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Liver steatosis mediates the association between metabolic score for insulin resistance and obstructive sleep apnea

Shangyi Song[2,3], Xuhao Li[2,3], Yecun Liu[1], Xingxin Wang[2], Wenhui Zhang[2], Jiguo Yang[2]✉ & Yuanxiang Liu[1]✉

Obstructive sleep apnea (OSA) is associated with metabolic disorders such as insulin resistance and liver fat accumulation. However, the specific mediating role of liver-related metabolic indicators in this association has not been fully studied. The purpose of this study was to investigate the relationship between Metabolic Score for Insulin Resistance (METS-IR) and OSA, focusing on the mediating effects of liver fat percentage (PLF) and hepatic steatosis index (HSI). Understanding these mechanisms may provide insights into targeted interventions for OSA. A total of 12,655 participants from the National Health and Nutrition Examination Survey (NHANES) were included in this analysis. Obstructive sleep apnea (OSA) was assessed using the NHANES questionnaire. Weighted multivariate logistic regression was employed to assess the relationship between METS-IR and OSA, with a mediation model constructed to explore the mediating roles of key liver and metabolic markers, including PLF, HSI, SII and OBS. Among 12,655 subjects, 31.04% had OSA. METS-IR was closely related to the increased risk of OSA, and the highest quartile group of METS-IR had a significantly increased risk of OSA (OR = 2.36, 95% CI 1.73–3.23). Mediating effect analysis showed that PLF and HSI mediated 6.95% and 17.87% of the effects, respectively, while systemic immunity-inflammation index (SII) and oxidative balance score (OBS) had no significant mediating effect. METS-IR is an important predictor of OSA risk, primarily mediated by hepatic lipid accumulation. Addressing insulin resistance and hepatic metabolic health is crucial for the effective management of OSA and provides valuable guidance for clinical risk assessment in susceptible populations.

Keywords Metabolic score for insulin resistance, Obstructive sleep apnea, Percentage of liver fat, Hepatic steatosis index, NHANES

Abbreviations

NHANES	National Health and Nutrition Examination Survey
CDC	Centers for Disease Control and Prevention
METS-IR	Metabolic Score for Insulin Resistance
PLF	Percentage of liver fat
HSI	Hepatic Steatosis Index
SII	Systemic Immunity-inflammation Index
OBS	Oxidative Balance Score
NAFLD	Non-alcoholic fatty liver disease
BMI	Body mass index
PIR	A ratio of family income to the poverty threshold

Obstructive sleep apnea syndrome (OSA) is a prevalent sleep disorder characterized by repeated partial or complete blockage of the upper airway during sleep, leading to intermittent breathing interruptions and hypoxemia[1]. These recurring episodes of apnea not only severely disrupt the patient's nighttime sleep quality, but also lead to excessive daytime sleepiness, cognitive impairment, and a significant reduction in overall quality

[1]College of First Clinical Medical, Shandong University of Traditional Chinese Medicine, Jinan, China. [2]College of Acupuncture and Massage, Shandong University of Traditional Chinese Medicine, Jinan, China. [3]Shangyi Song and Xuhao Li contributed equally to this work. ✉email: Sdyangjiguo@126.com; lyxlwtg@126.com

of life[2]. More critically, OSA is closely linked to a range of metabolic disorders and cardiovascular diseases, including type 2 diabetes, hypertension, coronary artery disease, and stroke[3,4]. In recent years, the global rise in obesity rates has contributed to a rapid increase in OSA prevalence, posing significant challenges for public health[5].

Although a large number of studies have revealed the correlation between OSA and cardiovascular and metabolic diseases, there is still a lack of in-depth understanding of its potential metabolic mechanisms[6]. Insulin resistance is considered to be one of the core mechanisms linking OSA and metabolic syndrome. Insulin resistance is not only closely related to metabolic syndrome, but also interacts with pathological processes such as visceral fat accumulation, chronic inflammation and oxidative stress, which may play a key role in the pathogenesis of OSA[7]. The excessive activation of sympathetic nerve and oxidative stress induced by intermittent hypoxemia in OSA patients are important causes of insulin resistance, and insulin resistance further aggravates metabolic disorders.

In recent years, the metabolic insulin resistance score (METS-IR), as a new metabolic index, can effectively evaluate the individual's insulin resistance[8]. METS-IR combines a variety of metabolic-related parameters, such as waist circumference, triglyceride (TG) and fasting blood glucose, serving as a reliable alternative indicator of metabolic syndrome and metabolic dysfunction. In view of the important role of insulin resistance in the pathogenesis of OSA, METS-IR provides a new perspective to understand how metabolic disorders affect OSA.

Hepatic steatosis involves abnormal liver fat accumulation, is often linked to obesity, insulin resistance, and metabolic syndrome. Percentage of liver fat (PLF) and hepatic steatosis index (HSI) are key markers for assessing liver fat buildup and functional impairment[9,10]. In OSA patients, liver fat accumulation is common and correlates with heightened insulin resistance and metabolic disturbances[11]. Over time, excessive liver fat can lead to non-alcoholic fatty liver disease (NAFLD), further disrupting metabolic balance and elevating the risk of cardiovascular events[12]. Liver dysfunction may also exacerbate OSA by worsening insulin resistance and systemic inflammation.

Systemic inflammation plays a significant role in the metabolic consequences of OSA. OSA often triggers sympathetic overactivation, driving a chronic inflammatory state. The systemic immunity-inflammation index (SII), based on neutrophil, platelet, and lymphocyte ratios, measures systemic inflammation. Elevated SII in OSA patients suggests ongoing low-grade inflammation, which not only aggravates insulin resistance but may also directly contribute to OSA progression by affecting the respiratory system's inflammatory state[13].

Oxidative stress arises when the body's antioxidant defenses are overwhelmed by free radicals, resulting in cell damage[14]. OSA-induced intermittent hypoxia increases oxidative stress, particularly in the cardiovascular and respiratory systems[15]. This stress impairs endothelial function, promoting vascular sclerosis and increasing the risk of cardiovascular events[16]. Elevated oxidative balance score (OBS) in OSA patients indicate persistent oxidative stress, highlighting its role as another key mechanism linking OSA to metabolic dysfunction[17,18].

