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Association between METS-IR index and obstructive sleep apnea: evidence from NHANES

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Insulin resistance (IR) is strongly associated with obstructive sleep apnea (OSA). Whereas, few studies have focused on the potential association between the Metabolic Score for Insulin Resistance (METS-IR), a novel non-insulin-dependent IR index, and OSA. Subjects from the National Health and Nutrition Examination Survey (NHANES) spanning 2005-2008 and 2015-2018 were recruited. The potential relationship between METS-IR and other IR indices with OSA was explored through three logistic regression analysis models and restricted cubic spline (RCS) curves. Receiver operating characteristic (ROC) curves were used to assess the diagnostic value of these indicators for OSA. On the basis of age, sex, race, body mass index (BMI), hypertension, diabetes， and cardiovascular disease (CVD), subgroup analyses were conducted to test the robustness of the METS-IR and OSA relationship. A total of 8,306 participants were enrolled, with an OSA prevalence of 30.69%. After adjusting for potential confounders, METS-IR, the triglyceride to high-density lipoprotein cholesterol (TG/HDL-C) ratio, the triglyceride glucose Index (TyG), and the homeostatic model assessment of insulin resistance (HOMA-IR) showed positive associations with OSA prevalence. In the highest tertile of METS-IR, TG/HDL-C, TyG index, and HOMA-IR, OSA prevalence was 2.96-fold, 1.42-fold, 1.29-fold, and 1.41-fold higher, respectively, compared to the lowest tertile (METS-IR: OR = 2.96, 95% CI: 2.50, 3.52, P < 0.0001; TG/HDL-C: OR = 1.42, 95% CI: 1.17, 1.73, P < 0.001; TyG index: OR = 1.29, 95% CI: 1.07, 1.55, P = 0.008; HOMA-IR: OR = 1.41, 95% CI: 1.18, 1.69, P < 0.001). ROC analysis revealed that METS-IR had the highest diagnostic accuracy for OSA (AUC = 0.652). The positive associations between these four IR indices and OSA remain stable across most cases (P for interaction > 0.05); however, all of them show significant interactions with diabetes (P for interaction < 0.05). The METS-IR index is positively associated with the prevalence of OSA and shows superior diagnostic accuracy compared to HOMA-IR, TG/HDL-C, and TyG index.

Keywords Insulin resistance, METS-IR, OSA, NHANES, Cross-sectional study

Abbreviations

OSA	Obstructive sleep apnea
IH	Intermittent hypoxemia
CVD	Cardiovascular disease
IR	Insulin resistance
HEC	Hyperinsulinaemic-euglycaemic clamp
HOMA-IR	Classical homeostasis model assessment of insulin resistance
FINS	Fasting insulin
TG/HDL-C	Triglyceride to high-density lipoprotein cholesterol
TyG	Triglyceride glucose
BMI	Body mass index
METS-IR	Metabolic Score for Insulin Resistance
FBG	Fasting blood glucose
HDL-C	High-density lipoprotein cholesterol
TG	Triglycerides
MetS	Metabolic syndrome

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CB	Carotid body
IH	Intermittent hypoxia
VAI	Visceral Adiposity Index
NHANES	National Health and Nutrition Examination Survey
NCHS	National Center for Health Statistics
HbA1c	Glycosylated hemoglobin A1c
PIR	Family income to poverty ratio
PA	Physical activity
MET	Metabolic equivalents
wtsaf2 year	Fasting subsample sampling weight
RCS	Restricted cubic spline
ROC	Receiver operating characteristic
AUC	Area under the curve
AHI	Apnea-hypopnea index
SO2	Oxyhemoglobin saturation
CPAP	Continuous positive airway pressure
AN	Autonomic neuropathy
HIF-1	Hypoxia-inducible factor

The recent inclusion of sleep as one of the criteria for assessing cardiovascular health by the American Heart Association has drawn increased attention to sleep-related issues among researchers[1]. Obstructive sleep apnea (OSA) ranks among the most prevalent sleep disorders. The global prevalence of OSA has been reported to affect up to 936 million individuals aged 30–69 years, with nearly half experiencing moderate to severe forms[2], particularly among male and obese populations[3]. During sleep, individuals with OSA suffer from recurrent upper airway collapses that obstruct airflow, leading to hypoventilation or apnea, which is characterized by intermittent hypoxemia (IH) and disrupted sleep patterns[4]. OSA has been identified as an independent risk factor for several non-communicable diseases, such as cardiovascular disease (CVD) and metabolic disorders[5–7], and is related to higher all-cause mortality risk[8,9]. Moreover, daytime sleepiness significantly impairs work productivity, contributing to a higher incidence of workplace and traffic accidents[10]. Thus, early identification of high-risk OSA populations and clarification of the underlying mechanisms are crucial for implementing appropriate interventions.

Insulin resistance (IR) refers to a pathophysiological condition where peripheral tissues exhibit reduced responsiveness to insulin due to a decrease in the number or binding capacity of insulin receptors, or diminished insulin sensitivity[11]. The hyperinsulinaemic-euglycaemic clamp (HEC) is widely regarded as the most accurate method for assessing insulin sensitivity in peripheral tissues[12]. However, the high price and complexity of the procedure hinder its widespread clinical application. The classical homeostasis model assessment of insulin resistance (HOMA-IR) appears to have relative advantages, but its calculation depends on fasting insulin (FINS) levels, limiting its utility in cases of β-cell insufficiency or exogenous insulin use[13]. Other readily available insulin-independent, non-invasive indices, such as the triglyceride to high-density lipoprotein cholesterol (TG/HDL-C) ratio and the triglyceride glucose (TyG) index, have demonstrated superiority over traditional indices (such as HOMA-IR) in predicting CVD and its mortality[14,15]. However, these indices fail to take into account the significant role of body mass index (BMI) in IR. Therefore, Bello-Chavolla et al. developed a novel indicator of IR, Metabolic Score for Insulin Resistance (METS-IR), based on fasting blood glucose (FBG), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), and BMI[16–18]. Based on its simplicity and validity, researchers have observed associations between METS-IR and conditions such as CVD, hypertension, and depression[19]. Notably, METS-IR has demonstrated greater accuracy than TyG, TG/HDL-C and even HOMA-IR in diagnosing testosterone deficiency, hyperuricemia, and predicting all-cause and cardiovascular mortality[20–22].

