤ 7. We searched for variables (including HbA_{1c}) significantly associated with short (<6 hours) or long (>8 hours) SD, in comparison to intermediate SD (6-8 hours). *Results*. Higher HbA_{1c} levels increased the chance of belonging to the group that sleeps <6 hours ($p \leq 0.001$). Better sleep quality, nocturnal diuresis, and morningness increased the chance of belonging to the group that sleeps >8 hours ($p < 0.05$). *Conclusions*. There is an independent association between short SD and elevated HbA_{1c}, in real-world T2DM outpatients. Future interventional studies could evaluate weather consistent, long-term sleep extension, from <6 hours to 7–9 hours per 24 hours, improves GC in T2DM outpatients.

1. Introduction

451 million people worldwide had diabetes mellitus in 2017, according to the International Diabetes Federation [1]. By 2045, numbers will increase to 693 million [1]. Recent data in Brazil (2014) estimates a prevalence of 19.7% in the general population [2], which is second only to China, India, and the USA [2]. Around 90% are cases of type 2 diabetes mellitus (T2DM). These estimates point to staggering increases in costs associated with the complications of this progressive disease: extremity amputations, end-stage renal disease, and cardio- and cerebrovascular disease [3]. The prevention of the emergence of the disease and the promotion of its adequate control are the only ways to reduce these impacts.

Since the Epic of Gilgamesh (second millennium BC), the ideal sleep duration (SD) and its deviations are a matter of medical debate [4]. The National Sleep Foundation (NSF) regularly reviews recommendations for SD, updating them according to the most current research. Presently, the NSF recommends 7 to 9 hours of sleep per day for the group with ages between 26 and 64 years old, safeguarding, however, that 6 to 10 hours may be appropriate [5]. Such directions originated from specialists' consensus and were supported by a review of 312 articles published between 2004 and 2014 [5]. SD is amenable to behavioral recommendations and interventions, inexpensive in biological terms.

Recent (2018) epidemiological studies suggest that both short and long SD are associated with an increased risk of acquiring T2DM, in comparison to intermediate SD [6, 7]. A small group of studies [8–13] analyzed whether short/long SD is deleterious to glycemic metabolism, in patients already diagnosed with T2DM. In some of these studies, short/long SD is associated with worse glycemic control (GC), assessed by glycohemoglobin (HbA_{1c}) levels [8–11].

The investigation of the association between SD and GC in T2DM patients is a challenging enterprise. Recent literature indicates that multiple confounding variables are to be

considered, particularly obesity [6], obstructive sleep apnea (OSA) [14], chronotype [15], sleep quality [16], and depressive symptoms [17]. In addition to that, in order to evaluate whether this association occurs independently, known mediating factors must be considered: diet [18], physical activity [19], nocturnal diureses [20], pain nocturnal [20], and alcohol use [21]. Finally, it is necessary to take into account that the relationship between SD and GC is bidirectional: SD interferes with GC [22], and hyperglycemia symptoms (particularly, nocturia and diabetic neuropathy) interfere with SD [20]. To the best of our knowledge, previous studies were not able to include all these factors simultaneously.

The pathophysiology of the sleep-T2DM association is not completely understood, and several hypotheses are to be considered. Experimental studies in healthy humans point that short SD can lead to glucose intolerance [23], decreased insulin sensitivity [24], and worsening of food intake quality [25]. Similar mechanisms were proposed to explain a relationship found between glycemic metabolism and long SD [26].

The aim of this study is to determine the association between SD and GC in real-world outpatients already diagnosed with T2DM persists, when all confounding and mediating variables that emerged in recent sleep-T2DM literature are simultaneously included in the study analysis.

2. Methods

2.1. Ethical Aspects. This work was approved by the Research Ethics Committee of the Federal University of Minas Gerais (protocol CAE: 63951317.5.0000.5149). All participants signed an informed consent form for this study, conforming to the standards of the Helsinki Declaration.

2.2. Design. Clinical data collection for this cross-sectional study took place from April to September 2017. A total of 140 patients diagnosed with T2DM, aged 40 to 65 years, from a health network of the metropolitan region of Belo Horizonte, Brazil, were included. The exclusion criteria were as follows: (1) age < 40 or >65; (2) pregnancy; (3) recent (<3 months) corticosteroid use; (4) recent (<1 year) diagnosis of T2DM; and (5) conditions that would render glycemic target (HbA_{1c} < 7%) more flexible (end-stage renal disease, recent acute coronary syndrome, and other major illnesses, such as cancer and hepatic insufficiency).

2.3. Clinical and Laboratory Evaluation. All participants were interviewed and examined by the same board-certified endocrinologist (WM). SD was evaluated with the question "How long do you sleep in a 24-hour period?" This encompassed both night- and daytime sleep segments. Previous studies on the association between SD and CG similarly analyzed sleep in a 24-hour period [8, 11]. Such methodology is supported by a work suggesting that diurnal naps can reduce the negative impact of sleep restriction in GC [5, 11]. Participants were divided into three categories according to SD: short sleep (<6 hours/24 hours), intermediate sleep (6-8 hours/24 hours), and long sleep (>8 hours/24 hours). The risk of OSA, a potential confounder of the relationship between SD and GC, was determined by the Brazilian version of the STOP-BANG questionnaire [27] (score ≥ 3 used as a risk indicator). Excessive daytime somnolence (EDS) was evaluated by the Brazilian version of the Epworth Sleepiness Scale [28] (score > 10 identified EDS). The Brazilian version of Stunkard and Messick's [29] Three Factor Eating Questionnaire R-21 [30] was utilized to assess three domains: (a) cognitive restraint of eating (eating behaviors involving obligations and prohibitions); (b) uncontrolled eating (as a result of a loss of control over the intake); and (c) emotional eating (in response to negative emotional states). To evaluate depressive symptoms, the Patient Health Questionnaire (PHQ-9) was utilized [31]. Because the study population was not composed of young students and consisted mostly in middle-aged patients, we separated Horne and Östberg's Morningness-Eveningness Questionnaire scores according to cut-off points recommended by Taillard et al. [32] (morning type ≥ 65; neither type 53 to 64; evening type ≤ 52), specifically determined to classify chronotypes in a population of middle-age adults. Sleep quality was assessed according to the modified Pittsburgh Sleep Quality Index (mPSQI), proposed by Knutson et al. [9], which evaluates sleep quality independently of SD. Weekly frequencies of nocturnal pain (suggesting diabetic neuropathy) and of nocturia (suggesting poorer glycemic control) were counted, in order to estimate the influence of hyperglycemia symptoms on SD. The weekly frequency of alcohol ingestion, a parameter relevant for both GC and SD [21], was taken into account. Physical activity was established according to the minutes of physical exercises per week. Body mass index (BMI) was obtained by dividing weight in kilograms by squared height in centimeters. HbA_{1c} was evaluated by high performance liquid chromatography.

2.4. Statistical Analysis. Because the study data did not fit a normal distribution pattern, we tabulated the continuous variables according to medians and 25% and 75% quartiles (Table 1). For categorical variables, frequencies and proportions were listed.

Two generalized log-binomial linear models were adjusted to carry out the study. In the first model, short SD was compared to intermediate SD. In the second model, long SD was compared to intermediate SD. All variables with p value ≤ 0.20 were included in the multivariate model. Variables with higher values of p were removed stepwisely, and variables with p values ≤ 0.05 remained in the multivariate model (Table 2). Since the study design is cross-sectional, the prevalence ratio (PR) was used as a measure of association. The level of significance was set at 0.05. SPSS software version 20.0 was employed.

3. Results

140 consecutive patients were included, and Table 1 shows the distribution of the main variables for all participants. The median age was 56 (50-61) years. The majority were female (61.4%), worked (68.1%), slept 6 to 8 hours in a 24-hour period (69.5%), and presented with an increased risk for OSA (60.5%). Only 29.3% of the patients utilized insulin. The median for BMI was 30 kg/m^2 (quartiles 25-75%: 26.9-

Table 1: 140 patients with type 2 diabetes mellitus.

Variables	*N* (%) or median (quartile 25% and 75%)
Age (years)	56 (50-61)
Female gender	86 (61.4)
Caucasian	68 (48.2)
Education (years)	11 (7-15)
Employed	96 (68.1)
Time since diagnosis of T2DM	7 (3-10)
Family history of T2DM	104 (74.3)
Endocrinologist visits/year	3 (2-4)
Physical activity (minutes/week)	0.0 (0-180)
% uncontrolled eating (TFEQ-21)	22.2 (11.11–47.0)
% emotional eating (TFEQ-21)	16.6 (0–4.4)
% cognitive restraint eating (TFEQ-21)	44.4 (7.7-61.1)
Number of insulin users	41 (29.3)
HbA_{1c} (%)	7.3 (6.5-8.7)
BMI (kg/m^2)	30 (26.9-33.5)
Systolic blood pressure	120 (120-140)
Diastolic blood pressure	80 (80-80)
Number of patients with nocturnal pain days per week ≥ 1	62 (44.3)
Nocturia days/week	2 (1-3)
Number of patients that used alcohol > 1 time/week	51 (36.4)
Number of smokers	13 (9.3)
Caffeine intake (mg/day)	190 (95-295)
Pittsburgh Sleep Quality Index (modified)	7 (5-10)
Epworth Sleepiness Scale score	9 (6-12)
Number of patients with Epworth score > 10	50 (35.7)
Chronotype (Morningness-Eveningness Questionnaire) score	64 (59-69)
Chronotype:	
Morningness	66 (47.7)
Intermediate	58 (41.4)
Eveningness	16 (11.4)
STOP-BANG Questionnaire score	3 (2-4)
Number of patients with STOP-BANG Questionnaire score ≥ 3	85 (60.7)
PHQ-9 score	9 (5-14)

N: number; T2DM: type 2 diabetes mellitus; HbA_{1c}: glycohemoglobin; BMI: body mass index; PHQ-9: Patient Health Questionnaire.

33.5 kg/m^2), and the median for HbA_{1c} was 7.3% (quartiles 25%-75%: 6.5%-8.7%).

Table 2 displays the variables that remained with $p < 0.2$ in a univariate comparison, for short SD versus intermediate SD (model S) and for long SD versus intermediate SD (model L). Model S shows that variables *time since TDM2 diagnosis*, *HBA_{1c} level*, and *PHQ-9 score* were significantly and positively associated with short SD, in comparison to intermediate SD ($p < 0.05$). Model L indicates that variables *education* and *modified PSQI* score were significantly and negatively associated with long SD, in comparison to intermediate SD. This model also showed that longer *time since DM2 diagnosis*, *insulin use*, higher *weekly frequency of nocturia*, and higher *STOP-BANG score* were significantly and positively associated with long SD ($p < 0.05$).

Table 3 displays the multivariate model for short SD in relation to intermediate SD. *HBA_{1c} level* was the only variable that remained in the model (PR 1.27, 95% CI: 1.12-1.44, $p \leq 0.001$), demonstrating that an increase in its value increases the probability that such patients belong in the short SD group, in comparison to the intermediate SD group, independently of other variables.

Table 4 displays the multivariate model for long SD in relation to intermediate SD. An increase in the *MEQ score* independently increased the probability of belonging to the group with SD > 8 hours, in comparison with the group with SD between 6 and 8 hours (PR 1.05, 95% CI: 11.10, $p = 0.004$). Higher *frequency of nocturia throughout the week* was also significantly associated with long SD (PR 3.13, 95% CI: 1.25-7.84, $p = 0.015$). The model also showed that a reduction in the *modified PSQI score* (indicating better sleep quality) was independently associated with long SD (PR 0.74, 95% CI: 0.59-0.093; $p = 0.009$).

4. Discussion

The present study demonstrated that higher levels of HbA_{1c} are significantly and independently associated with a short SD (<6 hours in 24 hours), in comparison to an intermediate SD (6 to 8 hours in 24 hours), in a real-world population of Brazilian T2DM outpatients. This association remained significant after the simultaneous inclusion, in the analysis, of all of the most likely mediating and confounding factors that emerged in recent T2DM-sleep literature (Table 1): age, gender, blood pressure, OSA, time since T2DM diagnosis, sleep quality, chronotype, depressive symptoms, use of alcohol, obesity, physical activity, diet, nocturia, night pain, caffeine intake, smoking, number of endocrinologist appointments per year, family history of T2DM, and use of sleep-inducing medication. An association between long SD and HbA_{1c} was not identified.

Relevant methodological diversity is among the reasons why current publications discussing SD-GC in patients already diagnosed with T2DM apparently exhibit discrepant results.

Cooper et al. [12] and Williams et al. [13] did not find an association between SD and HbA_{1c}. However, these two studies were primarily designed to evaluate cardiovascular risk in T2DM and were not designed for the evaluation of GC.

In comparison to intermediate SD, both short and long SD were associated with worse GC in patients already diagnosed with T2DM, in previous studies [8, 10, 11, 33]. The definition of short and long SD varied considerably in these studies, ranging from less than 4.5 to 7 hours for short SD and from 8 to 9 or more hours for long SD. For the present study, updated SD definitions were chosen, in conformity

Table 2: Prevalence ratios for short and long sleep durations, compared to intermediate sleep duration. Variables with $p \leq 0.2$ in the univariate log-binomial analysis.

Variables	Model S: short sleep duration PR (95% CI)	Model L: long sleep duration PR (95% CI)
Female gender	1.53 (0.83–2.81)*	1.50 (0.49–4.59)
Education (years)	0.95 (0.89–1.02)*	0.86 (0.76-0.98)**
Time since T2DM diagnosis (years)	1.06 (1.01–1.10)**	1.12 (1.02–1.22)**
Number of insulin users	1.33 (0.70–2.53)	4.40 (1.39–13.99)**
Number of patients that used alcohol > 1 time per week	1.75 (0.96–3.20)*	2.43 (0.80–7.44)*
HbA_{1c} (%)	1.28 (1.13–1.44)**	1.25 (0.94–1.66)*
Caffeine intake (mg/day)	1.001 (0.999–1.002)	1.001 (1.001–1.003)*
STOP-BANG Questionnaire score	1.11 (0.96–1.29)*	1.31 (1.03-1.68)**
Number of patients with STOP-BANG Questionnaire score ≥ 3	1.51 (0.78–2.95)	7.03 (0.93-53)*
Chronotype (MEQ score)	1.01 (0.98–1.03)	1.04 (0.99–1.10)*
Cognitive restriction (%)	0.987 (0.97–1.00)*	0.98 (0.96–1.02)
Emotional eating (%)	1.01 (0.99–1.020)*	0.98 (0.96–1.0)*
PHQ-9 score	1.06 (1.02–1.10)**	0.96 (0.85–1.07)
Nocturia days per week	0.98 (0.75–1.29)	3.47 (1.28–9.42)**
Number of patients with night pain days per week ≥ 1	1.80 (0.96–3.36)*	1.77 (0.57-5.45)
Modified Pittsburgh Sleep Quality Index	1.03 (0.94–1.13)	0.80 (0.67–0.95)**

PR: prevalence ratio; 95% CI: 95% confidence interval; T2DM: type 2 diabetes mellitus; HbA_{1c}: glycohemoglobin; MEQ: Morningness-Eveningness Questionnaire; PHQ-9: Patient Health Questionnaire; *$0.2 \geq p > 0.05$; **$p < 0.05$.

Table 3: Multivariate log-binomial model for short sleep duration.

Independent variable	Dependent variable: short SD compared to intermediate SD		
	Prevalence ratio	95% CI	p value
HbA_{1c}	1.27	1.12–1.44	$p \leq 0.001$

SD: sleep duration; 95% CI: 95% confidence interval; HbA_{1c}: glycohemoglobin.

Table 4: Multivariate log-binomial model for long sleep duration.

Independent variables	Dependent variable: short SD compared to intermediate SD		
	Prevalence ratio	95% CI	p value
MEQ score	1.05	1.00–1.10	0.040
Nocturia (days/week)	3.13	1.25–7.84	0.015
mPSQI	0.74	0.59–0.93	0.009

SD: sleep duration; 95% CI: 95% confidence interval; MEQ: Morningness-Eveningness Questionnaire; mPSQI: modified Pittsburgh Sleep Quality Index.

to current recommended standards [5], also employed in a recent systematic review and meta-analysis of SD and GC by Lee et al. [22]. In the present study, short SD was defined as <6 hours; intermediate SD, 6-8 hours; and, long SD, >8 hours. In the work of Lee et al. [22], both short and long SD were significantly related to higher HbA_{1c}, when compared to intermediate SD. Lee et al. [22] point that several confounding factors of association could not be studied in their analysis, since most of the papers included in their work did not present such data. Due to the absence of this relevant information, under- or overestimation of the relationships between SD and GC may have occurred.

In 2013, Ohkuma et al. [8] found both short and long SD significantly associated with higher levels of HbA_{1c}, when compared to intermediate SD (defined as 6.5 to 7.4 hours) (p for quadratic trend < 0.001). This work utilized self-reported SD, in a self-administered questionnaire: "How long is your usual sleep duration, including naps?". In spite of the fact that the present study also employed a subjective question for the assessment of SD ("How long do you sleep in a 24-hour period?"), a fundamental difference is to be noted. The same board-certified endocrinologist (WM) asked that question to all patients in the present study, during an office-based, doctor-patient clinical interview, for the good of reliability, in an outpatient real-world environment. Unlike the study of Ohkuma et al. [8], a significant association between long SD and HbA_{1c} was not found in the present study, possibly due to several design differences between the studies. Firstly, the relationship between long SD and HbA_{1c} is attenuated in subjects aged <70 years [8], which is one of the samples of the present study, which included only patients with age ≤ 65. In addition, the sample of the present study consisted in 140 patients only and was much smaller to the sample of 4870 patients studied by Ohkuma et al. [8]. Nevertheless, it is relevant to point out that the present study took in consideration a most relevant confounding factor between GC and long SD: OSA is an indicator of intermittent

hypoxemia. OSA is quite frequent among T2DM patients, with prevalences ranging from 58 to 86% [34]. Since the data of Ohkuma et al. [8] were not adjusted for OSA, a high prevalence of occult OSA in that study may have mediated the association between long SD and HbA_{1c}. One of the risk factors for OSA is older age [35]. The mean age of patients in the study of Ohkuma et al. [8] (>65 years) is higher than the mean of age of patients in the present study.

In the studies of Gozashti et al. [11] and of Tang et al. [10], short SD was associated with poor GC and long SD with improved GC, in T2DM patients. The results of Gozashti et al. [11] and Tang et al. [10] were in the same direction to the results of the present study, in regard to short SD, and in the opposite direction in regard to long SD. OSA might be the reason for this discrepancy regarding long SD. In studies of Gozashti et al. [11] and Tang et al. [10], OSA participants were excluded when they self-reported such condition. This might suggest that OSA did not interfere with the relation between long SD and poor GC in these two studies. However, OSA is frequently underdiagnosed in the diabetic population [36], and a considerable number of OSA cases may have remained undetected in the populations of Gozashti et al. [11] and Tang et al. [10]. Because OSA is such a relevant phenomenon for the long-term care of complications of T2DM [37], we avoided excluding OSA patients, and we opted to measure the *OSA risk*, in pursuit of a real-life clinical relevance. The STOP-BANG questionnaire [38], a validated method to evaluate the OSA risk, was chosen. The use of this improved method to appraise the influence of the *OSA risk* as a confounding factor may have determined the absence of association between long SD and HbA_{1c} in the present study, in contrast to the studies of Gozashti et al. [11] and Tang et al. [10]. In a study of 161 T2DM that excluded cases with long SD, Knutson et al. [9] did not exclude OSA cases and analyzed the OSA risk. However, it is relevant to point that the OSA risk was measured by means of an unvalidated subjective instrument: weekly frequency of nocturnal snoring.

In the same line of search, Siwasaranond et al. [39] examined factors associated with poorer GC in T2DM patients with untreated sleep-disordered breathing (SDB), an umbrella term for chronic conditions with breathing cessations in sleep, most frequently OSA. They used objective methods to rate both SDB and SD, in contradistinction to subjective questioning: SDB was diagnosed when the apnea-hypopnea index (AHI) was ≥5, assessed by an overnight in-home somnographic monitoring device (WatchPAT 200), and SD was recorded by wrist actigraphy for 7 days. An association between OSA severity and GC in patients T2DM was suggested in a previous work [40], which was not confirmed by Siwasaranond et al. [39]. Only shorter SD was independently associated with higher HbA_{1c}, in this study of Siwasaranond et al. [39].

The relevance of short SD as a mediator of worse GC in T2DM patients was also identified in a study that focused on sleep timing. Studying GC of T2DM patients in Thailand, Reutrakul et al. [33] showed that later bedtime on weekends was associated with poorer GC ($p = 0.01$). However, in a hierarchical logistic analysis, this association was totally mediated by shorter SD. Employing distinct methodologies, both Reutrakul et al. [33] and de Medeiros et al. [30] found a relevant association between short SD and GC, which was confirmed with a different study design in the present study.

In our first univariate analysis (Model S, Table 2), results were similar to those previously obtained by Ohkuma et al. [8]: a significant association between short SD and *depressive symptoms* (PHQ-9). Nevertheless, HbA_{1c} was the only variable associated with short SD, in comparison to intermediate SD. Therefore, the association between higher HbA_{1c} level and short SD was not mediated by variables related to hyperglycemia symptoms, like *nocturia* and *nocturnal pain*. Confounding factors like *OSA*, *sleep quality*, *chronotype*, and *depressive symptoms* did not explain this association. Besides that, other factors commonly associated with poor GC in T2DM, like *sedentary lifestyle* and *inadequate diet*, were not significantly different in the studied groups. As the study design is cross-sectional, it is not possible to conclude that worse GC caused a shortening in SD, nor that short SD was the cause of worse GC. Therefore, an independent association between higher levels of HbA_{1c} and short SD was shown, without pointing to the cause-effect direction.

In the second univariate analysis (Model L, Table 2), long SD was negatively associated with *education* (years) and positively associated with *time since T2DM diagnosis*, *insulin use*, and *OSA risk* (STOP-BANG questionnaire score), in comparison with intermediate SD. *Education* median was high enough (11 years; Table 1) so as not to interfere with comprehension of the clinical interview, or with the use of questionnaires. Although *education* was significant in this univariate analysis (Model L, Table 2), it did not persist association with SD in the multivariate analysis. Similar associations between long SD and longer *duration of T2DM* and *insulin use* were also present in the study of Ohkuma et al. [8]. However, in the final analysis in the present study (multivariate, Model L, Table 2), only higher *MEQ score* (indicating morningness), higher number of *nocturia* days per week (indicating sleep interruptions), and lower *modified PSQI score* (indicating better quality of sleep) were independently associated with the probability of belonging to the group that slept >8 hours. The association found between long SD and better-quality sleep in the present study is contrary to the line of reasoning in the work of Ferrie et al. (The Whitehall II Study) [41] that long SD might be a mechanism to compensate for poor sleep quality due to OSA, depression, and other comorbidities. An increase in the number of *nocturnal diuresis* events was shown in our patients with long SD. Nonetheless, sleep quality was better in this group, in comparison to the group with intermediate SD. This may indicate that poor sleep quality at night caused by *nocturia* was compensated by some sort of sleep extension along the 24 hours of the day. This improved sleep quality in a 24-hour period could be an explanation for the absence of an inadequate GC in our patients with long SD.