Based on this background, the purpose of this study is to systematically evaluate the association between METS-IR and OSA by analyzing large-scale data from the National Health and Nutrition Survey (NHANES), and to focus on the mediating role of PLF, HSI, SII and OBS in this association. However, it is important to note that while metabolic markers offer methods for evaluating participants, they cannot detect OSA in its early stages. By revealing the mediating effects of these metabolic markers, this study provides a new clinical perspective for the early identification and intervention of OSA.

Methods

Study design and participants

The National Health and Nutrition Examination Survey (NHANES) is an ongoing national program designed to gather comprehensive data regarding the dietary patterns and overall health of the U.S. population. Before beginning data collection, participants provided written informed consent, and all study procedures received approval from the ethical review board of the National Center for Health Statistics. Additional details about the NHANES program are available on its official website.

This cross-sectional study utilized data from the National Health and Nutrition Examination Survey (NHANES) from 2005–2008 and 2015–2020, including participants aged 20 years and older (n = 29,763). Participants with missing data required to calculate the Metabolic Score for Insulin Resistance (METS-IR) and the four mediators—percentage of liver fat (PLF), hepatic steatosis index (HSI), systemic immunity-inflammation index (SII) and oxidative balance score (OBS) were excluded (n = 17,105). Additionally, data from participants with missing or incomplete information required for an obstructive sleep apnea syndrome (OSA) diagnosis were excluded from the analysis (n = 3). The final sample size included in the analysis was 12,655 participants (Fig. S1).

Definitions of the exposure variable, mediating variable and outcome variable

The exposure variable in this study is the Metabolic Score for Insulin Resistance (METS-IR), which serves as a predictor for insulin resistance and metabolic health. Data for calculating METS-IR were obtained from the NHANES database. The formula used is: $\text{METS - IR} = \frac{Ln(2\times FPG+TG)}{Ln(BMI\times HDL-C)}$, where FPG stands for fasting plasma glucose, TG stands for triglycerides, BMI is the body mass index, and HDL-C refers to high-density lipoprotein cholesterol[8].

The mediating variables in this study were percentage of liver fat (PLF), hepatic steatosis index (HSI), systemic immunity-inflammation index (SII) and oxidative balance score (OBS). These markers are linked to liver fat accumulation, inflammation, and oxidative stress, which are key metabolic processes associated with OSA. The formulas for calculating each of these mediators are as follows:

$$\mathrm{PLF}\ (\%) = 10^{(-0.805+0.282\times\text{metabolic syndrome}+0.078\times\text{type2diabetes}+0.525\times\log(\text{insulin})+0.521\times\log(\text{AST})-0.454\times\log(\text{AST/ALT}))}.$$

AST stands for aspartate aminotransferase (a liver enzyme indicating liver damage when elevated), ALT stands for alanine aminotransferase (another enzyme indicating liver injury), and insulin represents fasting insulin levels. This formula incorporates metabolic syndrome and type 2 diabetes as binary variables (yes/no)[9].

$$\mathrm{HSI} = 8 \times \mathrm{ALT/AST} + \mathrm{BMI} + 2 \times (\text{if diabetes}) + 2 \times (\text{if female})\ .$$

BMI is body mass index, and ALT and AST are the liver enzymes. Diabetes and female sex are included as binary variables[19,20].

$$\mathrm{SII} = \frac{Platelet\ count \times Neutrophil\ count}{Lymphocyte\ \mathrm{count}}$$

The OBS combines 16 dietary components and four lifestyle factors, with higher scores indicating greater antioxidant exposure. Tobacco use was assessed via the cotinine test, and alcohol consumption was categorized into nondrinkers, nonheavy drinkers, and heavy drinkers, with scores of 2, 1 and 0, respectively. Antioxidants were scored higher in upper tertiles, while pro-oxidants were inversely scored[17].

In accordance with earlier studies, the outcome variable OSA is diagnosed when a person answers 'yes' to at least one of the following three NHANES questions[21]: (1) feeling excessively sleepy during the day despite getting at least 7 h of sleep per night, as reported 16–30 times; (2) experiencing episodes of gasping, snorting, or stopping their breath on three or more occasions per week; (3) snoring on three or more occasions every week.

Potential covariates

The self-reported sociodemographic characteristics included age, sex (male/female), race/ethnicity (non-Hispanic White, Mexican American, non-Hispanic Black, other Hispanic, or other Race/multiple Races), education level (less than high school, completed high school, or more than high school), marital status (married/living with a partner, never married, widowed, divorced, or separated) and family poverty index ratio (PIR, a ratio of family income to the poverty threshold). BMI was calculated as weight (kg) divided by height (m) squared. Physical activity was assessed by asking participants to report the types of physical activities they engaged in regularly, categorized into vigorous physical activities (e.g., running, playing basketball) and moderate physical activities (e.g., brisk walking, swimming, cycling). Alcohol consumption and smoking status were also treated as categorical variables.

The participants' alcohol consumption status was categorized into five groups: never (fewer than 12 drinks in a lifetime), former (12 or more drinks in a lifetime but none in the previous year), mild (1 + drinks/day for women, 2 + drinks/day for men), moderate (2 + drinks/day for women, 3 + drinks/day for men), and heavy (5 + drinks/day for women, 4 + drinks/day for men). This categorization was based on the number of alcoholic beverages consumed per day, with the following thresholds applied: ≥ 2 drinks/day for women and ≥ 3 drinks/day for men, binge drinking ≥ 2 days/month, and heavy drinking (≥ 3 drinks/day for women and ≥ 4 drinks/day for men, or binge drinking ≥ 5 days/month). The participants were divided into three smoking categories: never smokers (smoked fewer than 100 cigarettes), former smokers (smoked at least 100 cigarettes but not currently smoking), and current smokers (smoked at least 100 cigarettes and currently smoking daily or some days). The definition of metabolic syndrome (MetS) was in accordance with the updated National Cholesterol Education Program/Adult Treatment Panel III criteria for Americans[22]. A history of physician-diagnosed hypertension, a measured average systolic blood pressure of at least 140 mmHg, a measured average diastolic blood pressure of at least 90 mmHg, or a history of antihypertensive medication use were all considered indicators of hypertension[23]. A self-reported diagnosis of diabetes, a fasting plasma glucose level ≥ 7.0 mmol/L, glycosylated hemoglobin (HbA1c) ≥ 6.5%, and/or the usage of anti-diabetic medication were all considered indicators of diabetes[24].