OSA appears to exhibit a bidirectional association with diabetes and metabolic syndrome (MetS)[23–25]. IR is recognized as a key contributor to both MetS and diabetes, and is implicated in the development of CVD[26–28]. Therefore, the relationship between OSA and IR may also be bidirectional. Mechanistically, IR could potentially increase the risk of OSA by reducing carotid body (CB) sensitivity and impairing autonomic function, thereby disrupting ventilation[24,25]. Conversely, intermittent hypoxia (IH) and fragmented sleep patterns characteristic of OSA may exacerbate IR[29–32]. Clinically, several studies have reported associations between IR indices such as the TyG index, Visceral Adiposity Index (VAI), and HOMA-IR, and the risk of OSA[33–36]. Conversely, OSA has been suggested to be associated with increased IR[30,37]. Whereas, there do not exist studies focusing on the relationship between METS-IR and OSA, leaving uncertain whether a relationship exists between them.

Given the significant role of IR in OSA and the diagnostic advantages of METS-IR, this study will utilize the National Health and Nutrition Examination Survey (NHANES) to explore further the association between METS-IR and OSA, comparing it with other IR indicators. The aim is to further clarify the association between IR and OSA, and to provide a simpler and more effective method to identify individuals at high risk of OSA early.

Methods

Data sources

NHANES conducted a comprehensive assessment of nutrition and health status across the entire U.S. population through physical examinations and interviews. This survey involved demographic information, dietary assessments, medical history interviews, as well as laboratory and physical examinations. NHANES was approved by the Ethics Review Board of the National Center for Health Statistics (NCHS) and adhered to the ethical standards outlined in the Declaration of Helsinki and its subsequent amendments. In addition, each participant provided written informed consent voluntarily.

Study participants

Due to limitations in the sleep questionnaire, participants were recruited from the NHANES database for four cycles: 2005–2008 and 2015–2018. A total of 39,722 individuals were included, from which 22,202 participants older than 20 years were selected. What we can see in Fig. 1, a final cohort of 8,306 participants was enrolled after exclusions based on the following criteria: (1) pregnant women ($N = 521$) or participants with abnormal energy intake (total energy intake < 500 kcal or ≥ 5000 kcal per day, $N = 248$); (2) those lacking a diagnosis of OSA ($N = 10$) or with missing data on HDL-C, TG, BMI, and FINS levels ($N = 12{,}577$); (3) participants with incomplete covariates data (except for physical activity (PA), alcohol consumption, poverty income ratio (PIR)) and sample weight ($N = 540$).

Evaluation of METS-IR and other insulin resistance surrogate indices

In this study, the exposure variables included four alternative indicators of IR: HOMA-IR, TG/HDL-C ratio, TyG index, and METS-IR. METS-IR, TyG index, and TG/HDL-C ratio were calculated on account of FBG, TG, HDL-C levels, and BMI, independent of FINS levels. The calculation of HOMA-IR, however, required both FINS and FBG levels. The specific calculation formulas were as follows:[16,38–40]

$$\mathrm{METS-IR} = (\mathrm{Ln}\,[(2 * \mathrm{FBG}) + \mathrm{TG}] * \mathrm{BMI}) / [\mathrm{Ln}\,(\mathrm{HDL-C})]$$

$$\mathrm{TyG\ index} = \mathrm{Ln}[\mathrm{TG*FBG}/2]$$

$$\mathrm{TG/HDL-C\ ratio} = \mathrm{TG/HDL-C}$$

(The units for the above formulas of FBG, TG, and HDL-C are mg/dL, while BMI is measured in kg/m²)

