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ORIGINAL RESEARCH

The Triglyceride-Glucose Index Mediates the Association Between Obstructive Sleep Apnea and Non-Alcoholic Fatty Liver Disease: Findings From Two Cross-Sectional Datasets

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Purpose: Obstructive sleep apnea (OSA) contributes to non-alcoholic fatty liver disease (NAFLD) via pathways involving insulin resistance (IR). The triglyceride-glucose (TyG) index, a widely used marker of IR, is associated with both OSA and NAFLD. However, the role of the TyG index in linking OSA to NAFLD remains underexplored.

Patients and Methods: This study analyzed data from two cross-sectional studies: 920 participants from the Fifth Affiliated Hospital of Sun Yat-sen University and 1,603 participants from NHANES 2005–2008. Mediation analysis assessed the TyG index's role in the OSA-NAFLD relationship. Weighted multivariable logistic regression and restricted cubic spline (RCS) regression explored the association between the TyG index and NAFLD in patients with OSA.

Results: Mediation analysis showed the TyG index mediated the OSA-NAFLD association, accounting for 35.33% and 20.06% in Chinese and American participants, respectively ($P < 0.001$). Logistic regression revealed that higher TyG index values were significantly associated with increased NAFLD risk in patients with OSA, with ORs of 2.32 (95% CI: 1.78–3.07) for Chinese and 6.80 (95% CI: 4.42–10.45) for American participants ($P < 0.001$). RCS regression showed a linear increase in NAFLD risk with higher TyG index values in patients with OSA.

Conclusion: The TyG index significantly mediates the OSA-NAFLD relationship. Elevated TyG index values are significantly associated with NAFLD risk in patients with OSA. The TyG index is a biologically meaningful and effective biomarker of IR in the association between OSA and NAFLD, with potential for early identification of NAFLD in patients with OSA.

Keywords: insulin resistance, mediation analysis, non-alcoholic fatty liver disease, obstructive sleep apnea, triglyceride-glucose index

Introduction

Obstructive sleep apnea (OSA), the most widespread sleep-related breathing disorder, impacts an estimated 936 million adults aged 30–69 years worldwide.[1] With recurrent upper airway collapse, narrowing, and obstruction, OSA results in intermittent hypoxemia (IH), hypercapnia, and frequent nocturnal awakenings.[2] Beyond its direct respiratory impacts, OSA is frequently associated with a range of comorbidities, including hepatic, cardiovascular, renal, and neuropsychiatric disorders, and is considered an independent contributor to many of these conditions.[3] Nonalcoholic fatty liver disease (NAFLD), affecting about 25% of the global population, represents the most common chronic liver disorder associated with metabolic dysregulation, predisposing individuals to cirrhosis and hepatocellular carcinoma.[4] Emerging evidence underscores the co-occurrence of OSA and NAFLD, with substantial evidence supporting that OSA is involved in the

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initiation and progression of NAFLD.[5–8] The high prevalence and frequent co-occurrence of these two conditions impose a significant economic burden on global healthcare systems.

Recent research has drawn attention to the correlation between OSA and NAFLD, particularly the mechanisms by which OSA exacerbates NAFLD. IH, a hallmark of OSA, induces oxidative stress, inflammation, mitochondrial dysfunction, excessive sympathetic nervous system activation, and other maladaptive effects.[5,9] These physiological disruptions have been demonstrated to contribute to insulin resistance (IR), dysfunctional lipid metabolism, and hepatic steatosis and fibrosis, all of which are integral to the pathophysiology of NAFLD.[5,6] Among these mechanisms, IR is considered a critical mechanism through which OSA contributes to the development of NAFLD.[5,6]

The triglyceride-glucose (TyG) index, calculated as ln (fasting triglycerides [mg/dL] × fasting blood glucose [mg/dL]/2), is an established and widely recognized marker of IR.[10,11] The TyG index has shown superior efficacy in assessing IR, sometimes outperforming the steady-state model of IR assessment (HOMA-IR).[12–14] As a valuable tool in clinical and research settings, the TyG index has been employed in screening and predicting various systemic diseases, including cancer,[15] cardiovascular diseases,[16] cerebrovascular diseases,[17] renal diseases,[18] and OSA.[19,20] Its application in liver disease research, particularly with regard to NAFLD,[21–24] further underscores its relevance as an effective, biologically significant marker of IR.