All missing values in this study were handled using appropriate imputation methods: continuous variables were imputed with mean values, while categorical variables were assigned dummy variables[24]. The confounding variables and their detailed definitions are collated in Table S1 for reference. The missing covariates of study participants are summarized in Table S2.

Statistical analyses

The statistical analyses for this study were performed using the R statistical computing environment (version 4.4.0), with the "NhanesR" package (details provided in Table S3). All analyses accounted for the complex, multistage survey design of NHANES by applying sample weights, stratification, and clustering to ensure the results are representative of the U.S. population. Baseline characteristics were summarized using weighted means and 95% confidence intervals (CI) for continuous variables, while categorical variables were expressed as weighted frequencies and percentages. Continuous variables were analyzed using weighted t-tests or Wilcoxon rank-sum tests, depending on the distribution of the data, which was assessed using the Shapiro–Wilk test for normality. Categorical variables were compared using weighted chi-square tests or Fisher's exact tests, where appropriate. Statistical significance was set at $p < 0.05$ for all analyses.

The associations between METS-IR and OSA were investigated using multivariate logistic regression across four distinct models to provide a comprehensive assessment of their relationship. The crude model was unadjusted for covariates, while Model 1 adjusted for age, sex, and race/ethnicity. Model 2 further included education level, marital status, physical activity, smoking status, and alcohol consumption, addressing lifestyle factors that may confound the association. Model 3 incorporated additional controls for the poverty-to-income ratio (PIR), Body Mass Index (BMI), metabolic syndrome, diabetes, and hypertension, thereby accounting for

critical physiological and socioeconomic variables. This methodological framework enhances the reliability of our findings by enabling the simultaneous control of multiple independent variables and yielding odds ratios for binary outcomes like OSA. By thoroughly adjusting for known confounders, we reinforce our conclusions regarding the relationship between METS-IR and OSA, thereby contributing valuable insights into the factors influencing OSA risk. A further assessment of the heterogeneity between METS-IR and OSA was conducted through subgroup analysis, which included the following variables: age, sex, race/ethnicity, smoking status, alcohol consumption, marital status, physical activity, metabolic syndrome, diabetes and hypertension.

The indirect effect of METS-IR on the relationship between METS-IR and OSA was further explored through mediation analysis. Using causal mediation analysis, the indirect and direct effects were evaluated to determine the proportion of the total effect of METS-IR on OSA that could be explained by four mediators: PLF, HSI, SII and OBS. The indirect effect quantified how much of the association between METS-IR and OSA was mediated by these markers, while the direct effect measured the remaining effect not attributed to mediators. The non-parametric bootstrap re-sampling method was employed to estimate confidence intervals and significance levels for the mediation and direct effects, using 1000 bootstrap iterations. The proportion of mediation for each variable was calculated to identify the pathways through which METS-IR influences OSA.

Results

Baseline characteristics

The weighted baseline characteristics of the participants in the study are shown in Table 1. A total of 12,655 participants were included in the analysis, with a mean age of 48.08 years (95% CI 47.47, 48.68). Among them, 49.43% were male and 50.57% were female. The majority of participants identified as non-Hispanic white (66.39%), followed by non-Hispanic black (10.80%), Mexican American (8.52%), other Hispanic origin (5.84%), and other or multi-racial groups (8.45%).

In total, 31.04% of the participants were categorized as having OSA. Across the four METS-IR groups, all variables showed statistical significance. Compared to participants in the lower METS-IR group, those in the highest quartile (Q4) were more likely to be male, older, and non-Hispanic white. They also tended to have higher PLF, HSI, SII and BMI levels, were more likely to be never-smokers or mild drinkers, and had lower levels of physical activity, poverty income ratio (PIR) and OBS. Additionally, these participants exhibited higher educational attainment, were more often widowed, divorced, separated, or never married, and had a greater prevalence of metabolic syndrome and hypertension.

Association between METS-IR and OSA

In the restricted cubic spline (RCS) analysis, METS-IR was positively associated with OSA (Fig. 1). Table 2 presents the associations between METS-IR and the risk of obstructive sleep apnea (OSA) across different models. Whether confounding factors were adjusted or not, METS-IR consistently showed a significant positive correlation with OSA in all participants. In the multivariate regression analysis, METS-IR was divided into quartiles, using the Q1 group as the reference to assess the relationship with OSA.

After adjusting for age, gender, race, education level, marital status, physical activity, smoking, drinking status, PIR, BMI, metabolic syndrome, diabetes and hypertension, compared to the Q1 reference group, the Q2 group (OR: 1.49; 95% CI 1.25, 1.77), Q3 group (OR: 1.72; 95% CI 1.36, 2.19), and Q4 group (OR: 2.36; 95% CI 1.73, 3.23) all exhibited a significantly increased risk, showing a clear upward trend (p for trend < 0.0001). This trend was consistent across all models, indicating that the positive association between METS-IR and the risk of OSA remains stable regardless of adjustments for confounding factors.