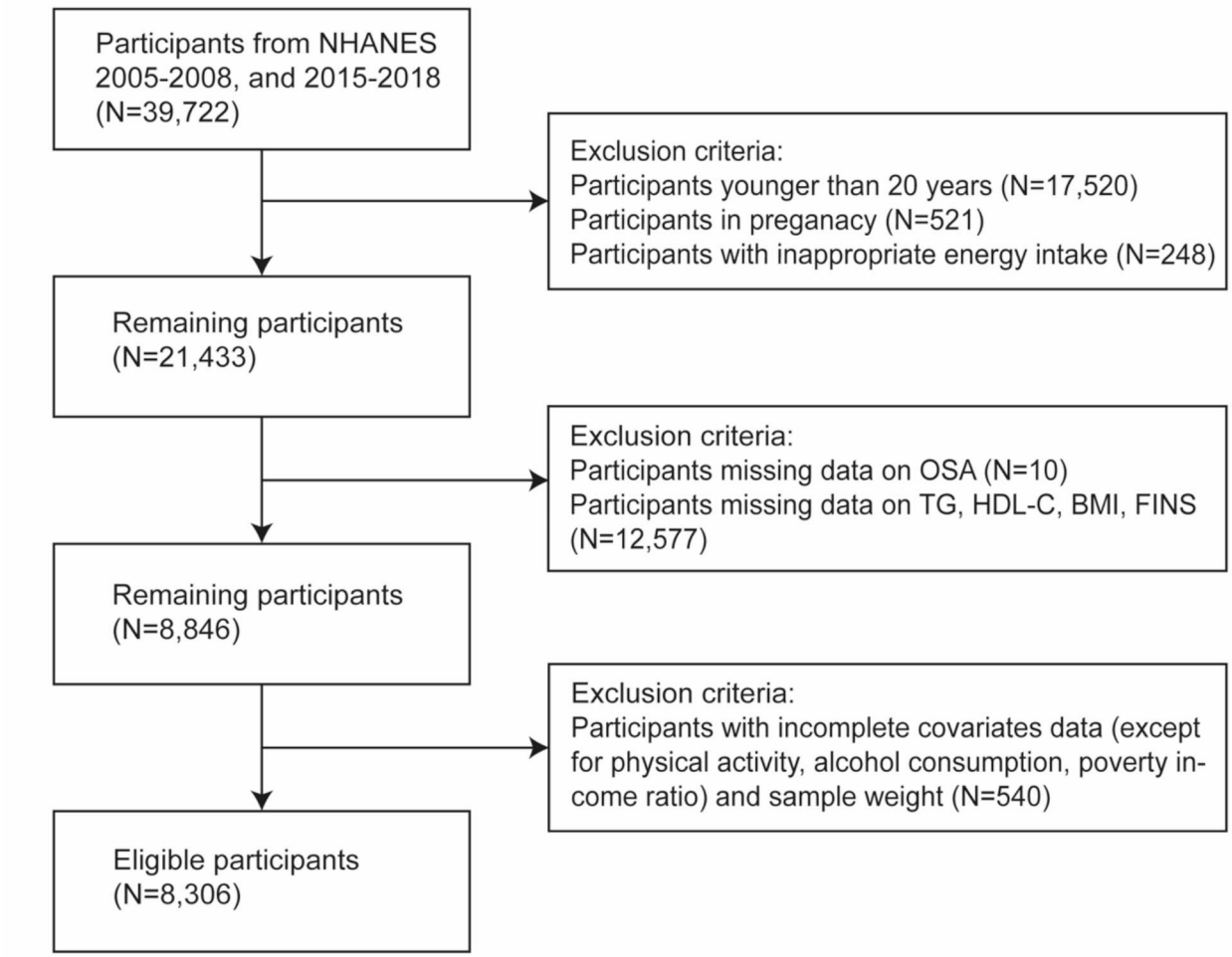

Fig. 1. Flow diagram of participants selection. OSA: obstructive sleep apnea; CVD: cardiovascular disease; FINS: fasting insulin; BMI: body mass index; FBG: fasting blood glucose; HDL-C: high-density lipoprotein cholesterol; TG: triglycerides.

$$\text{HOMA - IR} = \text{FPG (mmol/L)*FINS (mIU/L)} /22.5$$

Diagnosis of obstructive sleep apnea

According to previous studies, participants were considered at high risk for OSA if they met more than one of the following criteria: (1) self-reported snoring more than 3 nights per week; (2) feeling excessively sleepy 16–30 times per month despite having ≥ 7 h of nighttime sleep, whether on weekdays or weekends; and (3) self-reported episodes of apnea, wheezing, or snorting more than 3 nights per week[35,41].

Covariates

We referred to the covariates used in previous similar studies. Sociodemographic variables included age (continuous), sex (men, women), race (non-Hispanic White, non-Hispanic Black, Mexican American, other), marital status (married/living with partner, divorced/separated/widowed, never married), PIR (< 1.3, 1.3–3.5, ≥ 3.5, unknown), and educational attainment (less than high school, high school graduate, higher than high school). BMI was treated as a continuous variable. Lifestyle factors included smoking status (never smoker, former smoker, current smoker) and drinking status, categorized as never drinker, past drinker, current drinker, and unknown. Current drinkers were further categorized based on alcohol intake: mild (men: ≤ 2 cups/day, women: ≤ 1 cup/day or ≤ 1 binge per month), moderate (men: ≤ 3 cups/day, women: ≤ 2 cups/day or 2–5 binge per month), and heavy (men: ≥ 4 cups/day, women: ≥ 3 cups/day or ≥ 5 binge per month). Metabolic equivalents (MET) were used to quantify PA, calculated as recommended MET value multiplied by total weekly activity time. Participants were classified into three groups using a cutoff of 600 MET-min/week: low activity, high activity, and unknown.

A diagnosis of hypertension was considered if the average blood pressure, measured at the Mobile Examination Center, met the criteria for hypertension (average systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg), or if they reported being informed by a professional of hypertension or were taking antihypertensive medication. The diagnosis of CVD depended on self-reported history including stroke, coronary artery disease, angina pectoris, myocardial infarction, heart failure and so on. Diabetes was diagnosed if participants met any of the following criteria: (1) self-reported history of diabetes; (2) use of hypoglycemic medication to maintain normal blood glucose levels; (3) FBG ≥ 7.0 mmol/L; or (4) glycosylated hemoglobin A1c (HbA1c) ≥ 6.5%.

Statistical analysis

Following NHANES practice guidelines, appropriate weights were applied to account for the complex stratified sampling approach, aiming to generalize statistical results to the entire U.S. noninstitutionalized population. The fasting subsample sampling weight (wtsaf2 year) was adjusted as wtsaf2 year/4 to adhere to the principle of least-subsample weighting. Independent sample t-tests (for continuous variables) and chi-square tests (for categorical variables) were used to show the baseline characteristics of participants with and without OSA. Continuous variables were reported as means with standard errors, while categorical variables were presented as frequencies and percentages. Multifactorial logistic regression analysis was employed to investigate the relationship between METS-IR and other indicators of IR with the prevalence of OSA. Three models were constructed: Model 1 was a crude model; Model 2 was partially adjusted for age, sex and race; and Model 3 was fully adjusted, incorporating covariates such as race, gender, age, PIR, marital status, smoking and drinking status, education level, PA, BMI (excluding METS-IR), CVD, diabetes, and hypertension. Nonlinear relationships were assessed using restricted cubic spline (RCS) curves based on covariates adjusted in Model 3. The area under the curve (AUC) represented the diagnostic value of these IR indicators for OSA, in the receiver operating characteristic (ROC) curves. Subgroup analyses were conducted based on age, sex, race, BMI, hypertension, diabetes, and CVD to assess the robustness of the relationship between different IR indicators and OSA.

Results

Comparison of baseline characteristics

A total of 8,306 participants (4,098 men and 4,208 women) were included. The mean METS-IR was 43.12(0.26), and the prevalence of OSA amounted to 30.69%. As shown in Table 1, participants were stratified into OSA and non-OSA groups to compare their baseline characteristics. Individuals in the OSA group exhibited higher levels of METS-IR, TG/HDL-C, TyG index and HOMA-IR compared to the non-OSA group. Additionally, significant differences were observed in variables such as age, BMI, gender, marital status, education level, smoking status, alcohol consumption, PA, diabetes, CVD, and hypertension between the two groups.