In regard to pathophysiology, some experimental studies in healthy humans attempted to explain how sleep deprivation interferes with glycemic metabolism [23, 24, 42, 43]. Sleep restriction would lead to changes in satiety and hunger

hormones (leptin and ghrelin) [25], reduction of physical activity [19], increased insulin resistance mediated by elevated cortisol, catecholamines [23], growth hormone, inflammatory cytokines [42], melatonin hormone, and the expression of genes related to circadian rhythm and glycemic metabolism [43]. In regard to *diet* and *physical activity*, the present study did not show significant differences when the short and long SD groups were compared to the intermediate SD group. The influence of insulin resistance was not evaluated in the present study.

The strength of the current work lies in the simultaneous inclusion in the analysis of the most recent and significant studied variables that could mediate or confuse the multifaceted relationship between SD and GC. The absence of these variables can be a problem in studies in this area, particularly the OSA risk [8, 22]. Although the study of Knutson et al. [9] analyzed the OSA risk, it was measured by means of an unvalidated instrument: weekly frequency of nocturnal snoring. In their studies, Gozashti et al. [11] and Tang et al. [10] only excluded patients that self-reported OSA and may have missed other OSA patients. In order to avoid that, in the present work, OSA was screened with the STOP-BANG questionnaire [27], an instrument validated for this purpose. The influence of *nocturia* and *night pain*, two very important mediating factors in the case of T2DM, was taken into account and evaluated. Previous studies excluded these factors only by self-report. In addition, chronotype, a variable previously related to SD and glycemic control, was included [15]. Finally, the prevalence ratio was used as a measure of association, which is more adequate to evaluate the association of disorders of high prevalence in a population [44]. Because the prevalence of sleep disorders in patients with T2DM is high, this choice is particularly relevant. Previous studies [8, 10, 11] used the odds ratio, a measure of association that overestimates the results when the prevalence of a characteristic in a population is high. In this aspect, therefore, the results of the present study can be considered more robust, and this may have contributed to the lack of association found between long SD and GC.

The main limitations of the current work regard the lack of utilization of objective measurements (polysomnography to measure SD and to evaluate OSA and actigraphy to estimate SD). The OSA risk was evaluated with a subjective instrument (the STOP-BANG questionnaire), and SD was obtained in a subjective clinical interview. The subjective nature of these data may interfere with the reliability of the association between SD and GC. However, the methodology was based on previous studies indicating that SD measured by actigraphy or polysomnography correlates reasonably well with self-reported SD [45]. The risk of OSA was defined by a STOP-BANG *score* ≥ 3 (intermediate risk). Given the high sensitivity of this method [46], it is unlikely that patients with this disorder were not categorized in the at-risk group. In addition, the study had a cross-sectional design, and thus, causality and directionality between SD and GC cannot be inferred. Nonetheless, potential mechanisms that could influence the SD and CG of outpatients with T2DM were considered and none of them mediated this relationship.

5. Conclusion

This work demonstrated an association between SD < 6 hours per day and worse glycemic control in real-world T2DM outpatients. This association did not result from confounding or mediating factors that recently emerged in the sleep-diabetes scientific literature. The relationship between SD and GC is worth interventional studies, with consistent, long-term sleep extension, from <6 hours to 7–9 hours per 24 hours, to evaluate weather this modulates improvements in GC.

Data Availability

The database used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare no conflicts of interest.

Authors' Contributions

WM examined all the patients. WM and AT were responsible for the study concept, design, data collection, interpretation, and analysis, and both wrote and revised the manuscript and approved the final version.

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Research Article

Sleep-Disordered Breathing Is Associated with Metabolic Syndrome in Outpatients with Diabetes Mellitus Type 2

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Background. Metabolic syndrome (MS) and sleep-disordered breathing (SDB) are highly prevalent in patients with diabetes mellitus type 2 (DM2). The present study examined whether there is an independent association between SDB and MS in a sample of outpatients with DM2. *Methods*. MS was determined in 679 patients of the DIACORE-SDB substudy, a study of outpatients with DM2. According to the National Cholesterol Education Program (NCEP) criteria, MS is defined by at least three of the following five criteria: waist circumference of >102 cm (men)/>88 cm (women), blood pressure of ≥130/85 mmHg, a fasting triglyceride level of >150 mg/dl, high-density lipoprotein (HDL) of <40 mg/dl (men)/<50 mg/dl (women), and a fasting glucose level of ≥110 mg/dl. The apnea-hypopnea index (AHI) was assessed with a 2-channel ambulatory monitoring device and used to define the severity of SDB (AHI < 15.0: no/mild SDB; AHI 15.0-29.9: moderate SDB; AHI ≥ 30.0: severe SDB). *Results*. 228 (34%) of the 679 participants (mean age 66 years, mean body mass index (BMI) 31.2 kg/m^2, and mean AHI 14/hour) had SDB. MS was significantly more frequent in patients with more severe SDB (no/mild SDB vs. moderate SDB vs. severe SDB: 72% vs. 79% vs. 85%, respectively, $p = 0.038$). Logistic regression analysis adjusted for sex, age, obesity (BMI ≥ 30 kg/m^2), and the HOMA index showed a significant association between the AHI and the presence of MS (OR (95%CI) = 1.039 (1.011; 1.068); $p = 0.007$). Further, male sex, obesity, and the HOMA index were significantly associated with MS. *Conclusion*. SDB is significantly and independently associated with MS in outpatients with DM2.

1. Introduction

The most common type of sleep-disordered breathing (SDB) is obstructive sleep apnea (OSA) [1]. OSA is characterised by recurrent collapse of the upper airway during sleep leading to oxygen desaturation with consecutive arousals from sleep [2, 3]. The pattern of desaturation and reoxygenation results in intermittent hypoxia, which is the main reason for metabolic dysfunction in SDB and is associated with the components of metabolic syndrome, which means hypertension, visceral obesity, pathological glucose tolerance, and dyslipidaemia [4–7]. The pathological mechanisms of SDB that cause hypertension include baroreflex impairment as well as hypoxia-induced activation of chemoreflex sensors, which increase both the sympathetic tone and peripheral vascular resistance [8–10]. Endothelial dysfunction due to hypoxia and oxidative stress also contribute to cardiovascular disease and hypertension [11]. Obesity is strongly associated with OSA in a bidirectional manner: visceral obesity is a risk factor of OSA [12–14]. The accumulation of visceral fat reduces lung volume and thoracic compliance, thus generating negative thoracic pressure, which subsequently leads to pharyngeal occlusion [14]. In addition, the deposition of adipose tissue in the upper airway facilitates collapsibility by narrowing pharyngeal patency [15]. At the same time, OSA leads to weight gain mostly due to endocrine dysregulation and physical inactivity because of daytime sleepiness [13, 16–18]. Endocrine alterations and fragmentation of sleep are also involved in impaired glucose metabolism, leading to pathological glucose tolerance and insulin resistance [19–21]. Thus, SDB increases the risk of developing DM2 [1, 22]. The association between SDB and dyslipidaemia, defined as

an increase in triglyceride and a decrease in HDL levels, also contributes to intermittent hypoxia [23]. Treatment of SDB includes weight loss as well as therapy with continuous positive airway pressure (CPAP), which lowers blood pressure and improves glucose metabolism as well as the lipid profile [1, 10, 13, 22, 24, 25].

Overall, MS is strongly associated with SDB, and the reported prevalence ranges from 23% to 87% [5]. The present study examined whether there is an independent association between SDB and MS in a sample of outpatients with DM2.

2. Material and Methods

2.1. Study Design. The examined patients were participants of the DIACORE- (DIAbetes COhoRtE-) SDB substudy, a prospectively designed study of patients with DM2. Major diabetologists and medical insurance companies invited outpatients with DM2 in written form to participate in the study. Patients previously treated at the Department of Internal Medicine of the University Hospital Regensburg were also invited [26]. The diabetic status was determined by assessing diabetes medication or by validating self-report. Patients underwent a standardized physical examination and biosampling and had to fill in an online questionnaire [26]. Of 1036 individuals invited to participate in the DIACORE-SDB substudy, 721 agreed and were tested with a two-channel respiratory monitor (ApneaLink®, ResMed) [27]. Complete SDB parameters were recorded for 679 patients (94% of the 721 tested). MS could not be determined in two patients because of missing data on waist circumference and the triglyceride level. Thus, 677 participants were analysed with regard to the presence of MS. Follow-up is currently ongoing, so that the cross-sectional baseline data was used for the present investigation.

The protocol, the data protection strategy, and the study procedures were approved by the Ethics Committees of the participating institutes and were in accordance with the Declaration of Helsinki. Patients participated in the DIACORE study only after providing informed written consent.

2.2. Study Population. All DM2 outpatients living in the city and district of Regensburg were eligible for participating in the DIACORE-SDB substudy. Further inclusion criteria were the ability to fully understand the study information, to provide written informed consent, age ≥ 18 years, and self-reported Caucasian ethnicity [26]. Exclusion criteria were chronic renal replacement therapy (haemodialysis, peritoneal dialysis, or transplantation), history of active malignancy within the past five years, presence of an autoimmune disease potentially affecting kidney function, haemochromatosis, known pancreoprivic or self-reported type 1 diabetes mellitus, acute infection, fever, pregnancy, chronic viral hepatitis, and HIV infection [26]. Patients were included in the DIACORE-SDB substudy if they consented to undergo SDB screening and excluded if they currently used positive airway pressure therapy [27].

2.3. Assessment of SDB. SDB was assessed with the portable ApneaLink device (ResMed, Sydney, Australia) consisting of a nasal cannula and an oxygen clip to measure nasal flow and pulse oximetry. Trained study personnel instructed the participants on how to use the device at home. Several studies have validated the ApneaLink device (ResMed, Sydney, Australia) for the screening of SDB [28, 29]. The AHI, oxygen desaturation index, mean oxygen saturation, and minimum SpO_2 were assessed. The default settings of the screening device were used for the definitions of apnea, hypopnea, and desaturation: apnea was defined as a $\geq$80% decrease in airflow for $\geq$10 seconds, hypopnea as a decrease in airflow by $\geq$50-80% versus baseline for $\geq$10 seconds, and desaturation as a $\geq$4% decrease in oxygen saturation [27]. The cut-off for the diagnosis of SDB was an AHI $\geq$ 15/h. Patients with an AHI < 15/h were assumed to have no or mild SDB. An AHI $\geq$ 15 up to 29 was defined as moderate SDB and an AHI $\geq$ 30 as severe SDB [24]. A differentiation between obstructive and central sleep apnea was not possible because of the absence of a breast belt. Daytime sleepiness was assessed by means of the Epworth Sleepiness Scale (ESS), and a score of $\geq$11 was considered as excessive daytime sleepiness [30].

2.4. Assessment of Metabolic Syndrome. According to the NCEP criteria, MS is defined by at least three of the following five criteria [4]: visceral obesity, defined by a waist circumference of >102 cm in men or > 88 cm in women; dyslipidaemia, defined by high-density lipoprotein (HDL) of <40 mg/dl in men or < 50 mg/dl in women; a fasting triglyceride level of >150 mg/dl or use of triglyceride-lowering medication; hypertension, defined by blood pressure of $\geq$130/85 mmHg or use of antihypertensive medication; and presence of a pathological glucose tolerance with a fasting glucose level of $\geq$110 mg/dl.

Weight in light clothing was measured with a digital scale. Blood pressure and heart rate were measured with a vital signs monitor after the patient had been sitting at rest for at least five minutes. Waist circumference is defined as the smallest circumference between the upper iliac crest and the lower coastal margin. In case of obesity, waist circumference was measured midway between the upper iliac crest and lower costal margin. Blood samples (serum gel, EDTA, and sodium fluoride (Sarstedt, Germany) and PAXgene tubes (PreAnalytix GmbH, Switzerland)) were taken after the patient had been sitting at rest for 15 minutes [26].

2.5. Statistical Analysis. Descriptive data are presented as the mean (±SD). Normally distributed values of baseline characteristics were evaluated with Student's unpaired two-sided t-test. Metabolic parameters were compared with increasing severity of SDB (no/mild, moderate, and severe) by one factorial variance analysis (ANOVA) and the post hoc test (Bonferroni). The influence of the AHI on the presence of the metabolic syndrome and its criteria were assessed with logistic regression models. Known modulators such as age, sex, obesity, and insulin resistance were included as covariates. Insulin resistance was assessed by means of the Homeostasis Model Assessment index (HOMA index) that has been validated in previous studies [31–33]. Obesity was defined as a body mass index (BMI)

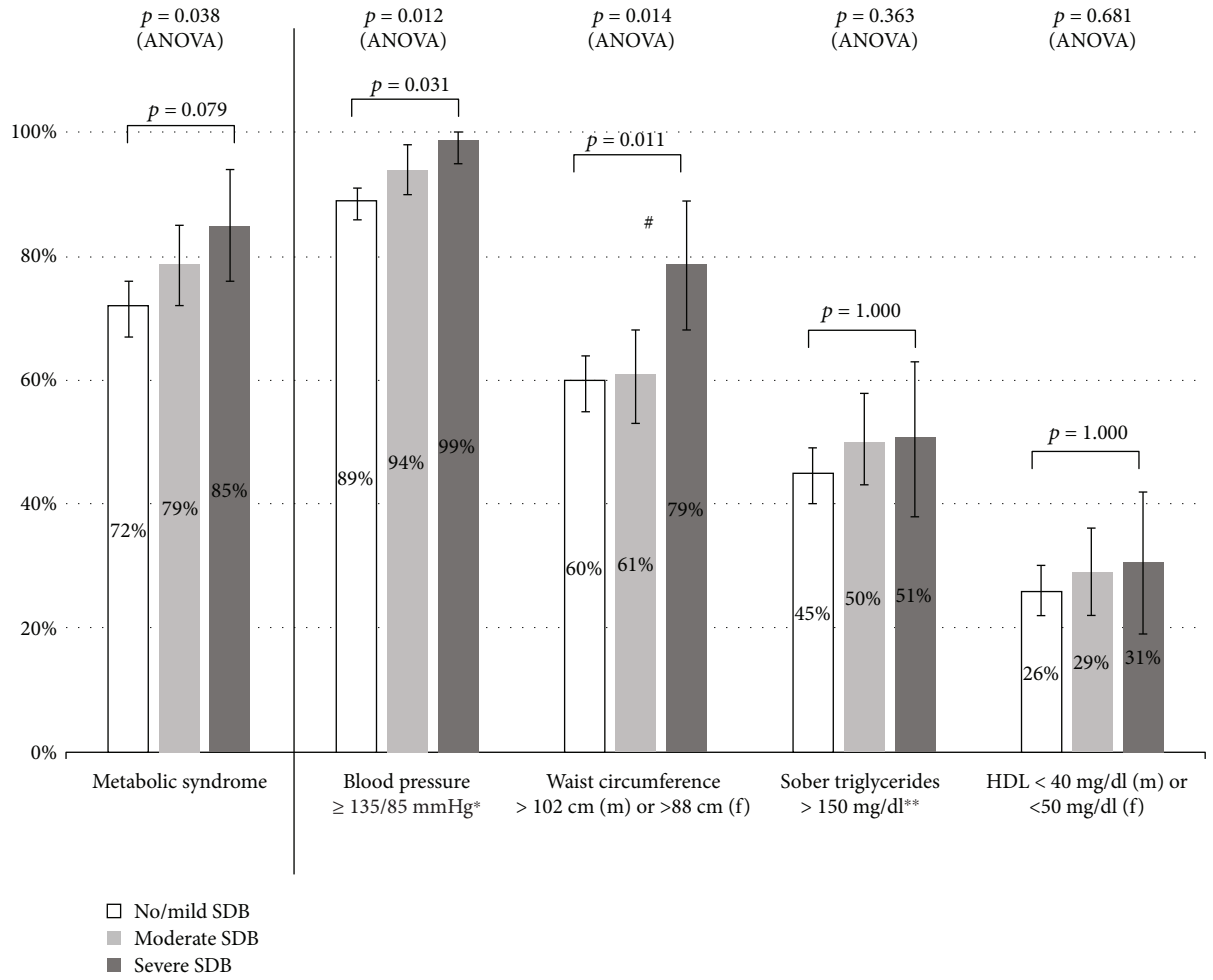

Figure 1: Prevalence of NCEP criteria (except elevated fasting glucose) in participants with no or mild, moderate, and severe SDB. Comparison of the prevalence of NCEP criteria with ANOVA and the post hoc test (Bonferroni) between no/mild and severe SDB. Results are shown with 95% confidence intervals. m: male, f: female; *or on antihypertensive medication, **or on triglyceride-lowering medication. #Significant difference between moderate and severe SDB ($p = 0.041$).

of ≥30 kg/m^2. Results are given as the odds ratio and 95% confidence interval; p values of <0.05 were considered significant. Data were analysed with the SPSS statistical software package (SPSS 23.0, IBM SPSS Statistics, Armonk, New York, USA).

3. Results

3.1. Patient Characteristics. The 679 patients of the SDB substudy (Figure 1) had a mean age of 65.6 years, and 61% were men. Patients were mostly obese (mean BMI 31.2 kg/m^2), and the mean duration of DM2 was 10.2 years. Anamnesis of medication showed that 81% of participants received antihypertensive medication, 47% cholesterol-lowering agents, and 85% antidiabetic agents. 27% of patients required insulin therapy (Table 1).

3.2. Characteristics according to Severity of SDB. Patients were classified into three groups according to the severity of SDB. Of the 228 patients with SDB, 163 had moderate (AHI ≥ 15/h and <30/h) and 65 severe (AHI ≥ 30/h) SDB. Baseline characteristics were compared among the three groups. Patients with SDB were predominantly older, male, and mostly obese with a significantly higher waist circumference, higher waist-hip ratio, and higher systolic blood pressure as well as a lower HDL level (Table 2).

3.3. SDB and MS. According to the NCEP criteria, MS was prevalent in 75% of the participants, and 80% of the patients with SDB had MS. The comparison of the severity of SDB among the three groups showed that MS as well as its components visceral obesity and hypertension was significantly more frequent in patients with more severe SDB (Figure 1). The criterion of elevated fasting glucose level was excluded, because DM2 was prevalent in all participants.

After adjusting for sex, age (in decades), obesity (defined as BMI ≥ 30 kg/m^2), and the HOMA index in a multivariate regression analysis, the AHI was significantly and independently associated with the presence of MS (OR (95% CI) = 1.039 (1.011; 1.068); $p = 0.007$). Male sex, obesity, and the HOMA index were independent modulators of MS. In the same multivariable regression, the AHI was also

Table 1: Baseline characteristics.

	$N = 679$
Age (years)	65.6 ± 8.8
Sex, male (n (%))	412 (60.7%)
AHI/h	14 ± 13
Metabolic parameters	
Waist circumference (cm)	100.8 ± 16.6
BMI (kg/m^2)	31.2 ± 5.5
Systolic BP (mmHg)	138 ± 18
Diastolic BP (mmHg)	75 ± 10
HDL (mg/dl)	52.8 ± 14.9
Triglycerides (mg/dl)	171.4 ± 131.5
Duration of DM2 (years)	10.2 ± 8.0
HbA1c (%)	6.8 ± 1.1
(mmol/mol)	51 ± 12
HOMA index*	6.2 ± 7.5
Medication N (%)	
Antihypertensive medication	
Antihypertensive medication altogether	547 (81%)
ACE inhibitor	280 (41%)
Angiotensin receptor blocker	164 (24%)
Renin inhibitor	3 (<1%)
Calcium channel blocker	191 (28%)
Beta-blocker	322 (47%)
Diuretics	267 (39%)
Fat metabolism	
HMG-CoA-reductase inhibitor	318 (47%)
Diabetes medication	
Antidiabetic agents altogether	575 (85%)
Biguanide	459 (68%)
Incretin	153 (23%)
Sulfonylurea	127 (19%)
Glinide	26 (4%)
Alpha-glucosidase inhibitor	9 (1%)
Exenatide	6 (1%)
Insulin	181 (27%)

Results are provided as mean ± standard deviation or n (%). AHI: apnea-hypopnea index; BMI: body mass index; BP: blood pressure; HbA1c: haemoglobin A1c; HOMA: Homeostasis Model Assessment (fasting, use of long-acting insulin); DM2: diabetes mellitus type 2; HDL: high-density lipoprotein; *413 patients included.

significantly associated with several components of MS: elevated waist circumference (OR (95% CI) = 1.031 (1.006; 1.056); $p = 0.014$), hypertension (OR (95% CI) = 1.049 (1.000; 1.100); $p = 0.048$), and hypertriglyceridemia (OR (95% CI) = 1.018 (1.002; 1.035); $p = 0.029$) (Table 3).

4. Discussion

The present study shows that, in patients with DM2, MS and its criteria hypertension and visceral obesity were significantly more frequent with increasing severity of SDB. Logistic regression analysis yielded a significant and independent association between increasing AHI and the prevalence of MS as well as visceral obesity, hypertension, and hypertriglyceridemia.

Our data confirm the results of previous studies describing a higher prevalence of MS in patients with SDB [34–38] (Table 4). However, the present study complements previous studies in the following manner.

First, previous studies were not conducted in a sample of outpatients with DM2. Although some studies included patients with DM2 or with pathological glucose tolerance, the percentage is still rather low (5-30%) [5, 34, 37–40]. Thus, to our knowledge, the present study is the first to exclusively analyse the association of SDB with MS and its components in patients with DM2.

Second, several previous studies defined SDB as an AHI ≥ 5 or ≥ 10 [5, 34, 37–41]. However, our participants with an AHI < 15/h were not sleepy, which was shown by the low ESS (Table 2); thus, they did not require any treatment. For this reason, we defined clinically relevant SDB as an AHI ≥ 15 and used the recommended classification of SDB severity [24].

With respect to the prevalence of MS criteria, our findings are mostly consistent with previous study results. The association of SDB with hypertension [34, 37–40] and obesity [37, 38], as in the present study, is well known. Nevertheless, Kono et al. and Lin et al. found a significant association of SDB with the components of MS in nonobese patients [39, 40]. Parish et al. did not find any significant differences in the BMI between patients with and without OSA and assessed hypertension as the main factor for MS in patients with OSA [34]. Although most of our patients were obese and obesity remains to be significantly associated with MS, we found an independent association of the AHI with MS in a logistic regression model.

Results concerning an association between SDB and dyslipidaemia according to NCEP criteria have been inconsistent [34, 37, 39]. In the present study, there was no significant association between SDB and dyslipidaemia. However, a significant association between the severity of SDB and decreased HDL could be found. Also, other studies which were calculated with continuous variables of dyslipidaemia instead of NCEP criteria showed an association between SDB and the lipid profile, such as elevated triglycerides and low HDL [35–39, 42–44].

SDB is associated with pathological glucose tolerance and insulin resistance [19, 20]. In the present study, the duration of DM2 was significantly longer in patients with SDB than in patients with no or mild SDB (11.4 ± 9.0 vs. 9.5 ± 7.4 years; $p = 0.005$).

With respect to the association of SDB and components of MS, Coughlin et al. discussed in their review whether SDB may be a component of MS [45]. When examining patients of the Wisconsin Sleep Cohort Study for metabolic parameters, Nieto et al. [41]. detected a significant association of SDB with MS independent of sex, age, BMI, sympathetic, and neuroendocrine parameters; thus, the authors considered SDB (defined as an AHI ≥ 5) to be a component

Table 2: Characteristics according to severity of SDB.