Subgroup analysis

Table 3 Subgroup analyses were conducted across various factors, including age (≤ 40 years, 40–60 years, > 60 years), sex (male, female), race/ethnicity (Non-Hispanic White, Non-Hispanic Black, Mexican American, Other Hispanic, and other races), education level (< High School, Completed High School, > High School), smoking status (former smoker, never smoked, current smoker), alcohol consumption (former drinker, heavy drinker, mild drinker, moderate drinker, never drank), marital status (Married/Living with Partner, Widowed/Divorced/Separated/Never married), physical activity (inactive, moderate activity, both moderate and vigorous, vigorous), and the presence of metabolic syndrome (yes or no) to evaluate the stability of the association between METS-IR and OSA. Interaction tests were performed to assess whether these factors influenced the strength of the association between METS-IR and OSA.

The results revealed significant interactions for age (p-interaction = 0.026), smoking status (p-interaction = 0.01), alcohol consumption (p-interaction = 0.029), education level (p-interaction = 0.037), diabetes (p-interaction < 0.0001), hypertension (p-interaction = 0.001) and metabolic syndrome (p-interaction < 0.001), indicating that these factors significantly modified the relationship between METS-IR and OSA. However, despite the significant interactions (p < 0.05), METS-IR remained positively correlated with OSA within these subgroups. No significant interactions were observed for Race/ethnicity (p-interaction = 0.304), sex (p-interaction = 0.507), marital status (p-interaction = 0.983), or physical activity (p-interaction = 0.29), suggesting that the association between METS-IR and OSA remained stable within these subgroups.

Mediation analysis

In this study, four key metabolic markers—PLF, HSI, SII and OBS—were used as mediating variables to explore the relationship between METS-IR and obstructive sleep apnea (OSA). Figures 2, 3, 4 and 5 showed the mediation analysis results.

The mediating effect of PLF was 0.00216 (p < 0.001), accounting for 6.95% of the total effect, while the mediating effect of HSI was 0.00556 (p < 0.001), accounting for 17.87%. In contrast, SII (− 0.0127198, p = 0.95)

Characteristic	Overall	METS-IR Quartiles				*p* value
		Q1 (< 34.596)	Q2 (34.596 to < 41.919)	Q3 (41.919 to < 50.674)	Q4 (≥ 50.674)	
Age, years, mean (95% CI)	48.08 (47.47, 48.68)	45.13 (44.19, 46.06)	49.63 (48.57, 50.70)	49.87 (48.80, 50.93)	48.06 (47.31, 48.81)	< 0.0001
PIR, mean (95% CI)	3.05 (2.98, 3.11)	3.18 (3.09, 3.27)	3.13 (3.03, 3.22)	3.01 (2.92, 3.10)	2.85 (2.74, 2.96)	< 0.0001
BMI, mean (95% CI)	29.19 (28.96, 29.41)	22.30 (22.20, 22.40)	26.76 (26.65, 26.87)	30.43 (30.29, 30.58)	38.29 (37.97, 38.61)	< 0.0001
PLF, mean (95% CI)	4.88 (4.77, 4.99)	2.07 (2.01, 2.13)	3.53 (3.41, 3.66)	5.24 (5.08, 5.41)	9.11 (8.85, 9.37)	< 0.0001
HSI, mean (95% CI)	38.42 (38.16, 38.69)	30.28 (30.13, 30.43)	35.56 (35.38, 35.73)	40.01 (39.82, 40.20)	49.06 (48.71, 49.42)	< 0.0001
OBS, mean (95% CI)	17.90 (17.50, 18.30)	19.65 (19.09, 20.21)	17.73 (17.19, 18.26)	17.02 (16.54, 17.50)	16.96 (16.46, 17.45)	< 0.0001
SII, mean (95% CI)	536.47 (526.25, 546.69)	525.43 (505.21, 545.65)	512.22 (497.06, 527.37)	532.42 (517.38, 547.46)	577.85 (563.82, 591.89)	< 0.0001
Sex, n (%)						< 0.0001
Female	6395 (50.57)	1853 (62.35)	1477 (46.61)	1445 (43.07)	1620 (48.67)	
Male	6260 (49.43)	1312 (37.65)	1685 (53.39)	1719 (56.93)	1544 (51.33)	
Race/ethnicity, n (%)						< 0.0001
Non-Hispanic White	4967 (66.39)	1341 (69.51)	1213 (66.48)	1207 (64.42)	1206 (64.70)	
Other race—including multi-racial	1636 (8.45)	587 (10.76)	448 (8.45)	339 (7.80)	262 (6.48)	
Non-Hispanic Black	2831 (10.80)	692 (9.85)	683 (10.89)	685 (10.44)	771 (12.14)	
Mexican American	1962 (8.52)	305 (5.25)	507 (8.49)	565 (10.17)	585 (10.62)	
Other Hispanic	1259 (5.84)	240 (4.62)	311 (5.69)	368 (7.17)	340 (6.07)	
Educational level, n (%)						< 0.0001
< High school	1290 (5.28)	204 (3.38)	357 (5.77)	391 (6.38)	338 (5.85)	
Completed high school	4676 (34.61)	1135 (30.83)	1116 (33.94)	1194 (35.84)	1231 (38.36)	
> High school	6681 (60.08)	1825 (65.78)	1684 (60.25)	1577 (57.68)	1595 (55.79)	
Marital status, n (%)						< 0.1
Married/Living with partner	5394 (50.41)	1269 (48.34)	1368 (49.86)	1446 (52.82)	1311 (50.91)	
Widowed/Divorced/ Separated/Never married	7254 (49.55)	1894 (51.63)	1792 (50.13)	1717 (47.09)	1851 (49.07)	
Alcohol consumption, n (%)						< 0.0001
Former	1229 (8.77)	221 (6.00)	302 (8.65)	356 (9.87)	350 (10.95)	
Heavy	2203 (18.82)	550 (19.79)	532 (18.07)	516 (18.72)	605 (18.57)	
Mild	4001 (35.21)	1030 (34.60)	1047 (35.54)	981 (35.76)	943 (35.02)	
Moderate	1804 (16.09)	524 (20.05)	418 (15.62)	427 (14.10)	435 (14.01)	
Never	1403 (8.87)	372 (9.49)	355 (9.02)	362 (8.72)	314 (8.18)	
Smoking status, n (%)						< 0.0001
Never smoking	6898 (53.53)	1784 (55.91)	1742 (53.35)	1757 (53.16)	1615 (51.35)	
Former smoker	3195 (26.59)	641 (22.46)	780 (25.47)	842 (28.54)	932 (30.50)	
Current smoker	2549 (19.83)	737 (21.59)	635 (21.12)	563 (18.23)	614 (18.11)	
Physical activity, n (%)						< 0.0001
Inactive	5771 (37.67)	1233 (30.03)	1375 (34.80)	1515 (41.09)	1648 (45.90)	
Moderate	2600 (22.43)	638 (21.35)	660 (23.29)	639 (21.52)	663 (23.70)	
Both moderate and vigorous	1653 (15.64)	570 (22.08)	443 (17.05)	373 (13.95)	267 (8.52)	
Vigorous	743 (6.37)	224 (7.60)	191 (6.29)	174 (6.61)	154 (4.81)	
Metabolic syndrome, n (%)						< 0.0001
No	7830 (65.08)	3054 (97.25)	2456 (80.64)	1555 (53.03)	765 (24.58)	
Yes	4825 (34.92)	111 (2.75)	706 (19.36)	1609 (46.97)	2399 (75.42)	
Diabetes						< 0.0001
No	9810 (83.49)	2929 (95.18)	2656 (89.57)	2343 (81.39)	1882 (66.02)	
Yes	2845 (16.51)	236 (4.82)	506 (10.43)	821 (18.61)	1282 (33.98)	
Hypertension						< 0.0001
Continued						