Association of METS-IR and other surrogate indices of insulin resistance with OSA

As we can see in Table 2, all four IR indices were positively related to the prevalence of OSA across three multifactorial logistic regression models. In model 3, for each unit increase in METS-IR, TyG index, TG/HDL-C, and HOMA-IR, the prevalence of OSA increased by 4%, 23%, 3%, and 1%, respectively (METS-IR: OR = 1.04, 95% CI: 1.03, 1.05, *P*-value < 0.0001; TyG index: OR = 1.23, 95% CI: 1.09, 1.39, *P*-value = 0.001; TG/HDL-C: OR = 1.03, 95% CI: 1.01, 1.05, *P*-value = 0.014; HOMA-IR: OR = 1.01, 95% CI: 1.00, 1.02, *P*-value = 0.037). After adjusting for all potential confounders, participants in the highest tertile of METS-IR had a prevalence of OSA 2.96 times higher than those in the lowest tertile (METS-IR: OR = 2.96, 95% CI: 2.50, 3.52, *P*-value < 0.0001). Similarly, participants in the highest tertiles of TyG index, TG/HDL-C, and HOMA-IR had ORs for OSA of 1.29, 1.42, and 1.41, respectively, compared to those in the lowest tertiles (TyG index: OR = 1.29, 95% CI: 1.07, 1.55, *P*-value = 0.008; TG/HDL-C: OR = 1.42, 95% CI: 1.17, 1.73, *P*-value < 0.001; HOMA-IR: OR = 1.41, 95% CI:

Variables	Total ($N=8,306$)	Non-OSA ($N=5,757$)	OSA ($N=2,549$)	*P*-value
Age (years)	47.58(0.35)	46.93(0.39)	49.03(0.43)	< 0.0001
Gender (%)				< 0.0001
Female	4208(51.34)	3026(53.94)	1182(45.56)	
Male	4098(48.66)	2731(46.06)	1367(54.44)	
Race (%)				0.696
Non-Hispanic Black	1715(10.98)	1182(10.88)	533(11.20)	
Non-Hispanic White	3450(67.03)	2362(66.75)	1088(67.64)	
Mexican American	1387(8.43)	977(8.59)	410(8.08)	
Other	1754(13.56)	1236(13.77)	518(13.09)	
Marital status (%)				< 0.0001
Never married	1372(17.17)	1026(18.91)	346(13.31)	
Divorced/separated/widowed	1846(18.50)	1319(19.24)	527(16.86)	
Married/living with partner	5088(64.33)	3412(61.85)	1676(69.83)	
Education (%)				< 0.001
Below high school	923(5.70)	663(5.93)	260(5.17)	
High school graduate	3095(34.75)	2109(32.88)	986(38.90)	
Above high school	4288(59.55)	2985(61.19)	1303(55.93)	
PIR (%)				0.054
<1.3	2115(17.63)	1464(17.63)	651(17.63)	
1.3–3.5	3069(34.85)	2087(33.72)	982(37.36)	
≥3.5	2382(40.81)	1667(41.64)	715(38.97)	
Unknown	740(6.71)	539(7.01)	201(6.04)	
PA (%)				0.049
<600	1635(20.80)	1128(20.23)	507(22.06)	
≥600	4497(58.89)	3144(59.98)	1353(56.47)	
Unknown	2174(20.31)	1485(19.79)	689(21.47)	
Drinking status (%)				0.011
Never	1037(9.89)	795(10.96)	242(7.52)	
Former	1153(11.17)	771(10.86)	382(11.84)	
Mild	2625(35.04)	1782(34.37)	843(36.51)	
Moderate	1137(15.57)	796(15.98)	341(14.67)	
Heavy	1448(19.26)	989(18.84)	459(20.21)	
Unknown	906(9.07)	624(8.99)	282(9.26)	
Smoking status (%)				< 0.0001
Never	4543(53.76)	3299(56.36)	1244(48.01)	
Former	2135(26.01)	1429(25.36)	706(27.44)	
Now	1628(20.23)	1029(18.28)	599(24.55)	
BMI (kg/m^2)	29.08(0.14)	28.05(0.16)	31.36(0.18)	< 0.0001
Hypertension (%)				< 0.0001
No	4674(62.30)	3427(66.01)	1247(54.06)	
Yes	3632(37.70)	2330(33.99)	1302(45.94)	
CVD (%)				< 0.001
No	7317(90.89)	5150(91.78)	2167(88.92)	
Yes	989(9.11)	607(8.22)	382(11.08)	
Diabetes (%)				< 0.0001
No	6633(85.67)	4749(87.99)	1884(80.54)	
Yes	1673(14.33)	1008(12.01)	665(19.47)	
HDL-C (mg/dL)	54.80(0.32)	56.42(0.38)	51.21(0.42)	< 0.0001
Continued				

Variables	Total ($N=8,306$)	Non-OSA ($N=5,757$)	OSA ($N=2,549$)	*P*-value
TG (mg/dL)	124.24(1.43)	117.12(1.62)	140.05(2.36)	< 0.0001
METS-IR	43.12(0.26)	41.06(0.28)	47.68(0.34)	< 0.0001
TG/HDL-C	2.74(0.04)	2.50(0.05)	3.26(0.08)	< 0.0001
TyG index	8.59(0.01)	8.52(0.01)	8.75(0.02)	< 0.0001
HOMA-IR	3.55(0.07)	3.10(0.07)	4.54(0.14)	< 0.0001

Table 1. Weighted comparison of baseline characteristics. Comparisons of categorical variables using the chi-square test. Continuous variables were compared using t-test. BMI: body mass index; PIR: poverty income ratio; PA: physical activity; CVD: cardiovascular disease; OSA: obstructive sleep apnea; HDL-C: high-density lipoprotein cholesterol; TG: triglyceride; METS-IR: metabolic score for insulin resistance; TyG index: triglyceride glucose index; HOMA-IR: homeostatic model assessment of insulin resistance.