	No/mild SDB ($N = 451$)	Moderate SDB ($N = 163$)	Severe SDB ($N = 65$)	p value	No/mild vs. moderate SDB	Moderate vs. severe SDB	No/mild vs. severe SDB
Mean AHI/h	7 ± 4	21 ± 4	46 ± 12	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Waist circumference (cm)	98.8 ± 16.4	102.3 ± 16.1	111.5 ± 15.4	**<0.001**	0.054	**<0.001**	**<0.001**
Waist-hip ratio	0.95 ± 0.08	0.98 ± 0.07	1.00 ± 0.08	**<0.001**	**<0.001**	0.093	**<0.001**
BMI (kg/m^2)	30.4 ± 5.1	31.3 ± 5.2	34.0 ± 6.8	**<0.001**	0.139	**0.002**	**<0.001**
Systolic BP (mmHg)	137 ± 18	140 ± 19	141 ± 17	**0.041**	0.135	1.00	0.179
Diastolic BP (mmHg)	74 ± 10	75 ± 10	76 ± 10	0.393	0.980	1.00	0.794
HDL (mg/dl)	54.0 ± 15.5	51.0 ± 13.6	49.6 ± 12.9	**0.016**	0.080	1.00	0.080
Triglycerides (mg/dl)	165.7 ± 125.1	181.1 ± 155.3	186.5 ± 107.0	0.273	0.597	1.00	0.699
HbA1c (%)	6.8 ± 1.1	6.9 ± 1.2	6.6 ± 0.7	0.111	0.867	0.110	0.340
(mmol/mol)	51 ± 12	52 ± 13	49 ± 7				
HOMA index*	5.6 ± 5.9	6.7 ± 9.1	7.9 ± 10.9	0.137	0.607	1.00	0.242
ESS	5 ± 3	5 ± 4	6 ± 3	0.148	1.00	0.863	0.195
Number of NCEP criteria	3 ± 1	3 ± 1	4 ± 1	**0.009**	0.306	0.350	**0.013**

Results are provided as mean ± standard deviation and p value (ANOVA). p values among groups were assessed by post hoc test (Bonferroni). AHI: apnea-hypopnea index; BMI: body mass index; BP: blood pressure; HDL: high-density lipoprotein; HbA1c: haemoglobin A1c; HOMA: Homeostasis Model Assessment (fasting, use of long-acting insulin), ESS: Epworth Sleepiness Scale; *413 patients included.

Table 3: Multivariable logistic regression analysis.

	Metabolic syndrome		Waist circumference > 102 cm (m) or >88 (f)		BP ≥ 130/85 mmHg*		Triglycerides > 150 mg/dl**		HDL <50 mg/dl (m) or <40 mg/dl (f)	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
AHI	1.039 (1.011; 1.068)	**0.007**	1.031 (1.006; 1.056)	**0.014**	1.049 (1.000; 1.100)	**0.048**	1.018 (1.002; 1.035)	**0.029**	1.012 (0.995; 1.030)	0.167
Sex	2.477 (1.377; 4.457)	**0.002**	6.874 (3.704; 12.757)	**<0.001**	0.620 (0.300; 1.284)	0.198	0.937 (0.611; 1.436)	0.765	1.372 (0.847; 2.222)	0.199
Age	1.010 (0.733; 1.392)	0.950	0.973 (0.689; 1. 373)	0.876	1.856 (1.253; 2.750)	**0.002**	0.909 (0.713; 1.161)	0.446	0.763 (0.578; 1.007)	0.056
Obesity	7.505 (3.689; 15.268)	**<0.001**	21.858 (11.129; 42.934)	**<0.001**	1.655 (0.733; 3.735)	0.225	1.411 (0.917; 2.172)	0.117	1.243 (0.760; 2.033)	0.386
HOMA index	1.313 (1.156; 1.491)	**<0.001**	1.106 (1.026; 1.192)	**0.008**	1.147 (0.996; 1.321)	0.058	1.038 (1.004; 1.074)	**0.029**	1.056 (1.021; 1.093)	**0.002**

Shown are adjusted odds ratios (OR) with 95% confidence intervals (95% CI) and *p* values. The variables used in the regression model were AHI, sex (male), age (decades), obesity (BMI ≥ 30), and the HOMA index. AHI: apnea-hypopnea index; HOMA: Homeostasis Model Assessment (fasting, use of long-acting insulin); *or on antihypertensive medication; ** or on triglyceride-lowering medication.

Table 4: Previous studies examining the association between SDB and MS.

	Study design and participants	Patients with pathological glucose tolerance	Definition and assessment of SDB	Main results
Neumann et al. (2019)	228 SDB patients, 451 controls; 61% men	100% (all participants had proven DM2)	SDB: AHI ≥ 15; ApneaLink	(i) In patients with DM2, MS as well as its criteria hypertension and visceral obesity was significantly more frequent in the case of more severe SDB
Bonsignore et al. [5]	529 OSA patients; 80% men	17% (DM2)	SDB: AHI ≥ 10; PSG	(i) The prevalence of MS increased with OSA severity (ii) Obesity and OSA led to metabolic abnormalities with different patterns between the two sexes (iii) Metabolic score increased with the HOMA index
Lin et al. [39]	113 OSA patients, 45 controls; 82% men; only nonobese subjects included; no difference in BMI among groups	18% (hyperglycaemia)	SDB: AHI ≥ 5; PSG	(i) Patients with OSA had significantly higher systolic blood pressure and triglyceride levels (ii) Dyslipidaemia, hypertension, and at least two of the NCEP criteria were significantly more frequent in the OSA group (iii) AHI was independently associated with increased triglycerides and insulin resistance (assessed with HOMA) in linear regression
Nieto et al. [41]	253 OSA patients, 293 controls; 56% men	Not given	Mild SDB: AHI 5-14.9, moderate to severe SDB: AHI ≥15 or CPAP PSG	(i) Logistic regression adjusted for age, sex, autonomic and neuroendocrine parameters, and BMI showed an association of MS with mild and moderate/severe SDB
Kono et al. [40]	42 OSA patients, 52 controls matched for age, BMI, and visceral fat accumulation; 100% men; only nonobese subjects included	5% (DM2)	SDB: AHI ≥ 5; PSG	(i) No significant differences in serum levels of triglycerides, HDL, and diastolic BP (ii) Prevalence of hyperglycaemia, dyslipidaemia, and hypertension was significantly higher in the OSA group (iii) Patients with OSA had more often at least two of the criteria hypertension, hyperglycaemia, and dyslipidaemia, independent of visceral fat obesity
Parish et al. [34]	146 OSA patients, 82 controls; 59% men	30% (hyperglycaemia)	SDB: AHI ≥ 5 and ≥10; PSG	(i) MS was more often present in patients with OSA (ii) Prevalence of hypertension was significantly higher in the OSA group (iii) No significant differences in hyperglycaemia and dyslipidaemia (iv) Prevalence of MS increased with severity of OSA
Gruber et al. [36]	38 OSA patients, 41 controls; percentage of men not given; MS is defined according to IDF	Not given	Minimal patient contact sleep diagnosis system (VISI-3, Stowood Scientific Instruments Ltd. (SSI), Oxford);	(i) The prevalence of MS was higher in the OSA group (ii) Logistic regression adjusted for age, BMI, and smoking showed an independent association of OSA and MS (iii) OSA was independently associated with the levels of triglycerides and glucose as well as the Epworth score values, whereas insulin resistance (assessed with HOMA) was not significant

Table 4: Continued.

	Study design and participants	Patients with pathological glucose tolerance	Definition and assessment of SDB	Main results
Lam et al. [37]	95 OSA patients, 160 controls; 59% men	7% (DM2)	SDB: AHI ≥ 5; PSG	(i) Patients with OSA were five times more likely to have MS (ii) OSA was independently associated with MS and some of its components (iii) Prevalence of MS increased with OSA severity
Sasanabe et al. [38]	819 OSA patients, 89 controls; 86% men	22% (hyperglycaemia)	SDB: AHI ≥ 5; PSG	(i) MS was significantly more frequent in patients with OSA (ii) The risk of MS was associated with the severity of OSA (iii) Hypertension, dyslipidaemia, and visceral obesity were more common in patients with OSA
Coughlin et al. [35]	61 OSA patients, 43 controls; 100% men	Not given	SDB:AHI > 15; PSG	(i) Patients with OSA had a greater waist circumference and higher systolic and diastolic blood pressure, were more insulin-resistant (assessed with HOMA), and had lower HDL and a higher prevalence of MS (ii) Patients with OSA were 9.1 times more likely to have MS

DM2: diabetes mellitus type 2; AHI: apnea-hypopnea index; PSG: polysomnography; OSA: obstructive sleep apnea; MS: metabolic syndrome; BP: blood pressure; BMI: body mass index; IDF: International Diabetes Federation; HDL: high-density lipoprotein; HOMA: Homeostasis Model Assessment; CPAP: continuous positive airway pressure.

of MS [41]. The present study also showed an increasing risk of MS as well as of visceral obesity, hypertension, and hypertriglyceridemia with a rising AHI. However, using a high cut-off and defining SDB as an AHI ≥ 15, the prevalence of SDB in patients with MS was rather low (36%) compared to the prevalence of hypertension (97%), visceral obesity (80%), and hypertriglyceridemia (61%) in patients with MS; therefore, there is no sufficient evidence to substantiate the claim that SDB is an integral component of MS.

The strength of our study is its large sample size with central data management and standardized protocols [26]. Furthermore, to our knowledge, this is the first study examining the association between SDB and MS in outpatients with DM2. There are some limitations that warrant discussion: First, a distinction between central and obstructive sleep apnea was not possible because of the use of a portable yet validated and established [28, 29] SDB monitoring device instead of polysomnography. Second, as our data stem from a cross-sectional analysis, we were only able to assess an association between SDB and MS but could not prove any causality. Third, since 100% of participants of the DIACORE-SDB substudy have diabetes, results cannot be extrapolated to patients with milder forms of altered glucose metabolism (fasting glucose < 126 mg/dl).

In summary, our findings showed that SDB is significantly and independently associated with MS in outpatients with DM2. As previous randomized controlled trials of CPAP treatment in patients with DM2 fell short of identifying an effect on glucose metabolism [46], future large-scaled long-term interventional studies are required.

Data Availability

The data of this study are available from the corresponding author upon request.

Ethical Approval

The protocol, the data protection strategy, and the study procedures were approved by the Ethics Committees of the participating institutes and were in accordance with the Declaration of Helsinki.

Consent

Patients participated in the DIACORE study only after providing informed written consent.

Disclosure

The abstract of this manuscript has been presented as a poster at the European Respiratory Society International Congress in Milan (2017) (10.1183/1393003.congress-2017.PA2322).

Conflicts of Interest

The authors have no conflicts of interest.

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Research Article

The Relationship between Simple Snoring and Metabolic Syndrome: A Cross-Sectional Study

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Purpose. This cross-sectional study was performed to assess the relationship between simple snoring and metabolic syndrome (MetS). *Methods*. A total of 5635 participants including 300 healthy volunteers without snoring allegedly were initially included from 2007 to 2016. Polysomnographic variables, anthropometric measurements, and biochemical indicators were collected. The polynomial linear trend test was used to assess the linear trend across snoring intensity for metabolic score, and logistic regression was used to evaluate the odds ratios (ORs) for MetS after controlling for age, sex, obesity, smoking status, and alcohol consumption. *Results*. The final study population consisted of 866 participants. Simple snorers showed more severe metabolic disorders and higher prevalence of MetS than nonsnorers. A significant linear trend was observed between snoring intensity and metabolic score. Simple snoring was significantly associated with increased odds for MetS among all participants (OR = 2.328, 95% CI: 1.340–4.045) and female participants (OR = 2.382, 95% CI: 1.136–4.994) after multivariable adjustment. With regard to MetS components, simple snoring was significantly associated with increased odds for hypertension (OR = 1.730, 95% CI: 1.130–2.650), abdominal obesity (OR = 1.810, 95% CI: 1.063–3.083), and hyper-triglycerides (TG) (OR = 1.814, 95% CI: 1.097–2.998) among all participants, with hypertension (OR = 3.493, 95% CI: 1.748–6.979) among males and with abdominal obesity (OR = 2.306, 95% CI: 1.245–4.270) and hyper-TG (OR = 2.803, 95% CI: 1.146–6.856) among females after multivariable adjustment. *Conclusions*. After excluding the influence of repeated apnea and hypoxia, simple snoring was still significantly associated with MetS, especially in women. Furthermore, the associations were more obvious for hypertension among males and for abdominal obesity and hyper-TG among females. In addition to OSA, simple snoring also should be valued.

1. Introduction

Snoring is commonly described as a coarse and vibratory sound during sleep resulting from partial obstruction of inspiration in the oropharynx [1]. The prevalence of snoring varies from 2% to 85% [1–3]. Simple snoring may represent the beginning of a sleep-disordered breathing (SDB) continuum, which ranges from partial airway collapse and mildly increased upper airway resistance to complete airway collapse and severe obstructive sleep apnea (OSA) lasting for 60 s or more [2, 4]. There is accumulating evidence that snoring is associated with several health problems, including sleepiness, cardiovascular diseases, metabolic syndrome (MetS), and all-cause mortality [5–7].

MetS, a combination of excess abdominal obesity, dyslipidemia, hypertension, hyperglycemia, and insulin resistance (IR) [8], is related to increased risk of cardiovascular events and mortality [9]. Previous studies have demonstrated a relationship between snoring and MetS, but patients with OSA were not excluded from the study populations [10–12]. Such association between snoring and MetS may be mediated by OSA, as heavy snoring is always accompanied

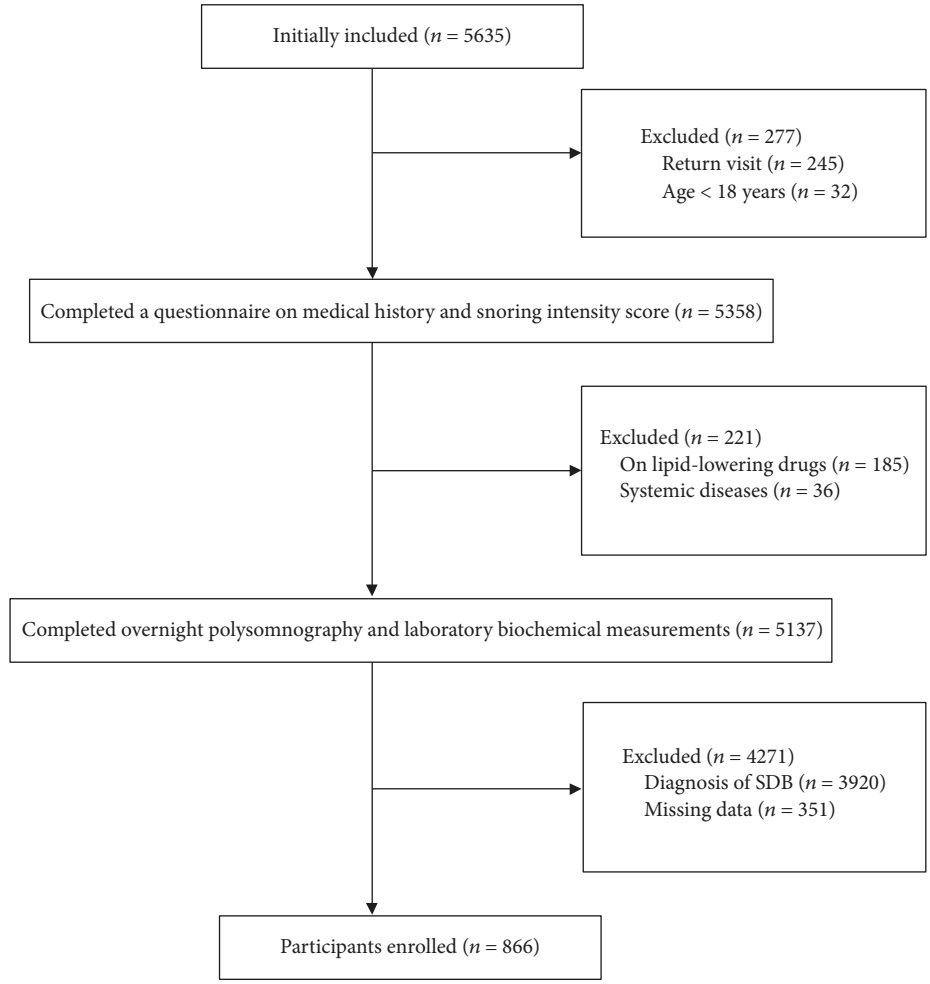

Figure 1: Flow chart of study population enrollment.

with sleep apnea [3], and both snoring and sleep apnea are related to mechanical obstruction of the upper airway [13]. However, most common snorers do not have OSA [4]. Therefore, further research is required to determine whether simple snoring itself, as a more common disease, is independently related to increased odds for MetS and its components.

To exclude the effects of more severe sleep apnea, we conducted a cross-sectional study among non-OSA participants to examine whether simple snoring itself is associated with increased odds for MetS and metabolic disorders, such as obesity, hypertension, dyslipidemia, and IR.

2. Methods

A total of 5635 participants were initially included in the study. Among them, 300 were healthy volunteers specially recruited without snoring allegedly; the other participants were patients referring to the sleep center of Shanghai Jiao Tong University Affiliated Sixth People's Hospital for suspected SDB from 2007 to 2016. They were mainly from cities in southeastern China and all completed surveys regarding smoking habits, alcohol consumption, and medical history. 4769 participants were excluded for the following reasons: return visit; age < 18 years; taking lipid-reducing medications prior to the study, which could affect the serum lipid profiles' levels; various systemic diseases (i.e., malignancy, chronic kidney disease, and unstable cardiopulmonary diseases, such as congestive heart failure or intrinsic pulmonary disease); diagnosis of SDB; and missing data (lacking information of smoking, drinking, lipid-lowering medication taking, etc.). Finally, a total of 866 participants including 187 nonsnorers and 679 simple snorers were enrolled in the analysis (Figure 1). Written informed consent was obtained from each participant according to the guidelines outlined by the National Ethics Regulation Committee. This study was approved by the Internal Review Board of the Institutional Ethics Committee of Shanghai Jiao Tong University Affiliated Sixth People's Hospital and was conducted in accordance with the tenets of the Declaration of Helsinki.

2.1. Anthropometric and Metabolic Measurements. All measurements were performed using the standard methods mentioned in our previous research [14], with the participants dressed in lightweight clothing and with bare feet. Body mass index (BMI) was calculated as body mass in kilograms divided by the square of the patient's height in meters. Neck circumference (NC) was measured at the level of laryngeal

prominence, waist circumference (WC) in the middle between the 12th rib and the iliac crest, and hip circumference (HC) at the level of the anterior superior iliac spine at the broadest circumference below the waist using a measuring tape. The waist-to-hip ratio (WHR) was determined as WC (cm)/HC (cm). In accordance with the guidelines of the American Society of Hypertension [15], blood pressure was measured at approximately 08:00 with patients in a seated position using a mercury sphygmomanometer after a 5 min rest. It was recorded as the mean of three measurements taken at 1 min intervals.

A fasting blood sample was taken from the antecubital vein of each patient in the morning after polysomnographic monitoring. Fasting serum glucose and lipid profiles were measured in the hospital laboratory using routine procedures. Serum lipid profiles included total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), apolipoprotein A-I (apoA-I), apolipoprotein B (apoB), apolipoprotein E (apoE), and lipoprotein(a) (Lpa) (Hitachi, Tokyo, Japan). An immunoradiological method was used to measure the fasting serum insulin level. Insulin sensitivity was evaluated using the homeostasis model assessment of insulin resistance (HOMA-IR): HOMA-IR = fasting glucose $(\text{mmol/L}) \times$ fasting insulin$(\mu\text{U/mL})/22.5$ [16].

2.2. Polysomnography. Overnight polysomnography (PSG) (Alice 4 or 5, Philips Respironics, Pittsburgh, PA) was performed from 22:00 to 06:00 according to the criteria of the American Academy of Sleep Medicine [17], including electroencephalogram (EEG), left and right electrooculogram (EOG), genioglossus electromyogram, electrocardiogram (ECG), pulse oxygen saturation, nose and mouth airflow, thoracic-abdominal movement, and body position. Apnea was defined as the complete cessation of airflow lasting for at least 10 s. Hypopnea was defined as a ≥50% reduction in airflow for at least 10 s with a decrease in oxyhemoglobin saturation of ≥3% or a ≥30% reduction in airflow for at least 10 s with a decrease in oxyhemoglobin saturation of ≥4%. The apnea hypopnea index (AHI) was defined as the number of apnea and hypopnea events per hour during sleep. The diagnosis of OSA was determined by AHI, and an AHI ≥5 events/h was defined as OSA [17].

2.3. Snoring Assessment. As snoring sounds are commonly described as a nuisance by the bed partner of the affected individual, information on snoring was collected from a bed partner or family member. Snoring intensity was evaluated using a 10 cm visual analogue scale (VAS) from 0 to 10: 0 represents no snoring, 1–3 represents minimally annoying, 4–6 represents moderately annoying, 7–9 represents annoying, and 10 represents extremely annoying [18]. We defined 0 as no snoring, 1–3 as mild snoring, 4–6 as moderate snoring, and 7–9 as severe snoring. Besides, in order to ensure a more even distribution for analysis, we incorporated 10 into the severe snoring group.

2.4. Metabolic Score. MetS was defined according to the NCEP ATP III criteria with the modified WC criteria for Asians [19] as the presence of at least three of the following five clinical features: (1) elevated WC: ≥90 cm in men and ≥80 cm in women; (2) elevated TG: ≥1.70 mmol/L; (3) reduced HDL <1.03 mmol/L in men and <1.30 mmol/L in women; (4) elevated blood pressure: SBP ≥130 mmHg or DBP ≥85 mmHg or on antihypertensive drug treatment in a patient with a history of hypertension; and (5) elevated fasting glucose ≥5.6 mmol/L or on drug treatment for elevated glucose. A metabolic score was established as the total number of positive diagnostic criteria of metabolic syndrome in each participant [14].

2.5. Statistical Analysis. All statistical analyses were performed using SPSS (version 23.0; SPSS Inc., Chicago, IL). All values were examined for normal distribution prior to statistical analysis. Data are presented as the median (interquartile range [IQR]), mean ± standard deviation (SD), or n (%) if they are skewed, normally distributed, or categorical. Normally distributed or skewed variables were analyzed using the independent samples t-test or Mann–Whitney U test, respectively. Categorical variables were analyzed using the chi-square test or Fisher's exact test. The polynomial linear trend test was used to assess the linear trends across snoring intensity for metabolic score. Independent associations between snoring and MetS and its components were analyzed, using multivariable logistic regression after adjusting for relevant covariates. Odds ratios (ORs) are presented with 95% confidence intervals (CIs). In all analyses, $P < 0.05$ was taken to indicate statistical significance.

3. Results

3.1. Basic Characteristics. The 866 participants were divided according to snoring intensity into the simple snoring group ($n = 679$) and nonsnoring group ($n = 187$). The proportion of males was greater in the simple snoring group than in the nonsnoring group (63.0% vs. 41.7%, respectively, $P < 0.001$). Compared to the nonsnoring group, simple snorers were more obese (evidenced by higher BMI, NC, WC, HC, and WHR, $P < 0.001$), had higher fasting glucose levels, insulin levels, and HOMA-IR levels ($P < 0.001$), and showed more severe lipid abnormalities (i.e., hyper-TC, hyper-TG, hyper-LDL, hyper-apoB, and hypo-apoA-I, $P < 0.05$). Furthermore, simple snorers had a higher prevalence of MetS (18.0% vs. 9.1%, respectively, $P = 0.003$), and among simple snorers, the percent of participants scored from 0 to 5 was 24.9%, 33.6%, 23.6%, 12.7%, 4.1%, and 1.2%, respectively; among controls, the percent was 31%, 40.6%, 19.3%, 6.4%, 2.7%, and 0, respectively. Simple snorers were more likely to be current smokers and alcohol drinkers ($P < 0.001$) (Table 1).