Characteristic	Overall	METS-IR Quartiles				*p* value
		Q1 (< 34.596)	Q2 (34.596 to < 41.919)	Q3 (41.919 to < 50.674)	Q4 (≥ 50.674)	
No	7054 (61.66)	2255 (77.10)	1822 (63.62)	1668 (58.42)	1309 (45.28)	
Yes	5601 (38.34)	910 (22.90)	1340 (36.38)	1496 (41.58)	1855 (54.72)	
OSA, n (%)						< 0.0001
No	8679 (68.96)	2586 (82.80)	2287 (72.22)	2125 (66.33)	1681 (52.47)	
Yes	3976 (31.04)	579 (17.20)	875 (27.78)	1039 (33.67)	1483 (47.53)	

Table 1. Baseline characteristics of participants in the NHANES 2005–2008 and 2015–2020 (n = 12,655). *NHANES* National Health and Nutrition Examination Survey, *Q* Quantile, *PIR* Ratio of family income to poverty, *BMI* Body mass index, *PLF* Percentage of liver fat, *HSI* Hepatic Steatosis Index, *SII* Systemic Inflammatory Index, *OBS* Oxidative Balance Score, *OSA* Obstructive Sleep Apnea, *METS-IR* Metabolic Score for Insulin Resistance.

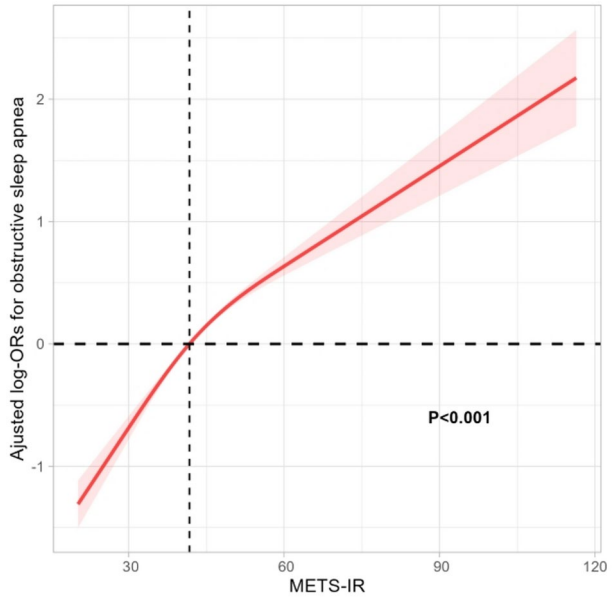

Fig. 1. Restricted cubic spline of the relationship between the METS-IR and the OSA. Age, sex, race/ethnicity, education level, marital status, physical activity, smoking status, alcohol status, the ratio of family income to poverty, body mass index, metabolic syndrome, diabetes and hypertension were adjusted for. The solid line represents the line of best fit, and the pale pink area represents the 95% confidence interval.

and OBS (− 0.000175, $p = 0.21$) did not show significant mediating effects, so no meaningful mediating ratios were calculated. These findings suggest that PLF and HSI play a key mediating role in the relationship between METS-IR and OSA, emphasizing the critical role of liver fat accumulation in this pathway. Conversely, the mediating effects of SII and OBS were not significant, indicating that systemic inflammation and oxidative stress may have a minimal impact on the association between insulin resistance and OSA.

Furthermore, the direct effect of METS-IR on OSA remains significant, highlighting the need to consider insulin resistance when assessing OSA risk. Addressing liver health through PLF and HSI may be an effective strategy to mitigate the risk of OSA associated with insulin resistance.

Discussion

This study is the first comprehensive analysis of how liver fat accumulation, systemic inflammation and oxidative stress mediate the relationship between METS-IR and OSA. We found that in a nationally representative sample, higher METS-IR scores were significantly associated with increased OSA risk, and liver fat accumulation estimated by PLF and HSI played a key mediating role. This suggests that insulin resistance captured by METS-IR promotes OSA mainly through liver metabolic dysfunction. Interestingly, SII and OBS did not show a significant mediating effect in this pathway, suggesting that although inflammation and oxidative stress are associated with OSA[14,15], they may not be the core mechanisms linking METS-IR and OSA. This highlights the importance of addressing liver health issues in managing OSA risk in people with high insulin resistance.