Exposures	Model1 [OR (95% CI) *P*-value]	Model2 [OR (95% CI) *P*-value]	Model3 [OR (95% CI) *P*-value]
METS-IR (Continuous)	1.04(1.04,1.05) < 0.0001	1.04(1.04,1.05) < 0.0001	1.04(1.03,1.05) < 0.0001
METS-IR (Tertiles)			
T1 (≤ 35.73)	ref	ref	ref
T2 (35.73–45.04)	1.70(1.39,2.07) < 0.0001	1.61(1.31,1.96) < 0.0001	1.57(1.28,1.93) < 0.0001
T3 (> 45.04)	3.31(2.80,3.90) < 0.0001	3.18(2.70,3.74) < 0.0001	2.96(2.50,3.52) < 0.0001
P for trend	< 0.0001	< 0.0001	< 0.0001
TG/HDL-C (Continuous)	1.07(1.05,1.10) < 0.0001	1.07(1.04,1.10) < 0.0001	1.03(1.01,1.05) 0.014
TG/HDL-C (Tertiles)			
T1 (≤ 1.29)	ref	ref	ref
T2 (1.29–2.50)	1.62(1.39,1.90) < 0.0001	1.58(1.35,1.86) < 0.0001	1.24(1.05,1.47) 0.013
T3 (> 2.50)	2.32(2.01,2.67) < 0.0001	2.21(1.90,2.58) < 0.0001	1.42(1.17,1.73) < 0.001
P for trend	< 0.0001	< 0.0001	< 0.001
TyG index (Continuous)	1.64(1.49,1.81) < 0.0001	1.59(1.43,1.76) < 0.0001	1.23(1.09,1.39) 0.001
TyG index (Tertiles)			
T1 (≤ 8.22)	ref	ref	ref
T2 (8.22–8.73)	1.55(1.32,1.81) < 0.0001	1.49(1.28,1.75) < 0.0001	1.17(0.97,1.39) 0.090
T3 (> 8.73)	2.12(1.81,2.47) < 0.0001	2.00(1.71,2.34) < 0.0001	1.29(1.07,1.55) 0.008
P for trend	< 0.0001	< 0.0001	0.008
HOMA-IR (Continuous)	1.05(1.04,1.07) < 0.0001	1.05(1.03,1.07) < 0.0001	1.01(1.00,1.02) 0.037
HOMA-IR (Tertiles)			
T1 (≤ 1.61)	ref	ref	ref
T2 (1.61–2.98)	1.53(1.31,1.80) < 0.0001	1.52(1.29,1.78) < 0.0001	1.19(0.99,1.42) 0.058
T3 (> 2.98)	2.56(2.18,3.01) < 0.0001	2.49(2.12,2.93) < 0.0001	1.41(1.18,1.69) < 0.001
P for trend	< 0.0001	< 0.0001	< 0.001

Table 2. Weighted logistic regression for association between METS-IR, TG/HDL-C, TyG index, HOMA-IR and the prevalence of OSA. Model 1: Adjusted for no variables. Model 2: Adjusted for race, gender, and age. Model 3: Adjusted for gender, age, race, PIR, alcohol consumption, smoking status, marital status, PA, BMI (exception of METS-IR), education level, hypertension, diabetes, and CVD.

1.18, 1.69, *P*-value < 0.001). These findings indicate that METS-IR exhibits the strongest association with OSA prevalence.

In the RCS curves adjusting for all potential confounders, the associations of METS-IR, HOMA-IR, and TG/HDL-C with OSA were nonlinear (*P* for nonlinear < 0.05) (Fig. 2A, B, D), while the association of TyG index with OSA was linear (*P* for nonlinear > 0.05) (Fig. 2C).

Comparing the diagnostic value of different surrogate indices of IR for OSA

Further weighted ROC curves were plotted to assess the diagnostic value of various surrogate indicators of IR for OSA. In diagnosing OSA, METS-IR exhibited the highest accuracy with an AUC of 0.652. The diagnostic values of the other indices in descending order were HOMA-IR (AUC = 0.616), TG/HDL-C (AUC = 0.600), and TyG index (AUC = 0.600) (Fig. 3).

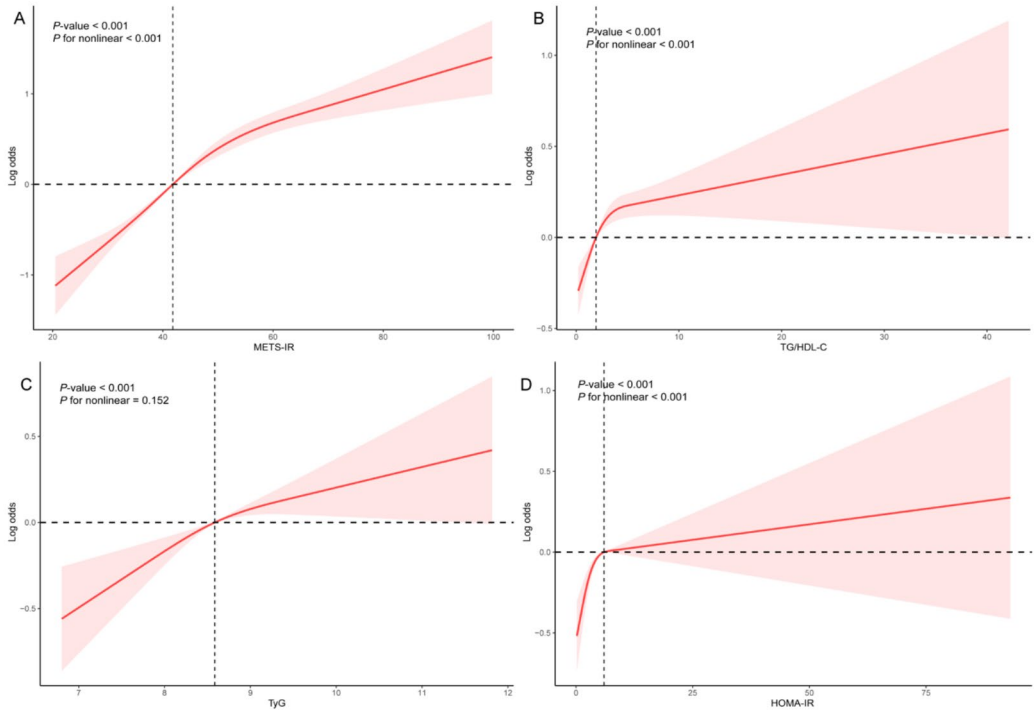

Fig. 2. Weighted RCS curves for association between METS-IR, TG/HDL-C, TyG index, HOMA-IR and the prevalence of OSA. Adjusted for gender, age, race, PIR, alcohol consumption, smoking status, marital status, PA, BMI (exception of METS-IR), education level, diabetes, hypertension, and CVD. The red shaded areas represent the 95% CI.