Compared to female simple snorers, males snored louder (higher VAS score, $P < 0.001$), were more obese (evidenced by higher BMI, NC, WC, HC, and WHR, $P < 0.05$), had higher systolic and diastolic blood pressure ($P < 0.001$), and had more severe dyslipidemia (i.e., higher TG, LDL, and apoB and lower HDL, apoA-I, and apoE, $P < 0.05$). In addition, males were more likely to be current smokers and alcohol drinkers than females ($P < 0.001$) (Table 2).

Table 1: Basic characteristics of nonsnorer participants and simple snorers.

	Nonsnorers ($n = 187$)	Simple snorers ($n = 679$)	P value
Age (years)	42.00 (33.00, 49.00)	36.00 (30.00, 46.00)	0.002
Male (%)	78 (41.7%)	428 (63.0%)	<0.001
BMI (kg/m^2)	23.04 ± 3.11	24.15 ± 3.59	<0.001
NC (cm)	34.67 ± 3.29	36.80 ± 3.55	<0.001
WC (cm)	83.09 ± 10.09	86.99 ± 10.41	<0.001
HC (cm)	94.37 ± 7.07	97.10 ± 7.07	<0.001
WHR (cm)	0.88 ± 0.07	0.90 ± 0.07	0.011
SBP (mmHg)	119.19 ± 10.71	119.83 ± 14.39	0.573
DBP (mmHg)	76.55 ± 8.18	76.24 ± 9.72	0.687
FPG (mmol/L)	4.99 (4.62, 5.29)	5.05 (4.73, 5.37)	0.036
FINS (μU/mL)	5.52 (4.08, 8.48)	7.85 (5.65, 11.30)	<0.001
HOMA-IR	1.20 (0.88, 1.90)	1.77 (1.23, 2.57)	<0.001
TC (mmol/L)	4.22 (3.49, 4.82)	4.37 (3.80, 4.96)	0.001
TG (mmol/L)	0.90 (0.63, 1.32)	1.18 (0.78, 1.72)	<0.001
HDL (mmol/L)	1.14 (0.96, 1.34)	1.09 (0.96, 1.29)	0.237
LDL (mmol/L)	2.39 (1.81, 2.93)	2.39 (1.81, 2.93)	<0.001
apoA-I (g/L)	1.14 (0.98, 1.29)	1.09 (0.96, 1.23)	0.023
apoB (g/L)	0.68 (0.57, 0.78)	0.76 (0.65, 0.88)	<0.001
apoE (mg/dL)	3.92 (3.24, 4.71)	3.90 (3.20, 4.79)	0.748
Lpa (mg/dL)	6.40 (3.75, 14.75)	8.10 (4.40, 16.80)	0.051
MetS, n (%)	17 (9.1)	122 (18)	0.003
Smokers, n (%)	15 (8.0)	149 (21.9)	<0.001
Alcohol drinkers, n (%)	16 (8.6)	198 (29.2)	<0.001

BMI: body mass index; NC: neck circumference; WC: waist circumference; HC: hip circumference; WHR: waist-to-hip ratio; SBP: systolic blood pressure; DBP: diastolic blood pressure; FBG: fasting blood glucose; FINS: fasting insulin; HOMA-IR: homeostasis model assessment of insulin resistance; TC: total cholesterol; TG: triglyceride; HDL: high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol; apoA-I: apolipoprotein A-I; apoB: apolipoprotein B; apoE: apolipoprotein E; Lpa: lipoprotein(a); MetS: metabolic syndrome.

3.2. Prevalence of MetS. The prevalence rates of MetS and its components in our study are shown in Table 2. The prevalence rate of MetS was higher in simple snorers (18.0% vs. 9.1%, respectively, $P = 0.003$). Among its components, the prevalence rates of hypertension (29.3% vs. 18.7%, respectively, $P = 0.004$) and hyper-TG (25.9% vs. 12.8%, respectively, $P < 0.001$) were significantly higher in simple snorers than in nonsnorers.

Subgroup analysis showed that there were differences between simple snorers and the nonsnoring group in both male and female participants. Among male participants, simple snorers only had a higher prevalence rate of hypertension compared with nonsnorers (33.2% vs. 14.1%, $P = 0.001$). Among female participants, simple snorers had a higher prevalence rate of MetS (19.1% vs. 9.2%, $P = 0.018$) and higher prevalence rates of abdominal obesity (30.7% vs. 22.0%, $P = 0.005$) and hyper-TG (16.3% vs. 6.4%, $P = 0.011$) compared with nonsnorers (Table 3).

3.3. Association between Snoring and MetS. A significant linear trend was observed between snoring intensity and metabolic score (P for trend = 0.008) (Figure 2). Simple snoring was associated with MetS, even after adjusting for age, sex, smoking status, and alcohol consumption (OR = 2.328, 95% CI: 1.340–4.045). Gender stratification analysis showed that such association was only significant among female participants (OR = 2.382, 95% CI: 1.136–4.994) (Table 4).

Focusing on separate MetS components (Table 5), simple snoring was significantly associated with hypertension (OR = 1.730, 95% CI: 1.130–2.650) among all participants after adjusting for confounding factors, such as age, gender, smoking status, alcohol consumption, and other MetS components. However, the results of gender stratification analysis showed that this relationship was only obvious in men (OR = 3.493, 95% CI: 1.748–6.979).

Simple snoring was significantly associated with abdominal obesity (OR = 1.810, 95% CI: 1.063–3.083) after adjusting for confounding factors, and this relationship was only significant in women (OR = 2.306, 95% CI: 1.245–4.270). Simple snoring was also significantly associated with hyper-TG (OR = 1.814, 95% CI: 1.097–2.998), and gender stratification analysis showed that this relationship was only significant in women (OR = 2.803, 95% CI: 1.146–6.856) after multivariable adjustment.

The associations between simple snoring and hypo-HDL/hyperglycemia were not significant.

Table 2: Basic characteristics of participants according to gender.

	Nonsnorers			Simple snorers		
	Male ($n = 78$)	Female ($n = 109$)	P value	Male ($n = 428$)	Female ($n = 251$)	P value
Age (years)	38.31 ± 12.64	42.16 ± 10.43	0.029	36.84 ± 11.42	40.60 ± 12.39	<0.001
BMI (kg/m^2)	23.14 ± 3.08	22.96 ± 3.15	0.074	24.44 ± 3.22	23.66 ± 4.11	0.010
NC (cm)	37.14 ± 2.98	32.89 ± 2.18	<0.001	38.42 ± 2.73	34.04 ± 3.07	<0.001
WC (cm)	86.08 ± 11.37	80.95 ± 8.49	0.001	89.22 ± 9.27	83.18 ± 11.15	<0.001
HC (cm)	95.25 ± 7.25	93.74 ± 6.90	0.154	97.80 ± 6.68	95.89 ± 7.55	0.001
WHR (cm)	0.90 ± 0.08	0.86 ± 0.06	0.001	0.91 ± 0.06	0.87 ± 0.07	<0.001
SBP (mmHg)	118.15 ± 8.27	119.93 ± 12.14	0.237	121.78 ± 13.74	116.50 ± 14.89	<0.001
DBP (mmHg)	76.19 ± 8.23	76.81 ± 8.17	0.614	77.38 ± 9.57	74.28 ± 9.69	<0.001
FPG (mmol/L)	5.06 (4.55, 5.30)	4.97 (4.66, 5.26)	0.969	5.23 ± 0.88	5.12 ± 0.85	0.094
FINS (μU/mL)	5.07 (3.42, 7.74)	5.87 (4.47, 8.59)	0.085	9.25 ± 5.75	10.28 ± 16.57	0.341
HOMA-IR	1.13 (0.76, 1.63)	1.29 (0.94, 2.03)	0.173	2.24 ± 1.89	2.43 ± 4.30	0.517
TC (mmol/L)	4.08 (3.39, 4.71)	4.25 (3.63, 4.85)	0.266	4.45 ± 0.84	4.40 ± 0.96	0.450
TG (mmol/L)	0.94 (0.67, 1.56)	0.87 (0.62, 1.19)	0.013	1.57 ± 1.26	1.23 ± 0.94	<0.001
HDL (mmol/L)	1.05 (0.88, 1.21)	1.21 (1.03, 1.41)	<0.001	1.08 ± 0.26	1.24 ± 0.28	<0.001
LDL (mmol/L)	2.41 (1.77, 2.99)	2.37 (1.90, 2.86)	0.934	2.79 ± 0.73	2.64 ± 0.83	0.016
apoA-I (g/L)	1.06 (0.92, 1.20)	1.22 (1.03, 1.34)	<0.001	1.07 ± 0.19	1.19 ± 0.23	<0.001
apoB (g/L)	0.68 (0.56, 0.78)	0.67 (0.58, 0.78)	0.833	0.78 ± 0.16	0.73 ± 0.18	<0.001
apoE (mg/dL)	3.62 (3.02, 4.25)	4.07 (3.45, 4.75)	0.160	4.04 ± 1.33	4.32 ± 1.40	0.013
Lpa (mg/dL)	6.10 (3.85, 11.55)	7.40 (3.70, 18.10)	0.051	13.76 ± 15.54	14.54 ± 18.06	0.578
MetS, n (%)	7 (9%)	10 (9.2%)	0.963	74 (17.3%)	48 (19.1%)	0.548
Smoking, n (%)	15 (19.2%)	0	<0.001	143 (33.4%)	6 (2.4%)	<0.001
Alcohol drinkers, n (%)	15 (19.2%)	1 (0.9%)	<0.001	177 (41.4%)	21 (8.4%)	<0.001

BMI: body mass index; NC: neck circumference; WC: waist circumference; HC: hip circumference; WHR: waist-to-hip ratio; SBP: systolic blood pressure; DBP: diastolic blood pressure; FBG: fasting blood glucose; FINS: fasting insulin; HOMA-IR: homeostasis model assessment of insulin resistance; TC: total cholesterol; TG: triglyceride; HDL: high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol; apoA-I: apolipoprotein A-I; apoB: apolipoprotein B; apoE: apolipoprotein E; Lpa: lipoprotein(a); MetS: metabolic syndrome.

No significant interaction between sex and snoring on MetS was observed through joint classification analysis (P for interaction = 0.836) (Figure 3).

4. Discussion

The present study indicated that simple snoring was associated with higher prevalence of MetS, and there was a positive linear trend for metabolic score across snoring severity after adjusting for multiple variables. Furthermore, we found that simple snoring was independently associated with MetS and that female snorers were more vulnerable to metabolic disorders. No interaction was observed between sex and simple snoring on MetS.

Previous studies have demonstrated a relationship between snoring and MetS, but did not exclude the impact of repeated apnea and hypoxia [10, 11, 20]. A similar relationship was still found after excluding OSA patients from the whole sample. Furthermore, some studies showed that associations between snoring and MetS/MetS components only existed among females [7, 13, 21–24]. In the present study, although men showed more typical symptoms, such as snoring, than women, the metabolic effects of snoring were even greater in women. Furthermore, simple snoring was significantly associated with MetS in female snorers but not in male snorers. After controlling for confounding factors, the association with abdominal obesity/hyper-TG was more obvious among women. However, no significant interaction was observed between sex and snoring in our study. The mechanism involved in this gender difference may be as follows. Firstly, approximately 7% of premenopausal women have polycystic ovary syndrome, show hyperandrogenism, and have increased vulnerability to sleep disorders and metabolic disorders [7, 21]. Secondly, the levels of sex hormone secretion are reduced in postmenopausal women, with the most pronounced changes seen in estrogen reduction. The hormone levels change from estrogen predominance to androgen predominance, followed by increased incidence of snoring and metabolic disorders. Thirdly, compared with men, women tend to accumulate less visceral fat, but there are fewer α-adrenergic receptors in visceral adipose tissue in men indicating higher rates of lipolysis [25]. Finally, there

Table 3: Prevalence of MetS in nonsnorers and simple snorers.

		Nonsnorers	Simple snorers	*P* value
Total	MetS	17 (9.1%)	122 (18.0%)	0.003
	Hypertension	35 (18.7%)	199 (29.3%)	0.004
	Abdominal obesity	23 (12.3%)	113 (16.6%)	0.148
	Hyper-TG	24 (12.8%)	176 (25.9%)	<0.001
	Hypo-HDL	101 (54.0%)	362 (53.3%)	0.866
	Hyperglycemia	21 (11.2%)	108 (15.9%)	0.112
Males	MetS	7 (9.0%)	74 (17.3%)	0.065
	Hypertension	11 (14.1%)	142 (33.2%)	0.001
	Abdominal obesity	5 (6.4%)	36 (8.4%)	0.551
	Hyper-TG	17 (21.8%)	135 (31.5%)	0.084
	Hypo-HDL	37 (47.4%)	207 (48.4%)	0.880
	Hyperglycemia	8 (10.3%)	72 (16.8%)	0.144
Females	MetS	10 (9.2%)	48 (19.1%)	0.018
	Hypertension	15 (19.0%)	57 (22.7%)	0.885
	Abdominal obesity	24 (22.0%)	77 (30.7%)	0.005
	Hyper-TG	7 (6.4%)	41 (16.3%)	0.011
	Hypo-HDL	64 (58.7%)	155 (61.8%)	0.587
	Hyperglycemia	13 (11.9%)	36 (14.3%)	0.539

MetS: metabolic syndrome; TG: triglyceride; HDL: high-density lipoprotein cholesterol.

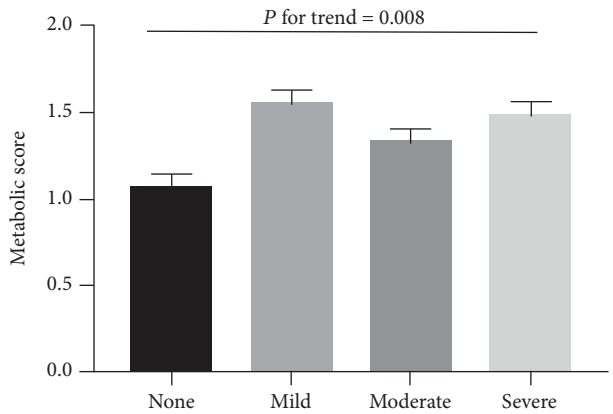

Figure 2: Adjusted mean metabolic scores across snoring severity. The data were adjusted for age, sex, smoking status, and alcohol consumption.

existed gene-by-sex interaction on hepatic steatosis and females could accumulate more hepatic TG than males genetically [26].

Obesity is considered a predisposing factor for severe snoring, whereas snoring may further promote the development of obesity [27]. Abdominal obesity is not only a component of MetS, but a promoting factor of other components of MetS, such as IR, resulting in more serious metabolic problems [28]. Thus, the relationships among snoring, obesity, and MetS are complex. Elmasry et al. [29] suggested that snoring and obesity lead to increased odds for diabetes, with obesity playing the leading role, whereas snoring further increases the odds for developing diabetes on the basis of obesity. Other studies [11, 29–31] have shown that snoring increases the odds for metabolic disturbances, but the effect of snoring may be significantly attenuated or even eliminated after adjusting for obesity-related indicators, such as BMI or WHR. Thus, obesity may play a leading role in the interaction between snoring and metabolic disorders by activating chronic inflammatory reactions, as well as adipokine disorders [11]. In this study, simple snorers were more obese, and simple snoring was significantly associated with abdominal obesity after adjustment, including for other MetS components.

The relationship between snoring and hypertension remains unclear. Lindberg et al. reported that snoring was an independent risk factor for hypertension in men younger than 50 years old, whereas snoring did not significantly affect hypertension in older adults [32]. Hu et al. reported that snorers had significantly higher systolic and diastolic blood pressure levels, and snoring was significantly associated with hypertension in women [23]. Bixler et al. reported that in both men and women, snoring was independently correlated with hypertension, which was more obvious in young and normal-weight participants [33]. Two related studies in the Korean population indicated that snoring significantly increased the prevalence of hypertension independent of obesity [20]. In contrast, Nieto et al. reported that AHI was significantly associated with hypertension, whereas the relationship between habitual snoring and hypertension was not obvious [34]. In the present study, simple snorers showed significantly higher prevalence rates of hypertension than nonsnorers, and simple snoring was an independent risk factor for hypertension, which was more obvious in men than in women. The main underlying mechanism may lie in estrogen, which could influence artery stiffness, inhibit vascular

Table 4: Odds ratios for MetS.

	Total		Males		Females	
	OR	95% CI	OR	95% CI	OR	95% CI
Unadjusted	2.190	(1.282–3.742)	2.120	(0.938–4.794)	2.341	(1.137–4.821)
Multivariable adjusted*	2.328	(1.340–4.045)	1.615	(0.931–4.936)	2.382	(1.136–4.994)

*Adjusted for age, sex, smoking status, and alcohol consumption.

Table 5: Odds ratios for MetS components.

		Total		Males		Females	
		OR	95% CI	OR	95% CI	OR	95% CI
Hypertension	Unadjusted	1.800	(1.203, 2.694)	3.024	(1.550, 5.902)	1.041	(0.606, 1.787)
	Multivariable adjusted*	1.730	(1.130, 2.650)	3.493	(1.748, 6.979)	0.899	(0.501, 1.613)
Abdominal obesity	Unadjusted	1.424	(0.880, 2.303)	1.341	(0.509, 3.531)	2.237	(1.262, 3.965)
	Multivariable adjusted*	1.810	(1.063, 3.083)	0.943	(0.335, 2.653)	2.306	(1.245, 4.270)
Hyper-TG	Unadjusted	2.376	(1.498, 3.771)	1.653	(0.930, 2.938)	2.845	(1.233, 6.562)
	Multivariable adjusted*	1.814	(1.097, 2.998)	1.443	(0.774, 2.690)	2.803	(1.146, 6.856)
Hypo-HDL	Unadjusted	0.972	(0.703, 1.345)	1.038	(0.640, 1.683)	1.135	(0.718, 1.796)
	Multivariable adjusted*	0.876	(0.615, 1.249)	0.808	(0.477, 1.368)	0.897	(0.551, 1.460)
Hyperglycemia	Unadjusted	1.495	(0.908, 2.461)	1.770	(0.816, 3.838)	1.236	(0.627, 2.437)
	Multivariable adjusted*	1.217	(0.709, 2.092)	1.696	(0.736, 3.911)	0.899	(0.425, 1.899)

*Adjusted for age, sex, smoking status, alcohol consumption, and other MetS components. TG: triglyceride; HDL: high-density lipoprotein cholesterol.

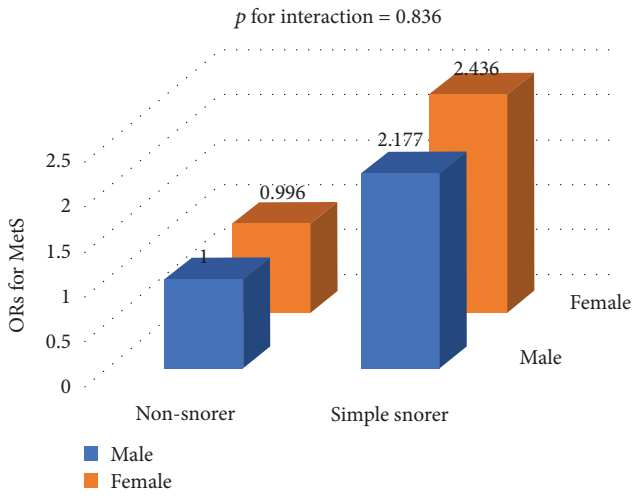

Figure 3: ORs for MetS according to gender and snoring status. ORs according to joint classification were adjusted for age, smoking status, and alcohol consumption.

remodel, and modulate the renin-angiotensin aldosterone system [35].

Previous studies have also drawn inconsistent conclusions regarding the relationship between snoring and IR. Some researchers reported that snoring was associated with diabetes and insulin sensitivity [29, 36], whereas other studies showed that although snoring was more common in men, it significantly increased the odds for diabetes or impaired glucose tolerance only in women [13, 21, 24]. A recent meta-analysis concluded that there was a strong association between snoring and diabetes in women, but not in men [7]. The association between simple snoring and hyperglycemia was not significant in our study, but simple snorers showed higher fasting glucose and insulin levels as well as a tendency for higher IR than nonsnorers.

There have been few previous studies on the relationship between snoring and dyslipidemia. Shin et al. reported that as snoring frequency increased, TG levels increased and HDL levels decreased and that snoring was associated with hyper-TG and hypo-HDL, but the effect of snoring was significantly attenuated after adjusting for other confounding factors. Cho et al. reported that snorers had higher prevalence rates of hyper-TG and hypo-HDL, but snoring did not increase the odds for dyslipidemia after taking various confounding factors into consideration [20]. In our study, simple snorers had higher levels of TC, TG, LDL, and apoB, lower apoA-I levels, and higher prevalence of hyper-TG than nonsnorers. Furthermore, the components of dyslipidemia may differ between genders, e.g., males showed higher TG, LDL, and apoB and lower HDL, apoA-I, and apoE than females. However, after multivariable adjustment, simple snoring was significantly associated with increased odds for hyper-TG only among females.

The mechanisms underlying the relationship between simple snoring and MetS have not been clarified. Through direct mechanical injury to the endothelium and local initiation of proinflammatory response, snoring vibration transmission may accelerate the development of carotid atherosclerotic plaque and contribute to MetS [37–40]. The physiological disturbances caused by snoring increase the

number of microarousals during sleep [22], which could disrupt the restorative value of sleep, increase the activity of the sympathetic nervous system, and have a harmful impact on the hypothalamic-pituitary-adrenal axis with consequent elevations in serum cortisol, ultimately contributing to metabolic dysfunction [13, 41–45].

To our knowledge, this is the first study to investigate the associations between MetS/MetS components and simple snoring excluding the impact of OSA. Our study showed that snoring without repeated apnea and hypoxia was significantly associated with increased odds for MetS, which requires more attention regarding hypertension among male snorers and abdominal obesity and hyper-TG among female snorers. Our study also had some limitations. First, although self-reported snoring and snoring reported by roommates were found to be reliable measures in epidemiological studies, as validated by all-night sleep recording [46, 47], these are subjective measures to evaluate snoring. Second, as the duration of snoring was not collected, its impact on MetS could not be assessed.

In conclusion, the present study investigated the relationships between simple snoring and MetS/MetS components and concluded that, after eliminating the effects of repeated apnea and hypoxia, simple snoring was still independently associated with increased odds for MetS, especially in women. Furthermore, it suggested that clinicians should implement interventions, such as suggesting low-fat diet, low-sugar diet, and increased exercise for simple snorers to prevent MetS.

Data Availability

The clinical data used to support the findings of this study are available from the corresponding authors upon request.

Conflicts of Interest

None of the authors has potential conflict of interests related to the content of the manuscript.

Authors' Contributions

Juanjuan Zou and Yiqun Fu designed the research. Fan Song, Yunyan Xia, and Huajun Xu conducted the research. Juanjuan Zou, Yingjun Qian, and Jianyin Zou analyzed the data. Juanjuan Zou wrote the first draft. Jian Guan, Bin Chen, and Shankai Yin made critical manuscript revisions. All authors read and approved the final manuscript. Juanjuan Zou and Fan Song contributed equally to this work.