METS-IR combines fasting blood glucose, triglycerides and BMI to form a comprehensive index of insulin resistance, which plays a key role in the pathophysiology of OSA. Insulin resistance exacerbates OSA through

METS-IR	Crude model[a]		Model 1[b]		Model 2[c]		Model 3[d]	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Continuous (per 10 units)	1.50 (1.44, 1.56)	< 0.0001	1.49 (1.44, 1.55)	< 0.0001	1.49 (1.43, 1.55)	< 0.0001	1.30 (1.10, 1.53)	0.002
Quartiles								
Q1 (< 34.596)	Reference		Reference		Reference		Reference	
Q2 (34.596 to < 41.919)	1.85 (1.56, 2.20)	< 0.0001	1.75 (1.47, 2.08)	< 0.0001	1.75 (1.47, 2.08)	< 0.0001	1.49 (1.25, 1.77)	< 0.0001
Q3 (41.919 to < 50.674)	2.44 (2.04, 2.93)	< 0.0001	2.30 (1.91, 2.77)	< 0.0001	2.30 (1.91, 2.77)	< 0.0001	1.72 (1.36, 2.19)	< 0.0001
Q4 (≥ 50.674)	4.36 (3.73, 5.10)	< 0.0001	4.24 (3.63, 4.94)	< 0.0001	4.18 (3.56, 4.90)	< 0.0001	2.36 (1.73, 3.23)	< 0.0001
p for trend	< 0.0001		< 0.0001		< 0.0001		< 0.0001	

Table 2. Multivariable logistic regression models for the association between METS-IR and OSA in adults:NHANES 2005–2008 and 2015–2020. In multivariate regression, samples with missing values for covariates in the model were encoded as dummy variables. The missing values were categorized as "Unknown" and included as a separate category in the analysis. [a]Crude Model: Unadjusted. [b]Model 1: Adjusted for age, sex, and race/ethnicity. [c]Model 2: Adjusted for the variables in Model 1 plus education level, marital status, physical activity,smoking status, and alcohol status. [d]Model 3: Adjusted for the variables in Model 2 plus ratio of family income to poverty,body mass index, metabolic syndrome, diabetes and hypertension. *CI* Confidence interval, *OR* Odds ratio, *Q* Quantile, *METS-IR* Metabolic Score for Insulin Resistance, *OSA* Obstructive Sleep Apnea.

a combination of metabolic disorders driven primarily by intermittent hypoxia (a hallmark of OSA)[25]. This intermittent hypoxia activates the sympathetic nervous system, leading to oxidative stress and systemic inflammation, which in turn deteriorates insulin sensitivity[26]. The resulting increase in visceral fat deposition and lipid metabolism dysfunction further aggravate the severity of OSA[27].

Visceral fat, especially liver and abdominal fat, due to its dual role, is the main trigger factor for OSA: mechanical compression of the upper airway, airway collapse deterioration, and secretion of inflammatory cytokines (such as TNF-α and IL-6)[28]. These pro-inflammatory signals interfere with insulin signaling, enhance insulin resistance and promote further fat accumulation[29]. This forms a vicious cycle, where metabolic dysfunction not only aggravates OSA but also accelerates other cardiovascular risks[30].

In addition, OSA-induced hypoxia leads to oxidative stress, which produces reactive oxygen species (ROS) that destroy the insulin receptor signaling pathway and impairs endothelial function[31]. This vascular health dysfunction is common in OSA patients, which can aggravate their overall metabolic status and promote cardiovascular complications[32]. Therefore, METS-IR can effectively capture these metabolic disorders and is of great significance in assessing OSA risk.

Through mediation analysis, PLF and HSI play a key role in assessing the relationship between liver fat content, METS-IR and OSA. PLF directly estimates liver fat content, reflecting the actual fat accumulation in liver tissue and is closely related to metabolic dysfunction such as insulin resistance and nonalcoholic fatty liver disease. Increased liver fat directly affects insulin signal transduction, aggravates insulin resistance, and promotes common metabolic disorders in OSA patients[33]. This link underscores the central role of liver fat in OSA progression and the need for clinical interventions aimed at reducing liver fat to reduce OSA risk, especially in individuals with high insulin resistance. On the other hand, HSI can be used as an indirect measurement of liver fat, calculated by metabolic factors such as liver enzyme levels (AST/ALT), BMI and the presence of diabetes. An increased HSI value indicates hepatic steatosis, which aggravates insulin resistance and is common in OSA patients. Since HSI is also associated with liver function, strategies to improve liver health such as optimizing liver enzyme levels and addressing NAFLD are crucial[19]. While reducing liver fat, improving liver function may further enhance insulin sensitivity and metabolic regulation[34]. This shows that by changing lifestyle, diet adjustment and drug intervention, not only focusing on lipid reduction but also on clinical strategies to improve liver function can more effectively reduce the impact of insulin resistance on OSA and improve the clinical outcomes of patients with metabolic disorders[35,36].

Although systemic inflammation and oxidative stress are known to play a role in the pathology of OSA, the results of this study show that SII and OBS do not mediate the METS-IR-OSA relationship[15]. This suggests that although chronic low-grade inflammation and oxidative stress are elevated in OSA patients, their effects may not be significant in the case of insulin resistance. Nevertheless, future research should further explore whether SII and OBS play a greater role in specific subpopulations, where the interaction between insulin resistance, inflammation, and oxidative stress may be more pronounced.

Moreover, even after considering the mediating effect of liver fat through PLF and HSI, METS-IR still showed a significant direct association with OSA. This suggests that insulin resistance itself is an independent driver of OSA. Clinicians should give priority to insulin resistance when assessing the risk of OSA.Improving insulin sensitivity by changing lifestyle (such as weight control, physical activity and diet adjustment) can be used as an effective strategy to reduce the risk of OSA.

This study has several advantages. First, the use of NHANES data provides a large, nationally representative sample that enhances the general applicability of the research findings. Additionally, by controlling for various confounding factors and conducting mediation analysis between METS-IR, PLF, HSI, SII, OBS and OSA, we gain a deeper understanding of the metabolic pathways involved in OSA.