Subgroup analysis

Subgroup analyses and interaction tests examine the robustness of the association between different IR surrogate indices and OSA. As depicted in Fig. 4, there is a significant interaction between METS-IR and diabetes, with the association between METS-IR and OSA is more pronounced in the non-diabetic population (*P* for interaction < 0.05). However, the association between METS-IR and OSA was not influenced by sex, age, race, BMI, hypertension, or CVD (*P* for interaction > 0.05). Furthermore, the associations between HOMA-IR, TG/HDL-C, TyG index, and OSA remain stable in most cases (*P* for interaction > 0.05). Nevertheless, all three indicators exhibit significant interactions with diabetes (*P* for interaction < 0.05), and their positive associations with OSA disappear in the diabetic population (Supplementary Figs. 1–3).

Discussion

This groundbreaking study investigates, for the first time, the association between METS-IR and OSA. We conducted large cross-sectional study of U.S. adults and found that increased levels of METS-IR were related to a higher prevalence of OSA, surpassing the associations observed with the TyG index, HOMA-IR and TG/HDL-C. The RCS curves demonstrated a nonlinear positive association between METS-IR levels and OSA. METS-IR also exhibited superior diagnostic accuracy for OSA compared to the other three surrogate indicators of IR. Furthermore, the positive associations between these four IR indices and OSA remain stable in most cases; however, all of them show significant interactions with diabetes.

OSA is a prevalent worldwide sleep disorder that poses a significant public health threat. There are evidence suggesting a bidirectional association between OSA and MetS as well as diabetes[23–25]. Large retrospective cohort studies have indicated that diabetic patients face a 48–53% increased risk of OSA compared to non-diabetic individuals[42,43]. Conversely, the risk of diabetes among those with OSA is 2.06 times higher than in those without OSA[43]. IR has an important effect on the pathogenesis of MetS and diabetes, sparking interest among researchers in exploring its potential relationship with OSA. In prospective studies involving diabetic patients, those requiring insulin to maintain normoglycemia demonstrated a higher risk of OSA compared to those not needing insulin therapy[42,43]. Moreover, intensive glucose-lowering therapy has shown benefit in reducing OSA severity, as evidenced by decreased apnea-hypopnea index (AHI) and reduced sleep time with oxygen saturation below 90%[44]. These findings suggest that IR may contribute to the risk of OSA. A prospective cohort study highlighted that increased FINS levels, but not HbA1c, associated with an increased risk of OSA[45]. A study conducted by Balkau et al. found that each unit increase in FINS or HOMA-IR was connected with a 31% increase in the risk of incident OSA after logarithmic transformation[36]. These studies demonstrated that IR may have a significant influence on the pathogenesis of OSA. Minimum oxyhemoglobin saturation (SO2) and the AHI are commonly used to assess OSA severity. A study involving Japanese subjects identified a positive association between HOMA-IR and AHI and SO2[37]. In addition, fragmented sleep, a hallmark of OSA, has been

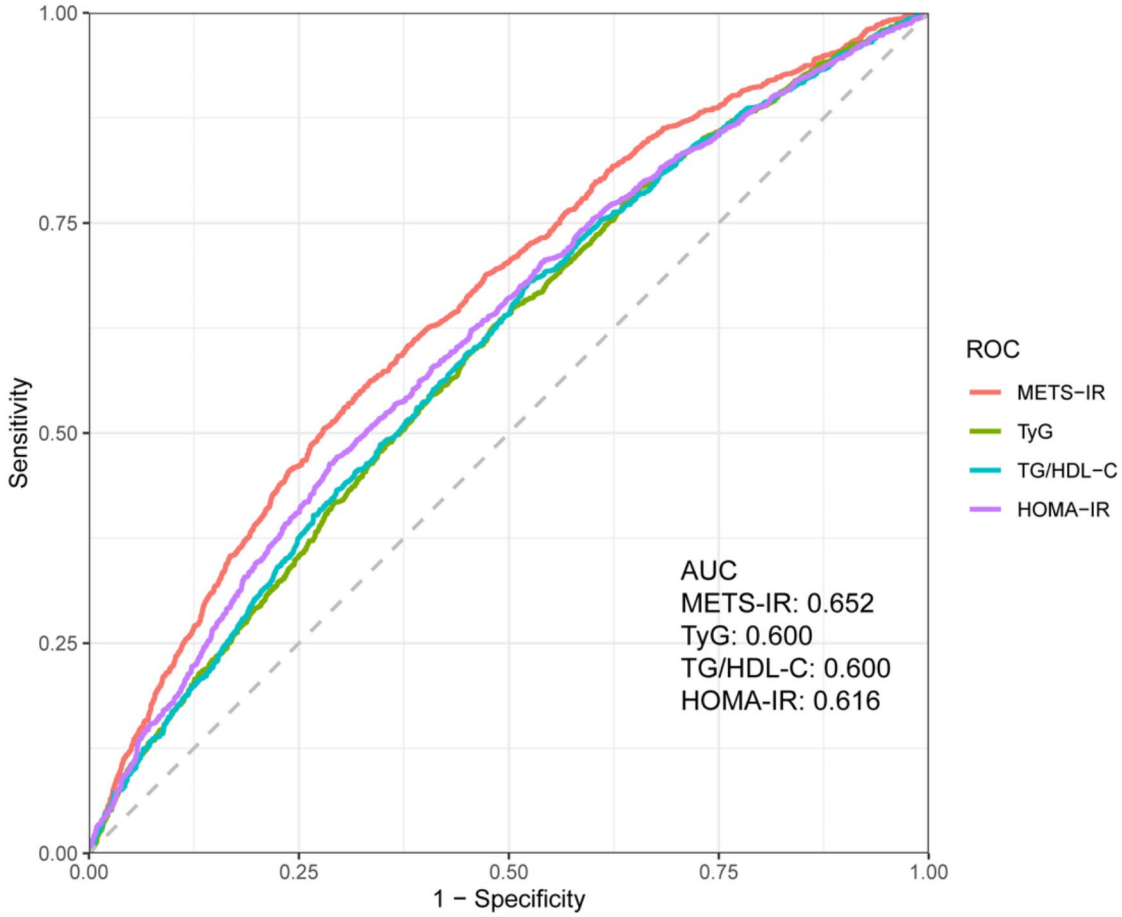

Fig. 3. Weighted ROC curves for METS-IR, TG/HDL-C, TyG index, HOMA-IR.