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Research Article

Effect of the Interaction between Obstructive Sleep Apnea and Lipoprotein(a) on Insulin Resistance: A Large-Scale Cross-Sectional Study

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Both obstructive sleep apnea (OSA) and decreased serum lipoprotein(a) (Lp(a)) concentrations are associated with insulin resistance. However, their interaction effect on insulin resistance has never been investigated. Therefore, we performed a cross-sectional study on OSA-suspected Chinese Han participants. Laboratory-based polysomnographic variables, biochemical indicators, anthropometric measurements, and medical history were collected. Linear regression and binary logistic regression analyses with interaction terms were used to investigate the potential effects of the interaction between the severity of OSA (assessed by the apnea-hypopnea index (AHI)) and Lp(a) concentrations on insulin resistance (assessed by the homeostasis model assessment of insulin resistance (HOMA-IR)), after adjusting for potential confounders including age, gender, body mass index, waist-to-hip circumference ratio, mean arterial pressure, smoking status, drinking status, and lipid profiles. A total of 4,152 participants were enrolled. In the OSA-suspected population, AHI positively correlated with insulin resistance and serum Lp(a) concentrations independently and inversely correlated with insulin resistance. In addition, the interaction analysis showed that the linear association between lgAHI and lgHOMA-IR was much steeper and more significant in subjects with relatively low Lp(a) concentrations, suggesting a significant positive interaction between lgLp(a) and lgAHI on lgHOMA-IR ($P = 0.013$). Furthermore, the interaction on a multiplicative scale also demonstrated a significant positive interaction ($P = 0.044$). A stronger association between AHI quartiles and the presence of insulin resistance (defined as HOMA-IR > 3) could be observed for participants within lower Lp(a) quartiles. In conclusion, a significant positive interaction was observed between OSA and decreased Lp(a) with respect to insulin resistance. This association might be relevant to the assessment of metabolic or cardiovascular disease risk in OSA patients.

1. Introduction

Obstructive sleep apnea (OSA) is the most common form of sleep-disordered breathing and is characterized by recurrent episodes of complete or partial upper airway obstruction during sleep [1]. These obstructive events lead to multiple adverse physiological changes, including intermittent hypoxia, sleep fragmentation, inflammation, oxidative stress, and increased sympathetic tone. Together, these changes could predispose OSA patients to a higher risk of insulin resistance [2–5], a pathological condition which plays important roles in the pathogenesis of various metabolic and cardiovascular diseases (CVD), including metabolic syndrome, type 2 diabetes, hypertension, atherosclerosis, and stroke [6–8].

Low serum lipoprotein(a) (Lp(a)) concentration is recognized as another risk factor for insulin resistance [9–14]. Lp(a) is a highly atherogenic lipoprotein composed of a low-density lipoprotein- (LDL-) like particle covalently bound to apo(a) [15]. Its serum concentrations have a more than 1,000-fold interindividual range and are primarily genetically determined by the LPA gene without other major anthropometric, dietary, or environmental influences [15–19]. Recently, observational studies demonstrated that decreased Lp(a) is associated with a higher risk of insulin resistance in several populations including diabetic, nondiabetic, hypertensive, and dyslipidemic patients, indicating that low Lp(a) levels may be associated with the development of insulin resistance [9–14, 20].

However, to our knowledge, no prior studies have investigated whether Lp(a) is related to insulin resistance in individuals with suspected OSA. In addition, it is also unknown whether there is any interaction between Lp(a) and OSA with respect to the severity of insulin resistance. These questions are of potential clinical importance as they are relevant to the assessments of metabolic and cardiovascular disease risk in OSA patients. For instance, because Lp(a) is highly atherogenic, it has been recommended that its concentrations should be lowered in individuals with a high risk of CVD [21–23]. However, this treatment may lead to an excessive risk of insulin resistance and subsequent adverse metabolic or cardiovascular consequences in OSA patients [24–26].

Therefore, we set up a cross-sectional study of 5,479 OSA-suspected participants with the aims to (1) investigate the relationships between Lp(a) and insulin resistance in an OSA-suspected population and (2) test for an interaction effect of Lp(a) and OSA on insulin resistance.

2. Methods

2.1. Study Population. Participants were enrolled from the Shanghai Sleep Health Study cohort, which included a total of 5,479 unrelated consecutive suspected OSA subjects who were referred to the Sleep Center of the Affiliated Sixth People's Hospital, Shanghai Jiao Tong University, from January 2007 to June 2017. Participants were mainly residents of cities in southern China, and all were Han Chinese. Informed consent was obtained in writing from each participant according to the guidance of the National Ethics Regulation Committee of China. This study was approved by the Institutional Ethics Committee of the Sixth Affiliated Hospital of Shanghai Jiao Tong University.

The exclusion criteria were as follows: (1) age less than 18 years; (2) history of OSA diagnosis or treatment; (3) use of lipid-lowering drugs; (4) use of insulin or oral hypoglycemic agents; (5) systemic steroid treatment or hormone-replacement therapy; (6) severe comorbid diseases, such as congestive heart failure, psychiatric disturbances, chronic liver disease, or chronic kidney disease; (7) acute inflammation; (8) recorded total sleep time < 4 h; (9) sleep disorders other than OSA, such as central sleep apnea or narcolepsy; and (10) unavailable clinical data. Finally, 1,327 met the exclusion criteria and were excluded from the study.

2.2. Medical History and Physical Measurements. Before overnight polysomnography (PSG), all participants were asked to complete a uniform questionnaire regarding medical histories, smoking status, and drinking status. Current smoking or drinking was defined as regular consumption of cigarettes or alcohol in the past six months [27]. Height and weight were measured using standard anthropometric methods, with the participants dressed in lightweight clothing and with bare feet. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Blood pressure was measured with participants in a seated position after a 5 min rest and recorded as the average value of three sequential measurements at 1 min intervals. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded. Mean arterial pressure (MAP) was calculated as $(SBP + 2 * DBP)/3$.

2.3. Overnight Polysomnography Parameters. Overnight PSG was conducted in the sleep center of the Shanghai Jiao Tong University Affiliated Sixth People's Hospital with an Alice 4 system (Philips Respironics Inc., Pittsburgh, PA, USA). Data recorded included electroencephalography, electrooculography, submental electromyogram, oronasal airflow (nasal pressure and thermistor), chest and abdominal movements, electrocardiogram, peripheral SpO_2, and body positions. All recordings were analyzed manually according to standard criteria by the same skilled technician [28]. Apnea was defined as the complete cessation of airflow lasting ≥10 s. Hypopnea was defined as either a decrease of airflow ≥ 50% for a duration of ≥10 s or a decrease of airflow $< 50\%$ but accompanied by a decrease in $SaO_2 \geq 4\%$ or an arousal. The apnea-hypopnea index (AHI) was defined as the total number of apneas and hypopneas per hour during sleep. OSA was diagnosed as AHI ≥ 5 events per hour.

2.4. Biochemical Indicators. For each participant, a fasting blood sample was drawn from the antecubital vein in the morning after polysomnographic monitoring. Blood samples were assayed by laboratory staff in our hospital unaware of participants' disease status. Serum Lp(a) concentrations were measured using a high-sensitivity immunoturbidimetric assay which was able to detect Lp(a) concentrations from 0 to 100 mg/dL. Blood samples with Lp(a) > 100 mg/dL were routinely diluted 1 : 10. The other biochemical indicators (fasting insulin and fasting blood glucose) and lipid profiles (total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein A-I (ApoA-I), and apolipoprotein B (ApoB)) were quantified according to manufacturer specifications using a Hitachi H-7600 analyzer.

The severity of insulin resistance was quantified by calculating the homeostasis model assessment of insulin resistance (HOMA-IR, calculated as the product of fasting glucose (mmol/L) and fasting insulin (mU/L) divided by 22.5). Insulin resistance was defined as HOMA-IR > 3.0 [29]. HOMA-IR correlates well with the hyperinsulinemia euglycemic clamp (the gold standard measure of insulin resistance), thus enabling accurate identification of individuals with insulin resistance [30].

Table 1: Characteristics of participants by AHI quartiles.

Events/h	Quartile 1 AHI ≤ 7	Quartile 2 7 < AHI ≤ 28	Quartile 3 28 < AHI ≤ 57	Quartile 4 AHI > 57	*P* for trend
N	1,053	1,031	1,017	1,051	—
Age (years)	37.0 (30.0, 47.0)	42.0 (33.0, 53.0)	44.0 (35.0, 55.0)	40.0 (33.0, 49.0)	<0.001
Male (%)	638 (60.6%)	812 (78.8%)	896 (88.1%)	959 (91.2%)	<0.001
BMI (kg/m^2)	23.8 (21.8, 25.9)	25.7 (23.7, 27.7)	26.6 (24.9, 28.7)	28.6 (26.5, 31.0)	<0.001
Waist-to-hip ratio	0.90 (0.85, 0.94)	0.94 (0.90, 0.97)	0.95 (0.92, 0.99)	0.97 (0.94, 1.00)	<0.001
SBP (mmHg)	120 (111, 125)	120 (114, 130)	125 (118, 135)	126 (120, 137)	<0.001
DBP (mmHg)	78 (70, 85)	80 (70, 85)	80 (74, 87)	80 (77, 90)	<0.001
MAP (mmHg)	91.7 (84.3, 95.0)	93.3 (86.3, 99.3)	94.3 (89.0, 102.3)	96.7 (91.0, 104.7)	<0.001
AHI (events/h)	2.2 (0.8, 4.2)	16.2 (11.0, 21.5)	42.5 (34.8, 49.7)	70.3 (63.7, 79.1)	<0.001
Lp(a) (mg/dL)	7.83 (4.10, 16.80)	7.40 (3.90, 14.26)	7.90 (4.18, 16.20)	6.50 (3.46, 13.10)	<0.001
FBG (mmol/L)	5.03 (4.69, 5.33)	5.16 (4.84, 5.55)	5.31 (4.96, 5.79)	5.48 (5.10, 6.10)	<0.001
FSI (IU/mL)	7.5 (5.2, 6.1)	9.8 (6.6, 14.4)	11.0 (7.4, 16.2)	14.6 (10.1, 20.4)	<0.001
HOMA-IR	1.63 (1.11, 2.48)	2.27 (1.40, 3.38)	2.62 (1.75, 4.10)	3.63 (2.44, 5.35)	<0.001
Insulin resistance (%)	169 (16.0%)	334 (32.4%)	424 (41.7%)	668 (63.6%)	<0.001
TC (mmol/L)	4.35 (3.76, 4.95)	4.60 (4.05, 5.22)	4.77 (4.20, 5.34)	4.85 (4.29, 5.48)	<0.001
TG (mmol/L)	1.13 (0.76, 1.61)	1.50 (1.05, 2.16)	1.62 (1.15, 2.30)	1.83 (1.34, 2.71)	<0.001
LDL-C (mmol/L)	2.66 (2.14, 3.20)	2.92 (2.43, 3.42)	3.00 (2.50, 3.51)	3.12 (2.59, 3.68)	<0.001
HDL-C (mmol/L)	1.10 (0.96, 1.30)	1.04 (0.91, 1.20)	1.02 (0.90, 1.17)	1.00 (0.87, 1.13)	<0.001
ApoA-I (g/L)	1.10 (0.97, 1.24)	1.06 (0.95, 1.21)	1.07 (0.96, 1.20)	1.06 (0.96, 1.19)	<0.001
ApoB (g/L)	0.74 (0.63, 0.86)	0.81 (0.71, 0.94)	0.84 (0.74, 0.96)	0.87 (0.76, 0.99)	<0.001
Current smoker (%)	135 (12.8%)	203 (19.7%)	237 (23.3%)	239 (22.7%)	<0.001
Current drinker (%)	106 (10.1%)	127 (12.3%)	153 (15.0%)	166 (15.8%)	<0.001

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; AHI: apnea-hypopnea index; FBG: fast blood glucose; FSI: fast serum insulin; HOMA-IR: homeostasis model assessment of insulin resistance; TC: total cholesterol; TG: total triglyceride; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol. Insulin resistance: HOMA-IR > 3.0.

2.5. Statistical Analysis. Descriptive variables were expressed as means ± SD, medians (interquartile ranges), or percentages, as appropriate. Baseline characteristics were compared among the Lp(a) quartiles or AHI quartiles using the Kruskal-Wallis *H* test, one-way analysis of variance (ANOVA), or the chi-squared test according to the distribution characteristics of the data. Variables with nonnormal distributions were log-transformed before analysis. The polynomial linear trend test was used to assess linear trends across Lp(a) quartiles or AHI quartiles for continuous variables, and the linear-by-linear association test was used for dichotomous variables. Simple and multiple linear regression analyses were used to investigate the association of AHI, serum Lp(a) concentration, and HOMA-IR. Binary logistic regression analyses were used to determine the odds ratios (ORs) and 95% confidence intervals (95% CIs) of the presence of insulin resistance across Lp(a) quartiles and AHI quartiles, using the top quartile of Lp(a) or the bottom quartile of AHI as the reference. All continuous variables were examined for linearity before logistic regression. Furthermore, the effect of the interaction between Lp(a) and AHI (as continuous variables) on HOMA-IR was assessed with linear regression analysis by adding an interaction term to the regression model. The multiplicative interaction between quartiles of Lp(a) and AHI with respect to insulin resistance was assessed with logistic regression analysis. Statistical analyses were performed using SPSS v.24.0.0 (IBM Corp., Armonk, NY, USA) and R software package 3.4.1 (http://www.r-project.org/). All *P* values given are two-sided, with the significance level set to 0.05.

3. Results

3.1. Basic Characteristics of Participants. Among the 4,152 included participants, 79.0% were found to have OSA and 21.0% were not, 79.6% were men and 20.4% were women, the median age was 41.0 years, the median Lp(a) concentration was 7.40 mg/dL, and the median AHI was 27.9 events/h. There were 1,595 participants with insulin resistance, and the prevalence rate was 38.4%.

3.2. Relationship between AHI and Insulin Resistance in an OSA-Suspected Population. The general characteristics of all participants categorized by AHI quartiles is shown in Table 1. Participants in the lowest to highest quartiles of AHI had a median AHI of 2.2, 16.2, 42.5, and 70.3 events/h, respectively. After multiple adjustments, lgAHI was independently and positively associated with lgHOMA-IR (Table 2; $\beta = 0.070$, $P < 0.001$). The adjusted odds ratios for insulin

Table 2: The association between lgAHI and lgLp(a) with insulin resistance-related traits.

Dependent	Independent lgAHI				Independent lgLp(a)			
	B	SE (β)	Beta	*P*	*B*	SE (β)	Beta	*P*
Unadjusted								
lgHOMA-IR	0.188	0.007	0.402	<0.001	−0.067	0.011	−0.098	<0.001
lgFBG	0.033	0.002	0.276	<0.001	−0.010	0.003	−0.060	<0.001
lgFSI	0.156	0.006	0.371	<0.001	−0.058	0.009	−0.094	<0.001
Adjusted								
lgHOMA-IR	0.070	0.007	0.150	<0.001	−0.034	0.009	−0.050	<0.001
lgFBG	0.012	0.002	0.103	<0.001	−0.007	0.003	−0.044	0.004
lgFSI	0.058	0.006	0.139	<0.001	−0.026	0.008	−0.044	<0.001

Values were calculated with unadjusted and multivariable-adjusted linear regression analyses. Adjusted variables include Lp(a) or AHI, age, gender, BMI, waist-to-hip circumference ratio, MAP, current smoking status, current drinking status, TC, TG, HDL-C, LDL-C, ApoA-I, and ApoB.

Table 3: The odds ratios for the presence of insulin resistance across AHI or Lp(a) quartiles.

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P* for linear trend
AHI quartiles					
n (cases/participants)	169/1,053	334/1,031	424/1,017	668/1,051	—
Unadjusted	1	2.51 (2.03, 3.10)	3.74 (3.05, 4.61)	9.12 (7.43, 11.25)	<0.001
Adjusted	1	1.61 (1.27, 2.05)	1.92 (1.50, 2.46)	2.87 (2.23, 3.70)	<0.001
Lp(a) quartiles					
n (cases/participants)	456/1,026	427/1,062	371/1,032	341/1,032	—
Unadjusted	1.62 (1.36, 1.94)	1.35 (1.14, 1.63)	1.14 (0.95, 1.36)	1	<0.001
Adjusted	1.40 (1.12, 1.74)	1.21 (0.98, 1.50)	1.16 (0.93, 1.43)	1	0.029

Odds ratios, 95% confidence intervals, and *P* values were calculated using logistic regression analyses. Insulin resistance was defined as the HOMA-IR index > 3. AHI quartiles 1-4 correspond to the AHI range of ≤7, 7.1-28, 28.1-57, and >57 events/h, respectively. Lp(a) quartiles 1-4 correspond to the serum Lp(a) concentration range of ≤3.90, 3.91-7.40, 7.41-15.10, and >15.10 mg/dL, respectively. Adjusted variables include Lp(a) or AHI quartiles, age, gender, BMI, waist-to-hip circumference ratio, MAP, current smoking status, current drinking status, TC, TG, HDL-C, LDL-C, ApoA-I, and ApoB.

resistance across AHI quartiles 2–4 were 1.61, 1.92, and 2.87, respectively, as compared to the lowest AHI quartile (Table 3; *P* for linear trend < 0.001), indicating an independent, positive relationship between OSA severity and insulin resistance.

3.3. Relationship between Lp(a) and Insulin Resistance in an OSA-Suspected Population. The general characteristics of participants according to the quartiles of serum Lp(a) concentrations are summarized in Table 4, and the *P* value for each relationship was calculated using each quartile of serum Lp(a) concentrations taken as a unit. Participants in the lowest to highest quartiles of Lp(a) had median serum Lp(a) concentrations of 2.50, 5.50, 10.40, and 25.10 mg/dL, respectively. Across the four quartiles, a significant increasing trend was found regarding age and fasting serum concentrations of TC, LDL-C, HDL-C, and ApoB (Table 4). Meanwhile, a significant decreasing trend was found regarding the percentage of male participants; AHI; BMI; fasting serum concentrations of glucose, insulin, and TG; HOMA-IR; and the percentage of participants with insulin resistance (Table 4). As shown, from the lowest Lp(a) quartile to the highest, a decreasing trend in HOMA-IR (from 2.74 to 2.22, *P* for linear trend < 0.001) and the presence of insulin resistance (44.4% to 33.0%, *P* for linear trend < 0.001) was observed.

Linear regression analysis demonstrated that lgLp(a) significantly and inversely correlated with lgHOMA-IR, both in the unadjusted model (Table 2, $\beta = -0.067$, $P < 0.001$) and the multivariable-adjusted model incorporating potential confounders including AHI, age, gender, BMI, waist-to-hip circumference ratio, MAP, current smoking status, current drinking status, and lipid profiles (Table 2, $\beta = -0.034$, $P < 0.001$). In addition, lgLp(a) was also inversely and independently correlated with lgFBG (fasting blood glucose; $\beta = -0.007$, $P = 0.004$) and lgFSI (fasting serum insulin; $\beta = -0.026$, $P < 0.001$) after adjustment.

With the highest quartile of Lp(a) as the reference group, univariate logistic regression showed significantly increased odds ratios for the presence of insulin resistance from Lp(a) quartile 4 to quartile 1 (Table 3, *P* for linear trend < 0.001). After further adjustment for confounding factors, the trend remained significant (*P* for linear trend = 0.029), with odds ratios of 1.16 (95% CI: 0.93–1.43) for Lp(a) quartile 3, 1.21 (95% CI: 0.98–1.50) for Lp(a) quartile 2, and 1.40 (95% CI: 1.12–1.74) for Lp(a) quartile 1, suggesting an inverse relationship between the Lp(a) level and insulin resistance in this OSA-suspected population.

Table 4: Characteristics of participants by Lp(a) quartiles.

mg/dL	Quartile 1 Lp(a) ≤ 3.90	Quartile 2 3.90 < Lp(a) ≤ 7.40	Quartile 3 7.41 < Lp(a) ≤ 15.10	Quartile 4 Lp(a) > 15.10	P for trend
N	1,026	1,062	1,032	1,032	—
Age (years)	39.0 (32.0, 49.0)	40.0 (33.0, 51.0)	42.0 (33.0, 53.0)	42.0 (34.0, 53.0)	<0.001
Male (%)	842 (82.1%)	854 (80.4%)	819 (79.4%)	790 (76.6%)	0.002
BMI (kg/m^2)	26.5 (24.1, 29.4)	26.4 (23.9, 29.1)	26.2 (24.0, 28.4)	25.7 (23.8, 28.4)	<0.001
Waist-to-hip ratio	0.95 (0.90, 0.98)	0.94 (0.90, 0.98)	0.94 (0.90, 0.98)	0.94 (0.90, 0.98)	0.045
SBP (mmHg)	123 (117, 134)	120 (115, 130)	122 (116, 132)	120 (115, 131)	0.061
DBP (mmHg)	80 (73, 86)	80 (72, 85)	80 (73, 86)	80 (71, 85)	0.043
MAP (mmHg)	93.3 (88.0, 101.7)	93.3 (87.7, 99.8)	93.3 (88.0, 101.3)	93.3 (86.7, 100.0)	0.041
AHI (events/h)	31.3 (8.4, 62.2)	28.4 (7.3, 58.6)	26.6 (7.3, 55.9)	26.3 (5.9, 53.1)	<0.001
Lp(a) (mg/dL)	2.50 (1.70, 3.20)	5.50 (4.60, 6.40)	10.40 (8.80, 12.40)	25.10 (19.50, 36.78)	<0.001
FBG (mmol/L)	5.28 (4.90, 5.73)	5.24 (4.90, 5.72)	5.22 (4.88, 5.68)	5.18 (4.87, 5.62)	<0.001
FSI (IU/mL)	11.2 (7.4, 17.2)	10.7 (7.0, 16.1)	10.0 (6.7, 15.3)	9.7 (6.6, 14.6)	<0.001
HOMA-IR	2.74 (1.65, 4.25)	2.53 (1.58, 3.91)	2.34 (1.50, 3.80)	2.22 (1.49, 3.50)	<0.001
Insulin resistance (%)	456 (44.4%)	427 (40.2%)	371 (35.9%)	341 (33.0%)	<0.001
TC (mmol/L)	4.54 (3.98, 5.18)	4.57 (4.00, 5.22)	4.66 (4.08, 5.29)	4.79 (4.22, 5.34)	<0.001
TG (mmol/L)	1.68 (1.09, 2.48)	1.57 (1.05, 2.29)	1.45 (1.04, 2.00)	1.41 (1.01, 2.01)	<0.001
LDL-C (mmol/L)	2.79 (2.27, 3.35)	2.88 (2.36, 3.40)	2.97 (2.47, 3.51)	3.06 (2.59, 3.56)	<0.001
HDL-C (mmol/L)	1.03 (0.89, 1.18)	1.02 (0.90, 1.18)	1.04 (0.91, 1.20)	1.06 (0.93, 1.23)	0.002
ApoA-I (g/L)	1.07 (0.95, 1.21)	1.07 (0.96, 1.20)	1.07 (0.96, 1.21)	1.09 (0.97, 1.23)	0.415
ApoB (g/L)	0.79 (0.68, 0.93)	0.81 ± 0.18	0.83 (0.72, 0.95)	0.85 (0.75, 0.98)	<0.001
Current smoking (%)	205 (20.2%)	205 (19.3%)	228 (22.1%)	176 (17.1%)	0.280
Current drinking (%)	129 (12.6%)	147 (13.8%)	148 (14.3%)	128 (12.4%)	0.993

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; AHI: apnea-hypopnea index; FBG: fast blood glucose; FSI: fast serum insulin; HOMA-IR: homeostasis model assessment of insulin resistance; TC: total cholesterol; TG: total triglyceride; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol. Insulin resistance: HOMA-IR > 3.0.