Character	95% CI	*p*	*p* for interaction
Age			0.026
≤ 40	1.047 (1.041, 1.053)	< 0.0001	
> 40, ≤ 60	1.042 (1.034, 1.049)	< 0.0001	
> 60	1.032 (1.024, 1.040)	< 0.0001	
Sex			0.507
Female	1.043 (1.039, 1.048)	< 0.0001	
Male	1.041 (1.035, 1.047)	< 0.0001	
Race/ethnicity			0.304
Non-Hispanic White	1.043 (1.038, 1.049)	< 0.0001	
Other race—including multi-racial	1.053 (1.041, 1.065)	< 0.0001	
Non-Hispanic Black	1.038 (1.033, 1.044)	< 0.0001	
Mexican American	1.041 (1.031, 1.051)	< 0.0001	
Other Hispanic	1.046 (1.033, 1.059)	< 0.0001	
Education level			0.037
< High school	1.034 (1.022, 1.047)	< 0.0001	
Completed high school	1.035 (1.029, 1.041)	< 0.0001	
> High school	1.045 (1.039, 1.051)	< 0.0001	
Smoking status			0.01
Former smoker	1.041 (1.034, 1.049)	< 0.0001	
Never smoking	1.047 (1.042, 1.052)	< 0.0001	
Current smoker	1.032 (1.024, 1.041)	< 0.0001	
Alcohol status			0.029
Former	1.038 (1.027, 1.049)	< 0.0001	
Heavy	1.032 (1.021, 1.043)	< 0.0001	
Mild	1.049 (1.041, 1.057)	< 0.0001	
Moderate	1.046 (1.035, 1.057)	< 0.0001	
Never	1.031 (1.018, 1.044)	< 0.0001	
Marital status			0.983
Married/Living with partner	1.041 (1.034, 1.049)	< 0.0001	
Widowed/Divorced/Separated/Never married	1.041 (1.037, 1.046)	< 0.0001	
Physical activity			0.29
Inactive	1.040 (1.033, 1.046)	< 0.0001	
Moderate	1.037 (1.029, 1.044)	< 0.0001	
Both moderate and igorous	1.053 (1.039, 1.067)	< 0.0001	
Vigorous	1.046 (1.027, 1.066)	< 0.0001	
Metabolic syndrome			< 0.001
No	1.047 (1.040, 1.054)	< 0.0001	
Yes	1.030 (1.024, 1.036)	< 0.0001	
Diabetes			< 0.0001
No	1.045 (1.040, 1.050)	< 0.0001	
Yes	1.028 (1.022, 1.034)	< 0.0001	
Hypertension			0.001
No	1.032 (1.026, 1.037)	< 0.0001	
Yes	1.046 (1.040, 1.053)	< 0.0001	

Table 3. Associations of METS-IR with OSA by different factors.

However, one limitation is that the assessment of OSA relied on self-report questionnaires, which may introduce recall and detection bias. Participants might misinterpret or fail to accurately remember their symptoms. Although this approach allows for a comprehensive sample, it introduces uncertainties regarding assessment accuracy. Future research should utilize objective measures, such as polysomnography, to validate these findings.

Despite this limitation, our results are significant as they reveal important pathways linking components of metabolic syndrome with OSA risk, highlighting the need to address metabolic health in this population. This can provide valuable insights into how targeted interventions aimed at improving metabolic health can help reduce the risk of OSA.

Looking ahead, future experiments could involve longitudinal studies to investigate how changes in metabolic syndrome components over time impact the development and progression of OSA. Additionally, randomized

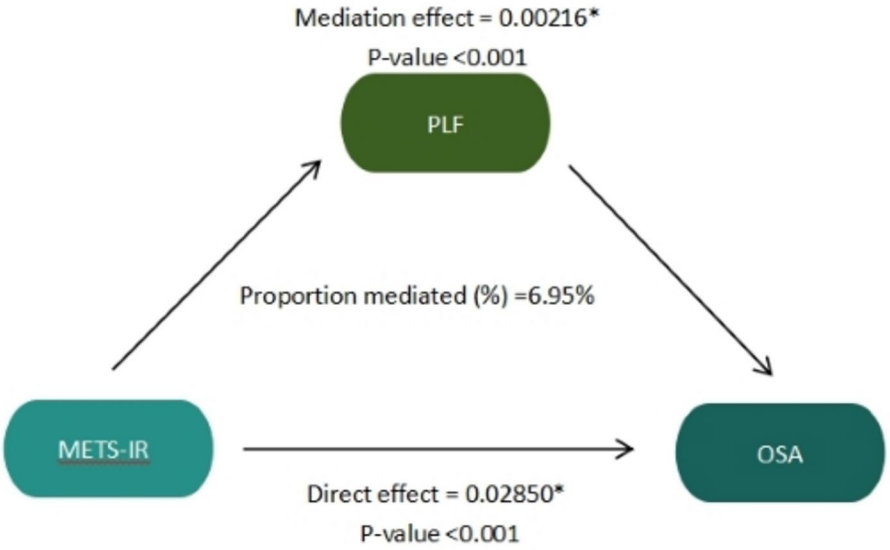

Fig. 2. PLF as a Mediator between METS-IR and OSA.