linked to decreased IR[30]. Moderate to severe OSA patients receiving continuous positive airway pressure (CPAP) treatment can reduce the risk of developing type 2 diabetes from 2.51 times to 1.35 times[46]. Taken together, these results reveal a potential bidirectional relationship between OSA and IR.

FINS presents challenges for generalization in developing and remote areas, and is susceptible to exogenous insulin and islet insufficiency, leading to the limitations of HOMA-IR[13]. Consequently, researchers have turned their attention to IR assessment metrics independent of insulin levels. The TyG index, a novel non-insulin-dependent metric, has gained popularity for predicting CVD and its prognosis. Wang et al. suggest a significant positive association between the TyG index and OSA[33], a finding consistent across Korean and non-obese, non-diabetic populations[34,47]. Another non-insulin IR metric, VAI, has emerged as a potential predictor of OSA, particularly among individuals under 60 years old[35]. In 2018, Bello-Chavolla et al. introduced the METS-IR concept, integrating TG, HDL-C, FBG, and BMI, demonstrating its superiority in predicting diabetes risk through prospective cohort studies[16]. METS-IR is increasingly recognized for its efficiency, simplicity, and affordability in IR assessment. Zeng et al. observed a 2.89-fold increase in hypertension prevalence among participants in the highest quartile of METS-IR compared to the lowest quartile, suggesting its potential utility in assessing hypertension risk[17]. Additionally, several studies have independently linked higher METS-IR levels with cancer, depression, and CVD[18,48,49]. METS-IR demonstrates superior diagnostic efficacy over TyG and TG/HDL-C index by effectively accounting for the impact of overnutrition on IR[16]. A recent prospective cohort study conducted in the U.S. revealed stronger associations of METS-IR with cardiovascular and all-cause mortality in general population compared to the TyG index, HOMA-IR, and TG/HDL-C[21]. METS-IR illustrated superior predictive accuracy for major adverse cardiovascular events relative to the TyG index and its variants (TyG-BMI, TyG-WC) as well as TG/HDL-C, especially in patients diagnosed with both MetS and heart failure[50]. In non-diabetic populations, METS-IR shows the strongest association with hyperuricemia and performs with optimal diagnostic accuracy[22]. Therefore, the present study focused on METS-IR. Consistent with findings from previous studies, our research confirms a potential positive association between METS-IR and OSA. Moreover, METS-IR exhibited superior diagnostic utility compared to the TyG index, TG/HDL-C, and HOMA-IR. Additionally, variables such as sex, age, race, BMI, hypertension, and CVD did not show significant interactions, highlighting the broad applicability of METS-IR. These findings indicate that improving IR may contribute to reducing the risk of OSA to some extent. Furthermore, METS-IR provides a simpler, inexpensive and more accurate method to early identify individuals at high risk of OSA in clinical practice.