3.4. Interaction between OSA and Lp(a) with regard to Insulin Resistance. As both increased AHI and decreased Lp(a) were correlated with a higher degree of insulin resistance, we next aimed to investigate whether there is a potential interaction effect of these two factors on insulin resistance. As shown in Figure 1, as Lp(a) concentrations decline (from the 90th to the 10th percentile), a steeper and more significant positive linear relationship between lgAHI and lgHOMA-IR is observed, suggesting a significant positive interaction between lgLp(a) and lgAHI on the lgHOMA-IR level (P interaction = 0.013, after multivariable adjustment including age, gender, BMI, waist-to-hip circumference ratio, MAP, current smoking status, current drinking status, and lipid profiles).

With multivariable-adjusted logistic regression analysis, we also found a significant positive interaction on a multiplicative scale between quartiles of Lp(a) and AHI with respect to the presence of insulin resistance (Figure 2, P interaction = 0.044). More significant trends in the relationship between AHI quartiles and the presence of insulin resistance were observed in subjects within lower Lp(a) quartiles (ORs of insulin resistance across AHI quartiles within Lp(a) quartile 4 were 1.00, 1.53, 1.92, and 2.36; those within Lp(a) quartile 3 were 1.47, 1.85, 1.87, and 2.72; those within Lp(a) quartile 2 were 0.86, 1.82, 2.12, and 3.88; and those within Lp(a) quartile 1 were 1.12, 1.96, 2.71, and 4.01).

4. Discussion

With this large-scale cross-sectional study, we first found an independent and inverse relationship between serum Lp(a) levels and the severity of insulin resistance as assessed by HOMA-IR in a population with suspected OSA, after adjustment for multiple potential confounders (Tables 2 and 3). Furthermore, the data revealed that as Lp(a) concentrations decline, the relationship between AHI and insulin resistance is steeper and more significant, suggesting a significant positive interaction between Lp(a) and AHI with respect to insulin resistance (Figures 1 and 2).

Lp(a) is a complex lipoprotein composed of an LDL-like particle covalently bound to apo(a) [15]. Its serum concentrations, which have a more than 1,000-fold interindividual range, are primarily genetically determined by the LPA gene and are thought to remain stable throughout the lifetime without other major influences [15–19]. The exact physiological function of Lp(a) is complex and diverse. First, it is demonstrated to be highly atherogenic; epidemiological and genetic evidence strongly indicates

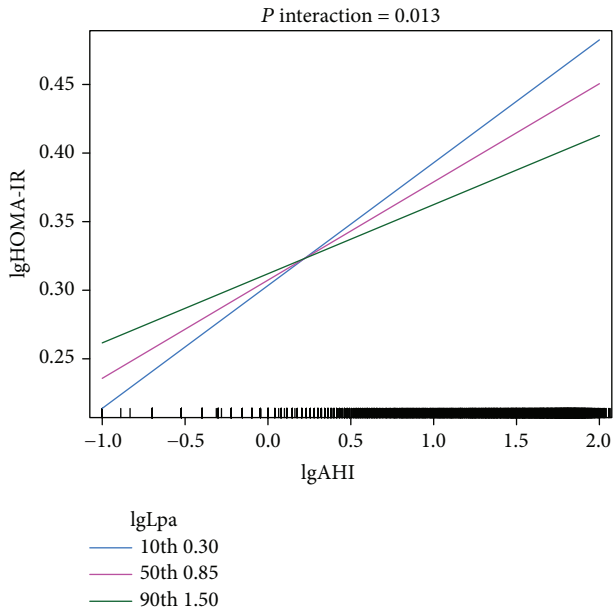

Figure 1: Interaction between lgAHI and lgLp(a) on the relationship with lgHOMA-IR. As depicted, the relationship between lgAHI and lgHOMA-IR is modulated by the level of lgLp(a). With lgLp(a) declining (from the 90th to 10th percentile), a more steep and significant positive linear relationship between lgAHI and lgHOMA-IR could be observed, suggesting significant positive interaction. The *P* value was calculated with multivariable linear regression analyses adjusted for age, gender, BMI, waist-to-hip circumference ratio, MAP, current smoking status, current drinking status, TC, TG, HDL-C, LDL-C, ApoA-I, and ApoB.

that elevated Lp(a) is a strong causal risk factor for CVD [21–23]. However, more recent observational studies have demonstrated that decreased Lp(a) is associated with a higher risk of insulin resistance in diabetic, nondiabetic, hypertensive, and dyslipidemic populations. In line with previous studies [9–14, 20], our results demonstrated that Lp(a) was independently and negatively associated with the degree of insulin resistance in an OSA-suspected population.

The mechanism of this inverse association is still unclear. Kamstrup and Nordestgaard suggested that the large Lp(a) isoform size, which is exhibited in subjects with low Lp(a) levels, may elevate the activity of lipoprotein-associated phospholipase A2 (Lp-PLA2) [20], which stimulates the production of inflammatory cytokines in adipose tissue and leads to insulin resistance [31]. This implies that, in addition to the direct atherogenic role of elevated Lp(a), decreased Lp(a) might in turn contribute to metabolic and cardiovascular risk through insulin resistance [6–8, 26]. However, a "reverse causation" could not be excluded, as several studies have shown that insulin may have a direct effect on serum Lp(a) levels. Haffner et al. found that in patients with type 1 diabetes, insulin therapy was associated with a significant reduction in Lp(a) levels [32]. Additionally, Neele et al. found that a high level of insulin decreased the synthesis of apo(a), a component of Lp(a) [33]. Conversely, a string of studies conducted in patients with type 2 diabetes opposed a direct effect of insulin on Lp(a) levels because no significant decline in Lp(a) was observed after oral hypoglycemic treatment, despite significant improvement in glucometabolism traits [34–36]. In summary, further studies are needed to clarify the underlying pathophysiological mechanism of the inverse relationship between Lp(a) and insulin resistance, as it may point to new targets for the prevention and treatment of insulin resistance and subsequent metabolic and cardiovascular diseases.

Furthermore, in the present study, we observed a significant positive interaction between increased AHI and decreased Lp(a) with respect to the severity of insulin resistance. As Lp(a) concentrations declined, a steeper and more significant positive relationship between AHI and insulin resistance was observed (Figures 1 and 2). This suggests that decreased Lp(a) concentrations, which are primarily genetically determined and remain stable over an individual's lifetime [15, 16], may biologically enhance the adverse pathophysiological effects of OSA on insulin resistance. Our finding is of clinical importance, as it may be relevant to the assessment of metabolic or cardiovascular disease risk in patients with OSA. For example, it has been recommended that Lp(a) concentrations should be lowered in individuals with a high risk of CVD; however, any treatment that lowers Lp(a) levels to reduce CVD risk may lead to an increased risk of insulin resistance and subsequent adverse metabolic and cardiovascular consequences in patients with untreated OSA [24–26]. Therefore, we suggest that to fully evaluate the risk of metabolic and cardiovascular diseases, the effect of the interaction between Lp(a) and OSA on insulin resistance must be appropriately considered. Besides, extra caution should be applied in interpreting our results, because multivariable linear and logistic analyses both showed that the positive relationship between AHI and HOMA-IR was independent of Lp(a) levels. Therefore, interaction between Lp(a) and AHI observed in this study may potentially benefit risk stratification in patients with suspected OSA; however, it should not influence treatment decision-making.

To the best of our knowledge, this is the first study to assess the association of Lp(a) concentrations and insulin resistance in an OSA-suspected population, as well as to explore the interaction of Lp(a) and AHI on the severity of insulin resistance. Our study has several strengths, including the large sample size, standard PSG recording, and fully adjusted models evaluating interaction effects, which increase the quality of our evidence. Meanwhile, some limitations must be stated. First, because of the cross-sectional study design, causality between AHI, Lp(a), and insulin resistance cannot be inferred. Second, Lp(a) kringle, renal function, inflammation, physical activity, daily alcohol consumption dose, and diet are factors shown to influence both Lp(a) levels and insulin resistance [37–40]. Regretfully, our study was not specifically designed to cover these potential confounders, so their effects could not be accounted for in the analysis. Third, cardiovascular damage or outcomes were not measured. Trials incorporating these outcomes are needed in the future to fully depict the joint effect of OSA, Lp(a), and insulin resistance. Finally, possible discrepancy between statistical effects and biological effects might exist. Further fundamental and intervention studies

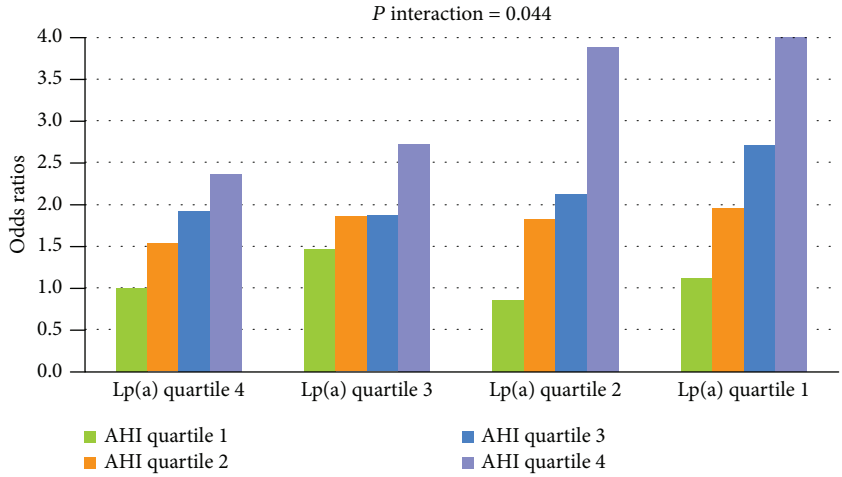

Figure 2: Multiplicative interaction between AHI quartiles and Lp(a) quartiles on the association with the presence of insulin resistance. More significant trends in the relationship between AHI quartiles and insulin resistance were found in the lower Lp(a) quartiles, indicating significant positive interaction. Odds ratios and *P* values were calculated with logistic regression analyses after adjusting for age, gender, BMI, waist-to-hip circumference ratio, MAP, current smoking status, current drinking status, TC, TG, HDL-C, LDL-C, ApoA-I, and ApoB. AHI quartiles 1-4 correspond to the AHI range of ≤7, 7.1-28, 28.1-57, and >57 events/h, respectively. Lp(a) quartiles 1-4 correspond to the serum Lp(a) concentration range of ≤3.90, 3.91-7.40, 7.41-15.10, and >15.10 mg/dL, respectively.

are needed to confirm the biological or clinical impact of our findings.

5. Conclusions

In an OSA-suspected population, serum Lp(a) concentrations inversely and independently correlated with insulin resistance following extensive adjustment. In addition, a significant positive interaction was noted between OSA severity and decreased Lp(a) with respect to the degree of insulin resistance. Proper evaluation of the metabolic and cardiovascular disease risk in OSA patients requires appropriate consideration of these associations. Our results also warrant further investigation into the mechanisms underlying the exacerbation of insulin resistance across OSA severities with declining Lp(a).

Data Availability

The data that support the findings of this study are available from the Department of Otolaryngology, Therapy Center for Obstructive Sleep Apnea, Shanghai Jiao Tong University Affiliated Sixth People's Hospital. But restrictions apply to the availability of these data, which were used under license for the current study, and so they are not publicly available. Data are however available from the authors upon reasonable request and with permission of the Department of Otolaryngology, Therapy Center for Obstructive Sleep Apnea, Shanghai Jiao Tong University Affiliated Sixth People's Hospital.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Yupu Liu and Juanjuan Zou contributed equally to this work.

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Research Article

Impaired Glucose Metabolisms of Patients with Obstructive Sleep Apnea and Type 2 Diabetes

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Aims. Obstructive sleep apnea (OSA) is a very common disorder which is associated with metabolic comorbidities. The aims of this study were to analyze clinical data of patients with OSA and evaluate influence of sleep-disordered breathing on glycometabolism and its underlying mechanisms. *Methods*. We designed a cross-sectional study involving 53 OSA patients in The First Hospital of Jilin University from March 2015 to March 2016. They underwent a full-night polysomnography, measurement of fasting blood glucose and blood lipid profiles. Besides, we chose 20 individuals with type 2 diabetes mellitus (T2DM) as a subgroup for an in-depth study. This group additionally underwent a steamed bread meal test and measurement of HbA1c, C-reactive protein, tumor necrosis factor-α, interleukin 6, morning plasma cortisol, and growth hormone. *Results*. The two groups which with or without T2DM showed no significant differences in baseline characteristics. As for OSA patients with T2DM, the severe OSA group had higher homeostasis model assessment of insulin resistance (HOMA-IR) ($P = 0.013$) than the mild-to-moderate OSA group, whereas had lower morning plasma cortisol levels ($P = 0.005$) than the mild-to-moderate OSA group. AHI was positive correlated with HOMA-IR ($r = 0.523$, $P = 0.018$), yet negative correlated with morning plasma cortisol ($r = -0.694$, $P = 0.001$). However, nadir SpO_2 was positive correlated with morning plasma cortisol ($r_s = 0.646$, $P = 0.002$), while negative correlated with HOMA-IR ($r_s = -0.489$, $P = 0.029$). *Conclusions*. Our study showed that sleep-disordered breathing exerted negative influence on glucose metabolisms. The impairment of hypothalamic-pituitary-adrenal axis activity may be one of the underlying mechanisms of the glycometabolic dysfunctions in OSA with T2DM patients.

1. Introduction

Obstructive sleep apnea (OSA), a common sleep-related breathing disorder, is characterized by repetitive upper airway narrowing during sleep and recurrent arousal from sleep that leads to sleep fragmentations. OSA affecting 10–25% of the general population worldwide is more likely to combine with metabolic dysfunctions [1, 2].

Increasing evidence has showed that OSA is associated with type 2 diabetes mellitus (T2DM) and may exert negative influence on glucose metabolisms [2–4]. Several large cohort studies have found a high prevalence of insulin resistance and T2DM in OSA patients, independent of age and obesity [5, 6]. Furthermore, severity of OSA is associated with development of insulin resistance, glucose intolerance, and T2DM [7, 8]. However, underlying mechanisms regarding relationship between OSA and T2DM have not been thoroughly explored.

The hallmarks of OSA, namely, sleep fragmentation and intermittent hypoxia, may contribute to impaired glucose metabolism by multifactorial process including sympathetic nerve activation, oxidative stress, inflammation, and hormonal changes [1]. Moreover, other mechanisms involving gut microbiota dysbiosis and endoplasmic reticulum stress are still under investigation [2].

Several studies have showed that OSA activates alterations in hormone secretory patterns [9]. Reciprocally, the change of cortisol and growth hormone levels may lead to

impaired glucose metabolisms [1, 10]. With respect to alterations in hypothalamic-pituitary-adrenal (HPA) activity, some studies found an increased nocturnal pulsatile cortisol release which may result in insulin resistance [11, 12], while others reported a decreased HPA axis activity presenting lower morning cortisol [13]. Another study also demonstrated lower cortisol responses in OSA patients than subjects without OSA [14]. Likewise, based on previous studies, it is evident that obese patients with OSA have impaired basal and stimulated growth hormone secretion [15]. In addition, growth hormone inhibits insulin activity and usually mounts in the first half of the sleep inducing impaired glucose metabolisms [16].

Except for hormonal alterations, inflammation response is the main pathogenesis of OSA-associated metabolic processes through the activation of inflammatory pathways [17, 18]. A meta-analysis has showed higher levels of C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), and interleukin 6 (IL-6) in patients with OSA compared to the control group [19], albeit inconsistent results reported by previous studies. OSA patients are in the condition of inflammation response leading to impaired glucose metabolisms [1]. Therefore, increasing studies on inflammatory pathways illuminate mechanisms of inflammatory response in OSA patients [1, 20].

To date, substantial studies have expanded our knowledge of relationship between OSA and T2DM. However, it is important to highlight that animal model could not involve all the major components of OSA patients due to technical difficulties. Thus, studies based on OSA patients to some extent seem to be more convincing. In this regard, we designed a cross-sectional study enrolling patients with OSA to investigate altered glucose metabolisms in OSA. Besides, we intended to apply clinical data to explore underlying mechanisms of impaired glucose metabolisms in OSA. Our in-depth elucidation on effect of sleep-disordered breathing on glucose metabolisms might be beneficial for patients with OSA and T2DM to make preventive and therapeutic strategies.

2. Materials and Methods

2.1. Subjects. A total of 53 patients were enrolled according to the following inclusion and exclusion criteria. All patients were newly diagnosed OSA at Respiratory Sleep Center in The First Hospital of Jilin University from March 2015 to March 2016. The diagnosis of OSA was in accordance with the guidelines of the American Academy of Sleep Medicine (AASM) [21]. Inclusion criteria were (1) newly diagnosed OSA; (2) at the age of 20-70 years old; and (3) diabetic duration less than 10 years and glycemic control by diet, exercise, or medication for at least 3 months. Exclusion criteria were (1) diagnosed viral hepatitis, cancer, chronic obstructive pulmonary disease, asthma, and other pulmonary diseases and (2) history of OSA treatment prior to the study.

Patients were classified into two groups based on diagnosis of T2DM: the non-T2DM group ($N = 33$) and the T2DM group ($N = 20$). In order to further investigate the relationship between OSA and T2DM, we defined patients with OSA and T2DM as a subgroup. Then, we divided the subgroup into two groups based on apnea-hypopnea index (AHI) and severity of OSA: the mild-to-moderate OSA group ($5 \leq \text{AHI} \leq 30$ events/h, $N = 7$) and severe OSA group (AHI > 30 events/h, $N = 13$).

All the participants enrolled in this study underwent a medical history questionnaire, physical examination. Body weight, height, waist circumference, neck circumference, and arterial blood pressure were measured in the morning.

The study was approved by the research ethics committee of The First Hospital of Jilin University. Informed consent was obtained from all participants included in this study.

2.2. Sleep Assessment. Full-night polysomnography (PSG) was performed in the sleep center (Alice 5LE, Philips Respironics). All data were manually scored and evaluated in accordance with guidelines of AASM. The duration of sleep study lasted more than 6 hours. The definitions of apnea, hypoxia, and oxygen desaturation index (ODI) were described as follows. Apnea was defined as a complete cessation of respiratory airflow more than 10 s. Hypopnea was defined as a decrease in airflow by more than 50% from baseline for at least 10 s, in association with a reduction in oxygen saturation of at least 3%. ODI was defined as a number of arterial oxygen saturation (SpO_2) reduction of 3% or more per hour. Total sleep time (TST), sleep efficiency, AHI, nadir SpO_2, ODI, and other polysomnographic parameters were measured and recorded after an overnight PSG.

2.3. Blood Sampling and Laboratory Testing. After an overnight fasting of at least 8 h, a venous blood sample was collected to measure the fasting blood glucose and lipid profile. As for the patients with OSA and T2DM, they additionally examined HbA1c, CRP, TNF-α, IL-6, morning plasma cortisol, and growth hormone and underwent a steamed bread meal test. Blood glucose, insulin, and C-peptide levels were determined at 0 and 120 min during a steamed bread meal test. Insulin resistance was assessed by homeostasis model assessment of insulin resistance (HOMA-IR) calculated as fasting serum insulin (mU/mL) multiplying fasting blood glucose (mmol/L) divided by 22.5 [22]. Levels of insulin, C-peptide, CRP, TNF-α, IL-6, morning plasma cortisol, and growth hormone were measured by enzyme-linked immunosorbent assay (ELISA) at the same clinical laboratory.

2.4. Statistical Analysis. Statistical analyses were carried out using the SPSS 22.0. Continuous data with normal distribution were expressed as mean ± standard deviation (SD), continuous data with nonnormal distribution were expressed as median (first quartile, third quartile), and noncontinuous data were expressed in percentage. Statistical comparisons were performed using a t-test, Mann-Whitney U test, or chi-square test. Use Spearman or Pearson correlation to perform correlation analysis. The statistical significance was set at $P < 0.05$.

Table 1: Characteristics of OSA with non-T2DM and OSA with T2DM.

Parameters	Non-T2DM ($N = 33$)	T2DM ($N = 20$)	P
Male	24 (72.73)	17 (85.00)	0.486
Female	9 (27.27)	3 (15.00)	
Age (years)	44.03 ± 11.60	47.70 ± 10.57	0.254
Weight (kg)	84.27 ± 13.58	87.94 ± 11.69	0.321
Height (m)	1.71 ± 0.08	1.73 ± 0.06	0.248
BMI (kg/m^2)	28.86 ± 3.50	29.36 ± 2.94	0.597
Waist circumference (cm)	105.00 (89.50, 108.00)	102.00 (97.00, 109.00)	0.508
Neck circumference (cm)	45.00 (39.00, 48.00)	45.00 (41.00, 46.00)	0.804
Comorbidities			
Obesity	19 (57.58)	15 (75.00)	0.200
Hypertension	28 (84.85)	13 (65.00)	0.182
Dyslipidemia	24 (72.72)	18 (90.00)	0.249
NAFLD	30 (90.91)	20 (100.00)	0.438
Sleep characteristics			
TST (min)	382.12 ± 59.48	391.60 ± 51.00	0.556
Sleep efficiency (%)	82.80 ± 12.25	83.76 ± 9.51	0.768
Stage N1/TST (%)	17.88 ± 11.92	21.34 ± 13.66	0.337
Stage N2/TST (%)	62.23 ± 10.10	61.83 ± 15.25	0.910
Stage N3/TST (%)	0 (0, 5.95)	0 (0, 2.81)	0.787
Stage REM/TST (%)	17.11 ± 6.71	15.92 ± 4.65	0.487
AHI (events/h)	31.60 (19.55, 72.05)	43.70 (21.90, 73.03)	0.633
N-REM AHI (events/h)	27.60 (18.25, 73.05)	40.25 (22.53, 74.90)	0.430
REM AHI (events/h)	53.90 (22.45, 65.25)	48.45 (25.13, 63.83)	0.577
Nadir SpO_2 (%)	82.00 (73.00, 87.00)	74.00 (50.50, 86.00)	0.139
Mean SpO_2 (%)	95.00 (93.00, 96.35)	93.00 (87.50, 95.88)	0.075
ODI (events/h)	21.40 (11.00, 73.80)	38.30 (17.50, 73.68)	0.271
Biochemical parameters			
FBG (mmol/L)	5.41 ± 0.58	8.82 ± 1.86	≤0.001*
Cholesterol (mmol/L)	4.84 ± 0.73	4.44 ± 1.04	0.111
Triglycerides (mmol/L)	2.25 ± 1.32	2.30 ± 0.91	0.889
HDL cholesterol (mmol/L)	1.14 ± 0.22	1.07 ± 0.18	0.221
LDL cholesterol (mmol/L)	3.09 ± 0.68	2.84 ± 0.85	0.245

Continuous data with normal distribution are presented as mean ± SD, continuous data with nonnormal distribution are presented as median (first quartile, third quartile), and noncontinuous data are presented as number (%). T2DM: type 2 diabetes mellitus; BMI: body mass index; NAFLD: nonalcoholic fatty liver disease; TST: total sleep time; AHI: apnea-hypopnea index; REM: rapid eye movement; N-REM: nonrapid eye movement; SpO_2: arterial oxygen saturation; ODI: oxygen desaturation index; FBG: fasting blood glucose; HDL: high-density lipoprotein; LDL: low-density lipoprotein (*$P < 0.05$).

3. Results

The study consisted of 53 OSA patients which were divided into two groups, the non-T2DM group and T2DM group. Baseline characteristics of the subjects are presented in Table 1. There were no statistically significant differences in anthropometric parameters, comorbidities, sleep characteristics, and lipid profiles between the groups. However, fasting blood glucose level was significantly higher in the T2DM group than non-T2DM group.