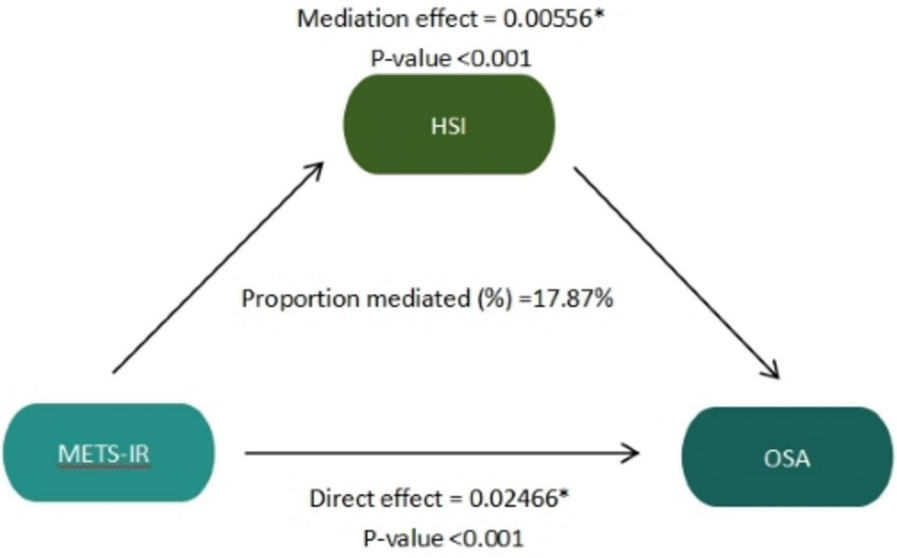

Fig. 3. HSI as a Mediator between METS-IR and OSA.

controlled trials of interventions that focus on improving metabolic health, such as dietary modifications or exercise programs, could provide further evidence of their effectiveness in reducing OSA risk. By expanding our research to include these experimental approaches, we can deepen our understanding of the connections between metabolic health and OSA and develop more effective preventative strategies for at-risk populations.

Conclusion

This study shows that the METS-IR is significantly associated with the risk of OSA, in which PLF and HSI play a key mediating role. As scoring systems, PLF and HSI capture liver metabolic abnormalities and play a crucial role in connecting insulin resistance and OSA. The results suggest that improving liver health and managing insulin resistance may be effective strategies to reduce OSA risk in people with high METS-IR scores. Future research should focus on improving these scoring systems in order to better predict and manage OSA risks and apply them to clinical practice.

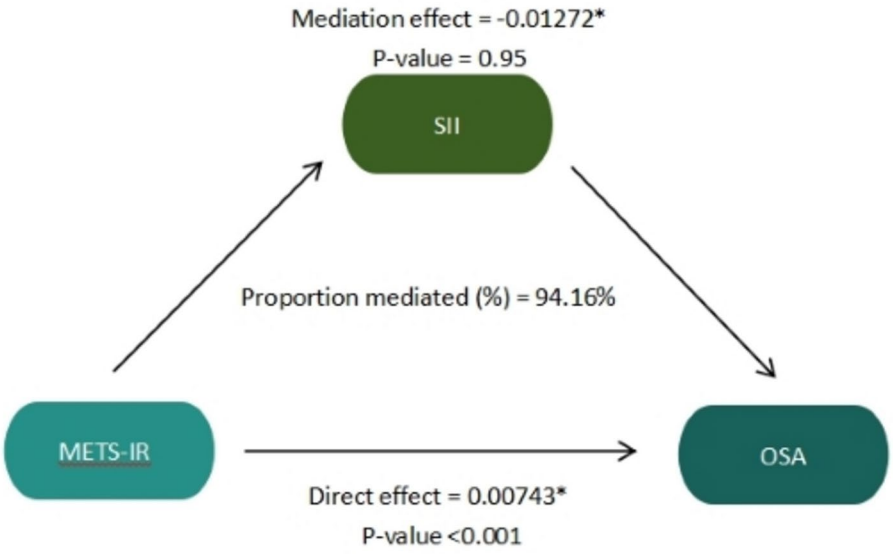

Fig. 4. SII as a Mediator between METS-IR and OSA.

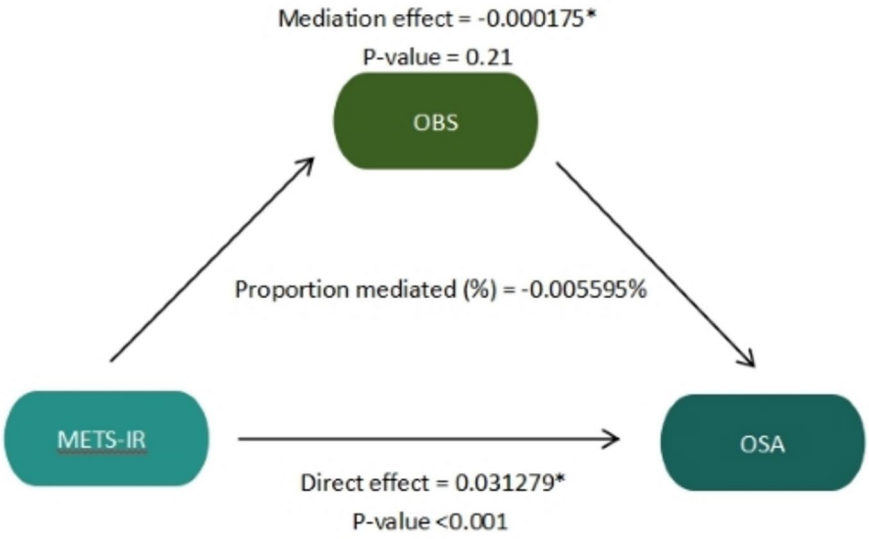

Fig. 5. OBS as a Mediator between METS-IR and OSA.

Data availability

The data used in this study are available on the National Health and Nutrition Examination Survey website: https://www.cdc.gov/nchs/nhanes/index.htm

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Author contributions

S.Y.S. participated in the literature search, study design, data collection, data analysis, data interpretation and wrote the manuscript. X.H.L., Y.C.L., X.X.W. and W.H.Z. conceived the study and participated in its design, coordination, data collection and analysis. J.G.Y. and Y.X.L. participated in the study design and provided critical revision. All the authors read and approved the final manuscript.

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Declarations

Competing interests
The authors declare no competing interests.

Ethics approval and consent to participate
The National Center for Health Statistics Research Ethics Review Board authorized the NHANES study protocols in compliance with the revised Declaration of Helsinki. All participants provided informed consent.

Additional information
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Correspondence and requests for materials should be addressed to J.Y. or Y.L.

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