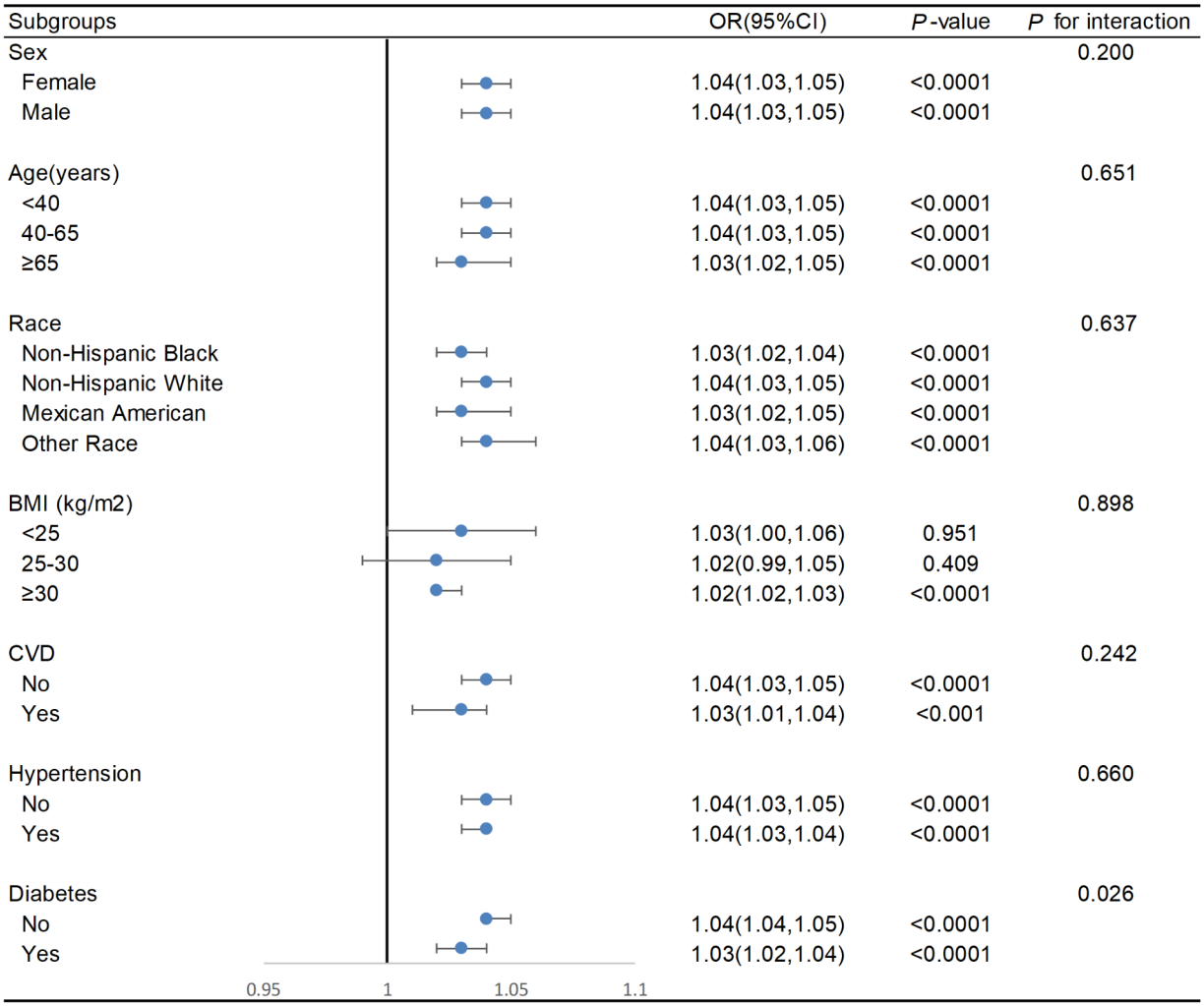

Fig. 4. Subgroup analysis of the association between METS-IR and the prevalence of OSA. Adjusted for gender, age, race, PIR, alcohol consumption, smoking status, marital status, PA, education level, diabetes, hypertension, and CVD, except the subgroup factors themselves. CVD: cardiovascular disease; BMI: body mass index; OR: Odds Ratio.

However, the specific mechanisms underlying the association between the increased prevalence of IR and OSA remain unclear and may involve several aspects. On the one side, IR potentially increases the risk of OSA. At the animal level, mice with diabetes or concurrent IR exhibit long-term chronic hyperglycemia, which desensitizes the CB to hypoxic and hypercapnic stimuli, thereby reducing respiration and impairing ventilation[51,52]. This ventilation abnormality can be effectively reversed with medications that counteract IR, such as metformin[53]. Clinically, in non-diabetic obese women, the severity of IR relates with the degree of upper airway collapse during sleep[54]. In addition, the prevalence of OSA in diabetic patients with autonomic neuropathy (AN) is higher than in those without AN[55]. The severity of IH in obese diabetic patients also associates with AN[56], suggesting that chronic hyperglycemia and AN in the context of IR may contribute to an increased risk of OSA. On the other side, OSA can exacerbate IR and abnormalities in glucose-lipid metabolism. IH and fragmented sleep patterns are hallmark features of OSA and are considered primary contributors to IR in these patients[57–59]. Specifically, nocturnal IH inhibits insulin receptor expression in peripheral tissues such as adipose and skeletal muscle cells[60], triggering pathological processes like oxidative stress and inflammation through repeated cycles of hypoxia and reoxygenation. These processes can lead to apoptosis of pancreatic islet β-cells, ultimately resulting in decreased insulin sensitivity and elevated glucose levels[61–63]. Furthermore, fragmented sleep exacerbates IR by stimulating sympathetic nerves and activating the adrenocortical axis[30]. Hypoxia-inducible factor 1 (HIF-1) serves as a critical regulator in the body's adaptive response to low oxygen levels[64]. Hyperglycemia or hyperlipidemia create a hypoxic environment within cells[65,66], inhibiting the stability and transcriptional activity of HIF-1α, leading to impaired adaptation to hypoxic conditions and compromised ventilation[67–69]. Conversely, knocking down HIF-1α in adipocytes significantly improves IR in mice[66].

Additionally, the subgroup analysis revealed significant interactions between METS-IR, TyG, TG/HDL-C, HOMA-IR, and diabetes. Specifically, the association between METS-IR and OSA was significantly stronger in the non-diabetic population compared to the diabetic population. The associations between TyG, TG/HDL-C, and HOMA-IR with OSA were only significant in the non-diabetic population. This may be explained by the fact that, compared to the non-diabetic population, the metabolic system in diabetic patients is impaired, with more pronounced insulin resistance. As a result, other factors, such as obesity, age, and genetic susceptibility, may become the primary drivers of OSA in diabetic patients.

Limitations and strengths

The participants in this study were exclusively from NHANES, ensuring a large sample size and reliable sample quality. Additionally, we weighted all samples to ensure the findings are applicable to a broad spectrum of U.S. noninstitutionalized residents. Further subgroup analyses could help assess the generalizability of this association across different populations. However, there are serval limitations in our study. First, this was cross-sectional study, making it difficult to identify the causal relationship between METS-IR and OSA. Secondly, the use of sleep questionnaires for diagnosing OSA has been applied in several previous NHANES studies, demonstrating that this method is reasonably reliable. However, it is important to note that, although individuals meeting the diagnostic criteria belong to a high-risk OSA group, they cannot be definitively diagnosed with OSA. This limitation may introduce a certain degree of bias in the study results. Lastly, the study was confined to adult Americans, necessitating validation in ethnically diverse populations for broader generalization of the findings.

Conclusion

In conclusion, the METS-IR index was positively associated with the prevalence of OSA and demonstrated superior diagnostic value for OSA compared to the HOMA-IR, TyG index, and TG/HDL-C. Therefore, active management of IR may deserve to be recommended for individuals at high risk of OSA. In comparison with other IR indices, the METS-IR index appears to be more suitable for early identifying individuals at high risk of OSA in clinical practice.

Data availability

The raw data for this article are publicly available in the NHANES repository (http://www.cdc.gov/nchs/nhanes/).

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Author contributions
H.Y.Y and W.H were responsible for processing and visualizing the data, and drafting the original manuscript. B.J.Y contributed to the design of the study and reviewed the manuscript. All authors read and approved the final manuscript.

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Declarations

Competing interests
The authors declare no competing interests.

Ethical approval
NHANES is a publicly available database, approved by the Institutional Review Board of the National Center for Health Statistics. All participants provided written informed consent when conducting a national survey in the United States. Since this study was a secondary analysis, ethical review and approval were exempted.

Additional information
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