To further investigate the relationship between OSA and T2DM, we defined patients with OSA and T2DM as a subgroup. Then, we divided it into two groups based on the severity of OSA, the mild-to-moderate OSA group ($5 \leq \text{AHI} \leq 30$ events/h) and severe OSA group ($\text{AH} > 30$ events/h).

The baseline characteristics of OSA and T2DM patients are presented in Table 2. There were no statistically significant differences in gender, age, and anthropometric parameters between the mild-to-moderate OSA and severe OSA groups. With respect to the characteristics of T2DM, the duration, therapies, and chronic complications of T2DM showed no statistically significant differences between the groups which are presented in Table 3.

The analyses of polysomnographic data of OSA with T2DM patients are presented in Table 4. AHI and ODI were significantly lower in the mild-to-moderate OSA group compared to the severe OSA group, while stage N3/TST, nadir

Table 2: Baseline characteristics of OSA with T2DM patients.

Parameters	Mild-to-moderate OSA ($N = 7$)	Severe OSA ($N = 13$)	P
Male	6 (85.71)	11 (84.62)	0.730
Female	1 (14.29)	2 (15.38)	
Age (years)	43.29 ± 6.40	51.38 ± 10.03	0.070
Weight (kg)	95.00 (83.00, 98.00)	82.00 (76.00, 95.15)	0.203
Height (m)	1.75 ± 0.04	1.72 ± 0.07	0.266
BMI (kg/m^2)	30.13 ± 2.65	28.94 ± 3.11	0.402
Waist circumference (cm)	103.00 (100.00, 110.00)	102.00 (94.00, 110.00)	0.781
Neck circumference (cm)	43.57 ± 3.17	43.77 ± 2.80	0.887

Continuous data with normal distribution are presented as mean ± SD, continuous data with nonnormal distribution are presented as median (first quartile, third quartile), and noncontinuous data are presented as number (%). BMI: body mass index.

Table 3: Baseline characteristics of T2DM.

Parameters	Mild-to-moderate OSA ($N = 7$)	Severe OSA ($N = 13$)	P
Duration of T2DM (months)	36.00 (24.00, 60.00)	36.00 (18.00, 114.00)	0.497
Therapies			
Diet and exercise	1 (14.29)	2 (15.38)	0.730
Oral antidiabetic agents	2 (28.57)	4 (30.77)	0.664
Insulin	3 (42.85)	5 (38.47)	0.608
Oral antidiabetic agents and insulin	1 (14.29)	2 (15.38)	0.730
Chronic complications			
Macrovascular complication	2 (28.57)	5 (38.47)	0.526
Nephropathy	3 (42.85)	1 (7.69)	0.101
Retinopathy	2 (28.57)	0 (0)	0.111
Neuropathy	1 (14.29)	3 (23.08)	0.561

Continuous data with nonnormal distribution are presented as median (first quartile, third quartile), and noncontinuous data are presented as number (%).

SpO_2, and mean SpO_2 were higher in the mild-to-moderate OSA group. Moreover, there were no significant differences in TST, sleep efficiency, stage N2/TST, and stage rapid eye movement (REM)/TST.

The results of biochemical parameters of OSA with T2DM patients are showed in Table 5. As for glucose metabolic parameters, the severe OSA group showed higher HOMA-IR and insulin levels than the mild-to-moderate OSA group. In order to further study the mechanisms of impaired glucose metabolism of OSA and T2DM patients, we examined CRP, TNF-α, IL-6, morning plasma cortisol, and growth hormone levels. The results showed no significant differences between the groups except for morning plasma cortisol. The severe OSA group had significantly lower morning plasma cortisol levels compared to the mild-to-moderate OSA group. In addition, there were no significant differences in lipid profiles between the groups.

In the correlation analysis of OSA and T2DM patients, AHI was significantly positive correlated with HOMA-IR ($r = 0.523$, $P = 0.018$), yet negative correlated with morning plasma cortisol ($r = -0.694$, $P = 0.001$) (Figure 1). However, nadir SpO_2 was significantly positive correlated with morning plasma cortisol ($r_s = 0.646$, $P = 0.002$), while negative correlated with HOMA-IR ($r_s = -0.489$, $P = 0.029$) (Figure 2).

4. Discussion

This study analyzed clinical data of OSA patients to investigate the relationship between OSA and T2DM. Moreover, we defined patients of OSA and T2DM as a subgroup to study the influence of OSA on glucose metabolisms and its underlying mechanisms. Accumulative evidence has showed that OSA is independently associated with T2DM and has negative influence on glucose metabolisms [2–4]. However, studies yielded inconsistent results and related mechanisms remained to be further investigated.

In our study, 53 patients were enrolled based on the inclusion and exclusion criteria. The mean age of OSA patients was 45.42 ± 11.26 years and male to female ratio was 3.42 : 1. The prevalence of T2DM, obesity, hypertension, dyslipidemia, and nonalcoholic fatty liver disease took up 37.74%, 64.15%, 77.36%, 79.25%, and 94.34%, respectively. There were no significant differences in metabolic comorbidities between the non-T2DM group and T2DM group. Several epidemiological studies have suggested that OSA is an

Table 4: Sleep characteristics of OSA and T2DM patients.

Parameters	Mild-to-moderate OSA ($N = 7$)	Severe OSA ($N = 13$)	P
TST (min)	378.71 ± 43.89	398.53 ± 54.83	0.422
Sleep efficiency (%)	78.90 ± 8.36	86.37 ± 9.34	0.094
Stage N1/TST (%)	10.60 ± 4.43	27.13 ± 13.50	0.006*
Stage N2/TST (%)	69.17 (57.23, 72.35)	55.93 (48.00, 71.81)	0.166
Stage N3/TST (%)	2.81 (0, 8.33)	0 (0, 0.05)	0.036*
Stage REM/TST (%)	17.45 ± 4.02	15.10 ± 4.90	0.292
AHI (events/h)	19.13 ± 7.38	62.68 ± 19.06	≤0.001*
N-REM AHI (events/h)	18.27 ± 8.42	63.40 ± 21.26	≤0.001*
REM AHI (events/h)	23.24 ± 16.28	55.42 ± 14.54	≤0.001*
Nadir SpO_2 (%)	86.00 (85.00, 86.00)	61.00 (42.50, 71.00)	0.001*
Mean SpO_2 (%)	96.00 ± 1.04	88.96 ± 5.20	0.003*
ODI (events/h)	15.01 ± 6.36	64.80 ± 23.67	≤0.001*

Continuous data with normal distribution are presented as mean ± SD, and continuous data with nonnormal distribution are presented as median (first quartile, third quartile). TST: total sleep time; AHI: apnea-hypopnea index; REM: rapid eye movement; N-REM: nonrapid eye movement; SpO_2: arterial oxygen saturation; ODI: oxygen desaturation index (*$P < 0.05$).

Table 5: Biochemical parameters of OSA with T2DM patients.

	Mild-to-moderate OSA ($N = 7$)	Severe OSA ($N = 13$)	P
HbA1c (%)	8.71 ± 1.57	8.41 ± 1.38	0.657
Glucose I (mmol/L)[a]	7.10 (6.86, 8.01)	7.33 (6.47, 7.01)	0.811
Glucose II (mmol/L)	12.00 ± 3.18	11.25 ± 1.82	0.507
Insulin (pmol/L)	61.87 ± 22.36	127.82 ± 57.99	0.010*
C-peptide I (nmol/L)	0.73 ± 0.20	1.00 ± 0.58	0.239
C-peptide II (nmol/L)	1.56 (1.28, 3.79)	1.56 (1.23, 3.92)	0.905
HOMA-IR	2.78 (2.20, 2.93)	4.93 (3.73, 8.37)	0.013*
Cholesterol (mmol/L)	4.60 ± 0.70	4.36 ± 1.21	0.636
Triglycerides (mmol/L)	2.21 ± 0.95	2.35 ± 0.93	0.760
HDL cholesterol (mmol/L)	1.06 ± 0.23	1.07 ± 0.16	0.882
LDL cholesterol (mmol/L)	3.00 ± 0.63	2.76 ± 0.96	0.575
CRP (mg/L)	3.30 (3.28, 4.16)	3.30 (3.29, 3.90)	0.656
TNF-α (ng/L)	226.50 (203.00, 327.50)	377.00 (195.00, 3099.25)	0.501
IL-6 (ng/L)	9.00 (6.00, 30.00)	18.50 (12.00, 40.50)	0.165
Cortisol (pmol/L)	272.03 ± 52.24	194.46 ± 51.75	0.005*
Growth hormone (ng/mL)	0.09 (0.07, 0.13)	0.134 (0.09, 0.28)	0.096

Continuous data with normal distribution are presented as mean ± SD, and continuous data with nonnormal distribution are presented as median (first quartile, third quartile). HOMA-IR: homeostasis model assessment of insulin resistance; HDL: high-density lipoprotein; LDL: low-density lipoprotein; CRP: C-reactive protein; TNF-α: tumor necrosis factor-α; IL-6: interleukin 6 (*$P < 0.05$). [a]I refers to fasting and II refers to 120 min after 100 g steamed bread meal load.

independent risk factor for the development of T2DM [23]. Furthermore, insulin resistance is a key factor in the pathogenesis of T2DM and other OSA-associated metabolic perturbations [1]. As for patients with OSA and T2DM, the effects of sleep-disordered breathing on glucose metabolisms and underlying mechanisms have not been thoroughly demonstrated. Therefore, we had a further study on relationships between OSA severity and glucose metabolisms.

The results of glucose metabolism disorders in our study suggested that the severe OSA group had higher HOMA-IR and insulin levels than the mild-to-moderate OSA group independent of age, gender, obesity, diabetic duration, and antidiabetic therapies. In line with these results, epidemiologic studies have proved an association of OSA and impaired glucose metabolism after adjustments of known confounders. Several cross-sectional studies found that OSA was associated with increased insulin resistance in spite of adjustment for obesity and other confounders [24–26]. Besides, sleep-disordered breathing may also contribute to poor diabetic control. Analyses of the European Sleep Apnea

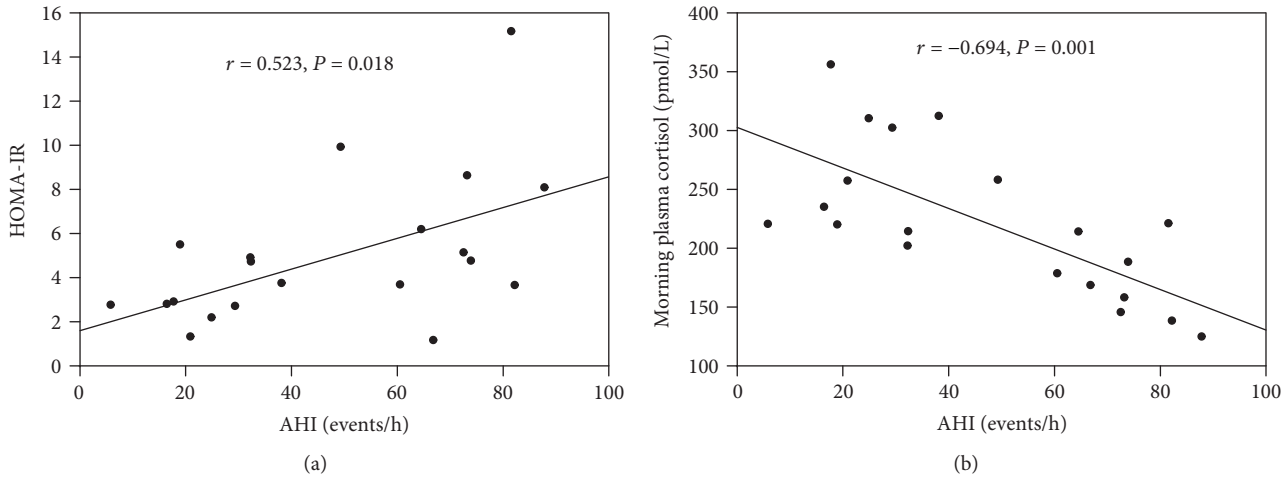

Figure 1: Correlation between AHI and HOMA-IR (a) and correlation between AHI and morning plasma cortisol (b) of OSA with T2DM patients. HOMA-IR homeostasis model assessment of insulin resistance. AHI: apnea-hypopnea index.

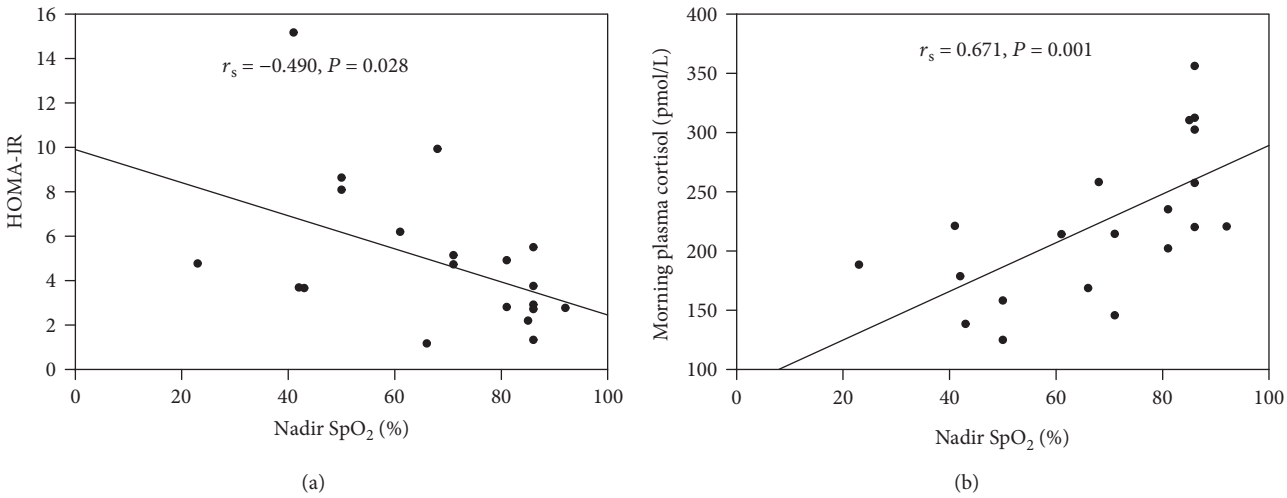

Figure 2: Correlation between nadir SpO2 and HOMA-IR (a) and correlation between nadir SpO2 and morning plasma cortisol (b) of OSA with T2DM patients. HOMA-IR homeostasis model assessment of insulin resistance. AHI: apnea-hypopnea index.

Database showed that OSA severity was related to increased HbA1c levels [27, 28]. However, we did not find significant differences in HbA1c and other glycometabolism between the groups. Considering the factors that all subjects had glycemic control by diet, exercise, or drugs for at least three months before enrolled in our study, plus the relatively small sample size, it seems reasonable to understand the inconsistent results on glycemic control.

To investigate if sleep-disordered breathing has an impact on HPA axis, we further examined plasma cortisol levels and then showed that the severe OSA group had significantly lower morning plasma cortisol levels compared to the mild-to-moderate OSA group. Additionally, severity of sleep fragmentation and intermittent hypoxia correlated with HOMA-IR in OSA with T2DM patients.

The effects of sleep-disordered breathing on the HPA axis and morning cortisol levels remain controversial. Some studies have reported no significant association [29–31] or increased HPA axis activity [32, 33], whereas others reported decreased HPA axis activity compared to controls [13, 14]. The inconsistent findings are partly due to obesity, timing of sample collection, and other possible confounders. As for morning plasma cortisol levels, some studies found that there are no significant differences in morning plasma cortisol levels [29, 34], while others showed lower morning cortisol levels than control subjects [13]. There are two possible explanations of lower morning plasma cortisol levels regarding change of HPA axis activity. Considering the temporary inhibition of cortisol caused by pulsatile cortisol release associated with nocturnal awakenings [35], OSA patients had lower morning plasma cortisol levels compared to normal individuals. Moreover, sleep-disordered breathing exacerbated negative feedback effect on the HPA axis which results in lower morning plasma cortisol levels. In parallel with our

findings, Bozic et al. reported negative association between severity of OSA and morning plasma cortisol levels [13]. Therefore, our study suggested that HPA axis activity gradually decreased as severity of OSA became worse.

Although changes of HPA axis in patients with OSA present different results, they mostly exhibit nocturnal hypercortisolism which is responsible for the negative effects on glucose metabolism [1, 36, 37]. Previous studies have showed that SA patients had higher nocturnal cortisol levels compared to control subjects [11, 12]. In line with the elevation of late-night serum cortisol, 24-hour urinary cortisol levels were also higher in OSA patients, indicating that night wakefulness boosts the activity of HPA axis and increases pulsatile cortisol release. Furthermore, Plat et al. reported that boosted nocturnal cortisol levels contribute to alterations in glucose tolerance, insulin sensitivity, and insulin secretion [10]. Our study showed positive correlation between AHI and HOMA-IR, whereas negative correlated with morning plasma morning cortisol. It suggested that impaired HPA axis activity may lead to insulin resistance, albeit devoid of data on nocturnal cortisol levels.

In our study, we did not find difference in morning growth hormone between the mild-to-moderate OSA group and severe OSA group. Nevertheless, based on previous elaboration, it is evident that obese patients with OSA showed an impairment of both basal and stimulated growth hormone secretions [15]. Sleep fragmentation and intermittent hypoxia negatively affect secretion of growth hormone [9]. Reciprocally, growth hormone inhibits insulin activity and usually peaks in the first half of the sleep period. Sleep restriction might be associated with elevation of growth hormone secretion at night causing impaired glucose metabolisms [16].

Admittedly, studies have showed that OSA induces changes in the levels or secretory patterns of several hormones. However, vascular and systemic inflammation is the main pathogenesis of OSA-associated cardiometabolic processes through the activation of inflammatory pathways [17, 18, 20]. Our study showed no differences in CRP, TNF-α, and IL-6 between the mild-to-moderate OSA group and severe OSA group. Increasing studies have addressed the increased levels of various circulating biomarkers of inflammation, and results have been diverse and heavily confounded by obesity. A meta-analysis of 51 studies showed higher levels of CRP, TNF-α, and IL-6 in patients with OSA compared to controls [19]. Although we found no differences in CRP, TNF-α, and IL-6 between the groups, it did not accurately implicate levels of inflammatory responses in other organs and tissues. Previous studies showed that intermittent hypoxia precipitates inflammatory response which has a detrimental effect on multiple systems, also leading to impaired glucose metabolisms [1]. Hypoxia-sensitive transcriptional factors, hypoxia-inducible factor-1 (HIF-1) and nuclear factor-κB (NF-κB), might mediate the inflammatory consequences of OSA [20, 38]. It is likely that crosstalk between NF-κB and HIF-1 plays a complex role in modulating the inflammatory response to intermittent hypoxia in OSA [39–41]. Therefore, there is no denying that multiple inflammatory mediators play key roles in the mechanisms of glucose metabolic dysfunctions.

An increasing number of studies have demonstrated an independent association between OSA, insulin resistance, and T2DM [28, 42]. Furthermore, mounting evidence has showed a link between OSA severity and development of insulin resistance and T2DM [7, 8]. In our study, the severe OSA group had higher HOMA-IR and insulin levels in patients with OSA and T2DM independent of age, gender, obesity, diabetic duration, and antidiabetic therapies. We also found that as sleep-disordered breathing became worse, evaluated by AHI and nadir SpO_2, the level of HOMA-IR increased. The impact of sleep-disordered breathing on glucose metabolisms seems to be insidious, but also harmful for patients with T2DM. In this regard, we attempt to reveal potential mechanisms of glucose metabolic dysfunctions in OSA with T2DM patients. As previously discussed, inhibition of morning plasma cortisol appears to be a manifestation of impaired HPA axis and nocturnal hypercortisolism might be responsible for insulin resistance. Therefore, we concluded that the impairment of HPA axis activity may explain the underlying mechanisms of the glycometabolic dysfunctions in OSA. Although we did not find significant differences in growth hormone, CRP, TNF-α, and IL-6 between the groups, inflammatory response in OSA might play a key role in impaired glucose metabolism based on previous studies. In addition, other mechanisms including sympathetic nerve activation and oxidative stress might integrally contribute to insulin resistance and T2DM.

There are a few limitations in our study. It might not sufficient to examine hormone levels at a single point. Instead, a 24-hour cortisol profile could provide more convincing results of HPA axis activity. Moreover, continuous glucose monitoring combined with PSG may be of additional value to study the effect of sleep-disordered breathing on nocturnal glycemic variations which is also beneficial to glycemic control for patients with T2DM. Besides, considering the relatively small sample size of our study, larger number of studies, especially cohort studies, would confirm the findings of this study.

In conclusion, our study showed that sleep-disordered breathing exerted negative influence on glucose metabolisms. The severe OSA group had significantly higher HOMA-IR, yet lower morning plasma cortisol levels than the mild-to-moderate OSA group. Furthermore, severity of OSA is positively correlated with HOMA-IR, whereas negatively correlated with morning cortisol levels. Although underlying mechanisms of association between OSA and impaired glucose metabolisms remain unclear, the change of HPA axis activity may be involved in the pathophysiological mechanisms among patients with OSA and T2DM. Further studies with larger sample size and more sufficient data are needed to confirm these findings.

Data Availability

The data used to support the findings of this study are included within the article, which are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Acknowledgments

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Research Article

Associations between Sleep-Disordered Breathing and Metabolic Risk Factors beyond Obesity

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Objective. Individuals with multiple metabolic risk factors often experience concomitant sleep-disordered breathing (SDB). We aimed to determine the associations of SDB with individual components of metabolic syndrome independent of obesity. *Methods*. A cross-sectional study was conducted in 1137 employees aged 30–64 years. Apnea-hypopnea index (AHI) was assessed using a portable monitor for obstructive sleep apnea by admission. Of these, 451 participants took an oral glucose tolerance test to assess homeostatic model assessment of insulin resistance (HOMA-IR) and Matsuda insulin sensitivity index (ISI). *Results*. The odds ratio (OR) of the highest category of the AHI (≥15 episodes per hour) compared to the lowest one (<5 episodes per hour) was significantly elevated for hypertension, for hypertriglyceridemia, and for low HDL-cholesterolemia when adjusted for age, sex, and alcohol and smoking status ($p < 0.05$). After further adjustment for body mass index (BMI) or waist circumference, the associations for hypertension still remained statistically significant ($p < 0.05$) while those for hypertriglyceridemia and low HDL-cholesterolemia were no longer significant. The association between higher insulin resistance as assessed by HOMA-IR and Matsuda ISI and higher categories of the AHI was also lost after adjustment for BMI. *Conclusion*. Obesity was a strong confounding factor in the association between SDB and most metabolic risk factors including insulin resistance, except for hypertension. Further longitudinal study is needed to examine the temporal or causal relationships between SDB and metabolic risk factors. This trial is registered with UMIN-CTR UMIN000028067.

1. Introduction

Obesity, particularly abdominal obesity, can cause individuals to develop multiple metabolic disorders including dyslipidemia, hyperglycemia, and/or hypertension. Clustering of metabolic risk factors is not incidental, but rather evidence of "metabolic syndrome" or "syndrome X" [1]. Individuals with "syndrome X" often experience concomitant sleep-disordered breathing (SDB) which acts synergistically to increase their risk for cardiovascular disease [2, 3]. Thus, some investigators have suggested that "syndrome X" may include SDB and must then be called "syndrome Z" [4].

Recently, SDB has been reported to be independently associated with metabolic syndrome [5, 6] and with its more fundamental factor, insulin resistance [7–9]. However, because both SDB and metabolic derangements are strongly correlated with indices of obesity, obesity becomes an important confounder in the relationship between SDB and metabolic abnormalities. It is unknown whether SDB is causally related to metabolic abnormalities or is just a bystander in the relationships between obesity and metabolic abnormalities.

The aim of this study was to determine the associations of SDB with individual components of metabolic syndrome independent of obesity. The degrees of insulin resistance were also examined in relation to the severity of SDB.

2. Materials and Methods

2.1. Participants. Participants included Japanese public school employees who received medical checkups at the Hokuriku Central Hospital between April 2006 and March 2010. On checkups, we recommended to take a sleep study to employees with sleep-related symptoms of obstructive sleep apnea including loud snoring, witnessed pauses in breathing, restless sleep, morning headaches, and/or daytime sleepiness or fatigue, unless they had already been treated for sleep apnea syndrome. Also, excluded from the study were those individuals who had <4 hours of quality data on record or missing data. Additionally, some participants spent one more night (total 2 nights) at the hospital and underwent an oral glucose tolerance test (OGTT) after an overnight fast, as previously reported [10]. Participants were considered smokers if they smoked at least 1 cigarette per day. Alcohol use was defined by the number of days per week it was consumed, regardless of the amount. Informed consent was obtained via an opt-out method, and the Institutional Review Board of the Kanazawa University approved the study protocol on June 21, 2017 (IRB no. 2497-1); the study protocol conformed to the provisions of the Declaration of Helsinki. The study was registered on the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR, http://www.umin.ac.jp/ctr, UMIN ID: UMIN000028067).

2.2. Blood Sampling and Anthropometric Measurements. After an overnight fast, blood samples were drawn from the antecubital vein to measure triglycerides, high-density lipoprotein (HDL) cholesterol, and fasting plasma glucose. Triglycerides and HDL cholesterol were measured using enzymatic analytical chemistry (Autoanalyzer BioMajesty JCA-BM1650, JEOL Ltd., Tokyo, Japan), and plasma glucose was assessed using the glucose oxidase method (Automatic Glucose Analyzer ADAMS Glucose GA-1160, Arkray, Kyoto, Japan) in the hospital laboratory. Insulin concentration assays were performed by the chemiluminescence immunoassay method at a commercial laboratory (BML Inc., Tokyo, Japan), with an intra-assay coefficient of variation (CV) of 2.4–3.2% based on 10 replicates of 3 different samples. Resting blood pressure was measured in the sitting position with an automatic device (Colin Model BP-203RV, Colin, Tokyo, Japan) after ≥5 minutes of rest. Measurements of body mass index (BMI) and waist circumference were conducted according to published methods [11].

2.3. Assessment of Metabolic Risk Factors and Calculation of Indices of Insulin Resistance. Participants were assessed with metabolic risk factors according to the following definitions: hypertension, a systolic/diastolic blood pressure ≥ 140/90 mmHg and/or taking antihypertensive medication; hypertriglyceridemia, triglycerides ≥ 150 mg/dL (1.69 mmol/L); low HDL-cholesterolemia, <40 mg/dL (1.04 mmol/L) for men and <50 mg/dL (1.30 mmol/L) for women; and impaired fasting plasma glucose (IFG), ≥110 mg/dL (6.1 mmol/L) [12]. Obesity was defined by BMI ≥ 25.0 kg/m^2 according to the Asian criterion of obesity [13]. The indices of insulin resistance were as follows: Matsuda insulin sensitivity index $(\mathrm{ISI}) = 10000/(\mathrm{Glu}_0 \times \mathrm{Ins}_0 \times \mathrm{Glu}_{120} \times \mathrm{Ins}_{120})^{0.5}$ and homeostatic model assessment of insulin resistance $(\mathrm{HOMA\text{-}IR}) = \mathrm{Glu}_0 \times \mathrm{Ins}_0/405$ [14], where Glu_x and Ins_y represented values at time x or y (min) during the OGTT.

2.4. Sleep Study. Sleep studies were conducted at the Health Check Department of Hokuriku Central Hospital for 1 night admission. Each participant's apnea-hypopnea index (AHI) was assessed using the PulSleep LS-100 (Fukuda Denshi, Tokyo, Japan) which digitally records nasal airflow via nasal cannula, oxygen saturation, and snoring sounds. AHI was defined as the average number of apneic plus hypopneic episodes per hour of sleep. Apnea was defined as a complete cessation of nasal airflow, and hypopnea was defined as a decrease in nasal airflow of at least 50% of baseline for ≥10 seconds. Both apnea and hypopnea must be by ≥4% decrease in oxygen saturation [15].

2.5. Statistical Analysis. All analyses were conducted using SPSS software version 24.0 for Windows (SPSS Inc., Chicago, IL, USA). Participants were classified using the AHI at commonly used clinical cut-off points. Three severity gradients or categories were used for the AHI in this study: none/minimal (<5 episodes per hour (reference)), mild (≥5 but <15 per hour), and moderate-to-severe (≥15 per hour). Data are presented as mean ± SD values for continuous variables and as a proportion for categorical variables. Tests to identify a linear trend across categories were performed by assigning the median value within each category and treating the categories as a continuous variable. Binary logistic regression analyses were performed to estimate the adjusted odds ratio (OR) for having metabolic risk factors in each category relative to the reference category (AHI < 5.0). The following covariates were used: age, sex, smoking (a 3-level variable: current, former, and never smoker), and alcohol use (a 3-level variable: drinking every day, drinking 1–6 days per week, and drinking <1 day per week). First, these nonadipose covariates were first included in the regression model. Subsequently, to assess whether the association between the stage of sleep disorder and each metabolic risk factor was independent of obesity, either BMI or waist circumference was additionally included in the model. Because the distribution of waist circumference was different between men and women, waist circumference was standardized to a mean of 0 and standard deviation of 1 in men and women, respectively, before the inclusion in the multiple regression model. Finally, in 451 subjects undertaking the OGTT, the levels of HOMA-IR and Matsuda ISI were compared among three different categories of the AHI. The comparisons were performed before and after adjustments for BMI, using analysis of covariance (ANCOVA). Analyses of HOMA-IR were conducted after logarithmic transformation because of their skewed distribution. A p value of <0.05 was considered statistically significant.

Table 1: Basic clinical characteristics of the study subjects according to the level of the apnea-hypopnea index (AHI).

	Overall ($N = 1173$)	AHI			p for the trend
		<5.0 ($N = 812$)	5.0–15.0 ($N = 250$)	≥15.0 ($N = 111$)	
Age (years)	51.1 ± 7.2	50.5 ± 7.3	52.9 ± 6.1	51.2 ± 8.0	0.02
Male gender (%)	75.8	69.5	86.4	98.2	<0.01
Anthropometries					
Body mass index (BMI) (kg/m^2)	24.7 ± 3.5	23.9 ± 3.0	25.8 ± 3.4	28.1 ± 4.6	<0.01
Obesity (%)*	40.1	31.0	56.4	69.4	<0.01
Waist circumference (cm) in men	86.5 ± 8.8	84.2 ± 7.5	89.0 ± 8.2	93.5 ± 10.6	<0.01
Waist circumference (cm) in women	81.5 ± 9.4	80.8 ± 8.9	86.1 ± 11.6	93.5 ± 13.4	<0.01
Metabolic parameters					
Systolic blood pressure (mmHg)	131.5 ± 19.0	128.4 ± 18.0	135.7 ± 17.9	144.6 ± 21.4	<0.01
Diastolic blood pressure (mmHg)	82.0 ± 11.8	80.1 ± 11.3	84.7 ± 11.2	89.8 ± 11.8	<0.01
Fasting plasma glucose (mg/dL)	100.8 ± 17.9	99.8 ± 18.4	102.8 ± 17.4	103.6 ± 15.2	0.01
Triglycerides (mg/dL)	78/109/156	73/102/145	85/125/184	104/146/193	<0.01
HDL cholesterol (mg/dL)	58.0 ± 14.2	60.0 ± 14.8	54.4 ± 12.4	51.4 ± 9.9	<0.01
HOMA-IR ($N = 451$)	0.8/1.0/1.5	0.7/1.0/1.4	0.8/1.1/1.7	1.0/1.4/2.1	<0.01
Matsuda ISI ($N = 451$)	11.0 ± 8.7	12.0 ± 8.9	10.0 ± 9.0	7.3 ± 4.9	<0.01
Habits					
Smokers (%)	19.6	18.1	22.0	25.2	0.04
Daily drinkers (%)	33.7	31.9	36.0	41.4	0.03
Taking medications					
Antihypertensive drugs (%)	15.0	12.6	17.2	27.9	<0.01
Lipid-lowering drugs (%)	7.5	6.5	10.4	8.1	0.24
Glucose-lowering drugs (%)	4.1	3.6	5.2	5.4	0.24

Data are expressed as mean ± SD, 25/50/75th percentile value, or number (%). *Obesity was defined by BMI ≥ 25.0 kg/m^2. HDL cholesterol: high-density lipoprotein cholesterol; HOMA-IR: homeostatic model assessment of insulin resistance; Matsuda ISI: Matsuda insulin sensitivity index.

3. Results

The overall study participants were composed of 1173 subjects with a mean age of 51.1 ± 7.2 years and a mean BMI of 24.7 ± 3.5 kg/m^2. Characteristics of the study participants according to AHI categories are presented in Table 1. Compared with those with lower AHI values, participants with higher AHI values showed a significantly higher proportion of men and significantly higher levels of BMI, blood pressure, fasting plasma glucose, triglycerides, and HOMA-IR and lower levels of HDL cholesterol and Matsuda ISI (p for the trend < 0.01). The proportions of smokers, daily drinkers, and those taking antihypertensive drugs were significantly higher in those with higher AHI values ($p < 0.05$).

Figure 1 shows the prevalence of metabolic abnormalities by an AHI category stratified by obesity. For both strata, the proportions of participants with hypertension and hypertriglyceridemia were significantly higher in higher categories of the AHI showed (p for the trend < 0.05). In participants without obesity, the prevalence of low HDL-cholesterolemia and hyperglycemia tended to be higher in higher categories of the AHI but the trend test did not reach statistical significance.

Table 2 shows the ORs for having individual risk factors according to the level of sleep-disordered breathing. When adjusted for age, sex, and alcohol and smoking status, the ORs of the highest category of the AHI were significantly elevated for hypertension, for hypertriglyceridemia, and for low HDL-cholesterolemia ($p < 0.05$). After further adjustment for BMI, the associations for hypertension still remained statistically significant ($p < 0.05$) while those for hypertriglyceridemia and low HDL-cholesterolemia were no longer significant. The elevated ORs for hypertension in the highest category of the AHI were also significant after adjustments for waist circumference in place of BMI ($p < 0.05$).

Finally, the levels of indices of insulin resistance were compared among categories of the AHI in 451 subjects (Figure 2). HOMA-IR was significantly higher, and Matsuda ISI was significantly lower in higher categories of the AHI (p for the trend < 0.01), but after adjusted for BMI, both indices no longer showed a significant trend, indicating that the association between AHI severity and insulin resistance was confounded by BMI. Adjustments for waist circumference in place of BMI showed similar results (data not shown). These 451 subjects took the OGTT not for any clinical signs but for financial reasons; they were slightly older (52.5 ± 6.7 yrs vs. 50.2 ± 7.4, $p < 0.05$), and the proportion of men was higher (80.0% vs. 73.1%, $p < 0.05$) than those who did not take the OGTT, but other characteristics including BMI was not significantly different.

4. Discussion

In this study, the independent association between severity of SDB and each metabolic risk factor was cross-sectionally

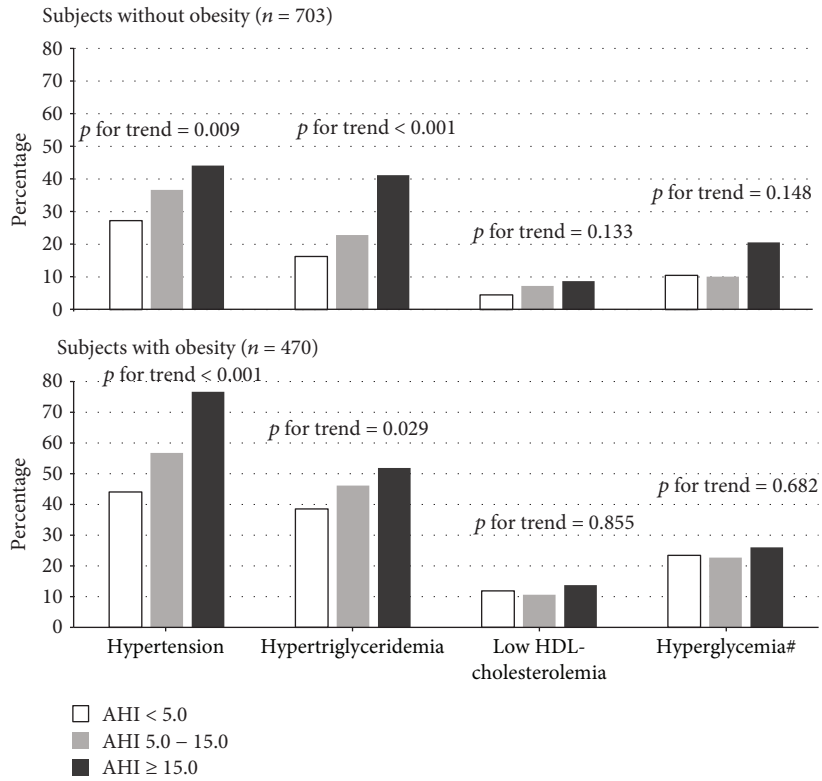

Figure 1: Prevalence of metabolic abnormalities by an AHI category stratified by obesity, using BMI ≥ 25.0 kg/m^2 as a cut-off. #Hyperglycemia was defined as fasting plasma glucose ≥ 110 mg/dL (6.1 mmol/L) and/or taking medications for diabetes. AHI: apnea-hypopnea index; BMI: body mass index; HDL: high-density lipoprotein; NS: not statistically significant.

Table 2: Multivariable analysis for metabolic abnormalities according to the apnea-hypopnea index (AHI) category.

	Odds ratios (95% CI) by an AHI category		
	<5.0 (N = 812)	5.0–15.0 (N = 250)	≥15.0 (N = 111)
Hypertension			
Crude	1.0	**1.9 (1.4–2.6)***	**4.2 (2.7–6.3)**
Multivariable-adjusted†	1.0	**1.6 (1.2–2.1)**	**3.6 (2.3–5.6)**
Multivariable and BMI-adjusted	1.0	1.1 (0.8–1.6)	**1.9 (1.2–3.1)**
Multivariable and waist-adjusted	1.0	1.1 (0.8–1.6)	**2.1 (1.3–3.3)**
Hypertriglyceridemia‡			
Crude	1.0	**1.9 (1.4–2.5)**	**3.1 (2.1–4.7)**
Multivariable-adjusted	1.0	**1.6 (1.1–2.2)**	**2.4 (1.6–3.7)**
Multivariable and BMI-adjusted	1.0	1.1 (0.8–1.6)	1.3 (0.8–2.0)
Low HDL-cholesterolemia			
Crude	1.0	1.4 (0.8–2.3)	1.8 (1.0–3.5)
Multivariable-adjusted	1.0	1.5 (0.9–2.6)	**2.2 (1.1–4.4)**
Multivariable and BMI-adjusted	1.0	1.2 (0.7–2.1)	1.4 (0.6–2.9)
Hyperglycemia‡			
Crude	1.0	1.2 (0.8–1.8)	**1.9 (1.2–3.0)**
Multivariable-adjusted	1.0	1.0 (0.7–1.5)	1.6 (1.0–2.6)
Multivariable and BMI-adjusted	1.0	0.7 (0.4–1.0)	0.7 (0.4–1.2)

*Bold font indicates that the odds ratio is statistically significant ($p < 0.05$). †Multivariable model adjusted for age, sex, alcohol intake, and smoking status. ‡Hyperglycemia was defined as fasting plasma glucose ≥ 110 mg/dL (6.1 mmol/L) and/or taking medications for diabetes. BMI: body mass index; CI: confidence interval.

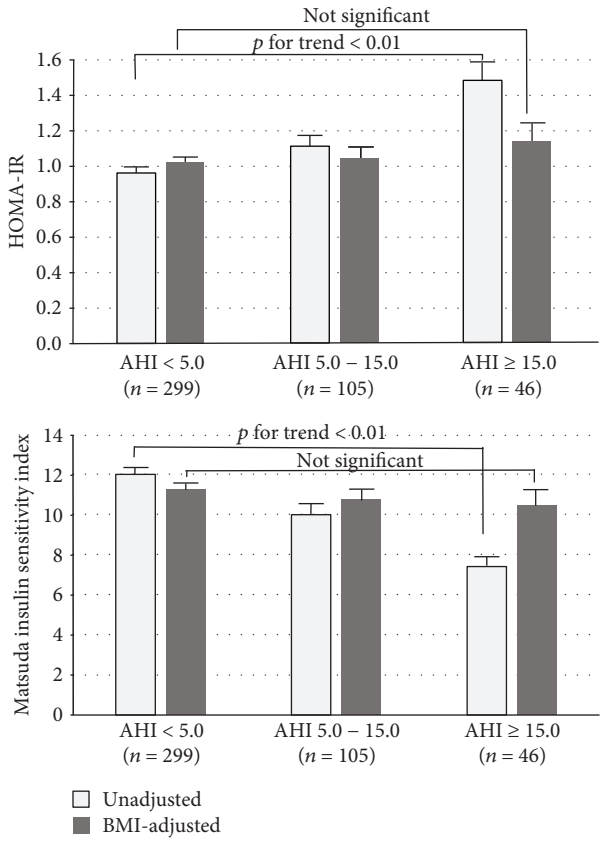

Figure 2: Unadjusted and BMI-adjusted indices of insulin resistance by an AHI category. HOMA-IR was log-transformed prior to analysis to reduce skewedness, and calculated values were untransformed after analysis. Error bars show standard error of the mean. AHI: apnea-hypopnea index; BMI: body mass index; HOMA-IR: homeostatic model assessment of insulin resistance.

examined in middle-aged Japanese men and women. After controlling for obesity, independent association was found for hypertension but not for dyslipidemia, hyperglycemia, and insulin resistance. These results suggest that SDB is an independent determinant for hypertension but may be only a bystander in the link between obesity and other metabolic abnormalities.

The link between SDB and hypertension was independent of obesity in this study, consistent with large community-based studies [6, 16, 17] and several randomized trials [18]. Their link was maintained after adjustment for waist circumference, an index of abdominal obesity, as well as BMI, an index of generalized obesity. In the CIRCS study, which demonstrated an independent association between SDB and metabolic syndrome in nonoverweight Japanese, the OR for hypertension in subjects with ≥15 hypoxia events/hour was highest (OR, 2.5; 95% CI, 1.4–4.6) among ORs for all components of metabolic syndrome [19]. Their results are in line with our observation that the OR for hypertension was only significantly elevated after controlling for obesity but not those for other metabolic risk factors. Although the effects of SDB on blood pressure have been reported to be weakened in elder subjects, at least in relatively younger subjects including our population, SDB seems to be an independent contributor to elevated blood pressure beyond obesity.

The association between hypertriglyceridemia and higher categories of the AHI was disappeared after adjustments for BMI in this study. There have been two large studies demonstrating an association between SDB and metabolic syndrome conducted in Japan [5, 6]. However, looked into the individual components of metabolic syndrome in these studies, after controlling for concomitant obesity, the association between hypertriglyceridemia and severity of SDB was diminished in one study [5] and was maintained only in nonoverweight subjects in the other with OR of 1.7 and 95% CI of 1.0–2.8 [6]. Moreover, the effects of OSA-targeted therapeutic intervention using CPAP on the lipid profile are controversial among investigators [20]. A metaregression analysis including 29 studies with 1958 subjects has concluded that CPAP treatment for OSA decreased total cholesterol and LDL cholesterol and did not affect TG levels [21]. Because hypertriglyceridemia is the strongest correlate with abdominal obesity among metabolic risk factors [22], the magnitude of association independent of obesity, if any, appears to be small relative to other components such as hypertension.

The prevalence of hyperglycemia, as assessed by fasting plasma glucose ≥110 mg/dL, was not significantly increased in higher categories of the AHI after controlling for BMI, consistent with prior studies [5, 6, 23]. The association between IFG and SDB was insignificant after adjustments for anthropometric indices in 1344 subjects from the Korean genome and epidemiology study [23] and in a male working population [5]. Although some prospective studies have demonstrated that SDB independently preceded and predicted the development of type 2 diabetes [19, 24, 25], even in these cases, the cross-sectional associations at baseline between SDB and diabetes after controlling for BMI [19, 25] and between SDB and fasting glucose levels [24] were not significant.

Why was the independent association between metabolic risk factors and SDB not seen in our study? In the CIRCS Study, the association between glucose abnormality and SDB after controlling for BMI was significant only in overweight subjects with OR of 1.6 and 95% CI of 1.0–2.6 and not in nonoverweight individuals with OR of 1.4 and 95% CI of 0.8–2.5 [6]. In study populations composed of less overweight subjects like this study, it may be difficult to detect the independent association between glucose abnormality and SDB. Further study is needed, comprising subjects without obesity and with SDB.

Furthermore, we failed to show the higher levels of insulin resistance in relation to severity of AHI categories after controlling for BMI. The discordance with prior epidemiological and clinical studies [7–9] may be attributed to relatively younger age of our study subjects. Because obesity is a major determinant of insulin resistance in younger subjects, a marginal influence of SDB in insulin resistance would be difficult to be demonstrated. Confounding effects of obesity also render it difficult to demonstrate an independent effect of CPAP therapy on insulin sensitivity. In

a study of 40 treatment-naïve, nondiabetic German subjects, insulin sensitivity as assessed by a hyperinsulinemic euglycemic clamp was not significantly improved in patients with obesity [26]. Negative effects of CPAP therapy on insulin resistance have been also reported in two previous randomized controlled trials in patients with obesity [27, 28] and in a recent meta-analysis [29].

The strength of this study was the simultaneous evaluation of multiple metabolic risk factors in relation to the severity of SDB, but several limitations should be considered. First, the measurement of blood pressure was performed approximately at 9 o'clock in the daytime. Sasaki et al. reported that approximately half the OSAS patients displayed morning hypertension [30], which may be missed by our evaluation. Second, insulin resistance was not measured by the glucose clamp technique, which is the gold standard for evaluating insulin resistance/sensitivity; however, it has been demonstrated that Matsuda ISI and HOMA-IR correlated well with directly measured insulin resistance and with metabolic abnormalities in nondiabetic subjects [31]. Third, obesity was assessed only by BMI and waist circumference. However, these two anthropometric indices are not inferior to visceral adipose tissue in correlation with insulin resistance [32] or with blood pressure [22] in Japanese men and women. Fourth, the sleep device in this study did not measure chest or abdomen movements, by which the strict differentiation between obstructive and central type of SDB was difficult. Finally, the cross-sectional design does not allow examination of the temporal or causal relationships between SDB and metabolic risk factors. Longitudinal studies are needed to confirm whether SDB is one of the secondary causes of incident hypertension in this population.

In conclusion, the cross-sectional associations of SDB with metabolic abnormalities vary across the individual risk factors. Obesity was a strong confounding factor in the association between SDB and most metabolic risk factors including insulin resistance. However, for hypertension, SDB had an independent association beyond confounding effects of obesity. Further longitudinal study is needed to examine the temporal or causal relationships between SDB and metabolic risk factors.

Data Availability

The datasets supporting the conclusions of this article are available in the University Hospital Medical Information Network Individual Case Data Repository. Please contact the corresponding author to access the data.

Conflicts of Interest

The authors declare that there are no conflicts of interest associated with this manuscript.

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