Considering the pivotal role of IR in linking OSA and NAFLD, the TyG index is hypothesized to be a significant factor in this relationship. However, research specifically examining the role of the TyG index in the connection between OSA and NAFLD remains limited. To address this gap, this research focused on evaluating the mediating role of the TyG index in the OSA-NAFLD connection and quantifying its contribution by mediation analysis. Based on the findings of the mediation analysis, we further investigate the association of the TyG index with NAFLD specifically in patients with OSA to better understand its potential clinical implications.

Method

Study Participants

This study conducted a cross-sectional analysis of 1,397 adult individuals (≥ 20 years old) who underwent overnight polysomnography at the Sleep Medicine Center of the Department of Otolaryngology at the Fifth Affiliated Hospital of Sun Yat-sen University from June 2022 to July 2023. We excluded 439 individuals with liver conditions other than NAFLD, or significant alcohol use (>20 g/d for women, >30 g/d for men), or incomplete abdominal ultrasonography data; 32 individuals with missing fasting blood glucose or triglyceride data; and 6 individuals with missing covariate data. As a result, 920 participants were included in the final analysis.

Among global populations, China reported the highest prevalence of OSA, followed closely by the United States.[1] To ensure the generalizability and reproducibility of our findings, we also performed a secondary cross-sectional analysis utilizing data from the National Health and Nutrition Examination Survey (NHANES) 2005–2008. Using a complex, multistage probability sampling approach, NHANES gathers data that represents the US population.[25] The 2005–2008 NHANES dataset included 20,497 participants, with 10,914 individuals aged 20 years and older eligible for analysis. After excluding 3 individuals lacking OSA diagnosis data, 9,213 individuals missing NAFLD diagnosis data[26] (including those with significant alcohol consumption, incomplete alcohol consumption information, presence of viral hepatitis [positive for serum hepatitis C antibody or for serum hepatitis B surface antigen], incomplete viral hepatitis information, or incomplete data needed for the calculation of the US Fatty Liver Index [USFLI] score[27]), 3 individuals with missing fasting blood glucose or triglyceride data, and 92 individuals with missing covariate data, 1,603 participants were ultimately included.

Definitions of Exposure, Mediator, and Outcome

For the Chinese participants in our study, all individuals underwent overnight polysomnography at the Sleep Medicine Center. OSA was diagnosed following the criteria in the International Classification of Sleep Disorders (Third Edition) (ie, Apnea-Hypopnea Index (AHI) ≥ 5/h accompanied by daytime or nighttime symptoms or comorbidities; AHI ≥ 15/h regardless of symptoms or comorbidities). OSA severity was classified into three subgroups: mild (AHI 5–15/h), moderate (AHI 16–30/h), and severe (AHI > 30/h). The control group consisted of subjects with an AHI < 5/h. For the American participants, OSA status was assessed using the four-item STOP questionnaire (covering Snoring, Tiredness, Observed apnea, and high

Pressure), which has been validated against polysomnography in diverse, multiethnic cohorts and has demonstrated high sensitivity.[28,29] This questionnaire has been widely applied in several previous studies.[30,31] OSA was defined by any of the following criteria, derived from self-reported sleep disorder questionnaires: diagnosed sleep apnea by a doctor; snoring at least three nights weekly; snorting, gasping, or stopping breathing at least three nights weekly; excessive daytime sleepiness occurring 16–30 times monthly on weekdays or work nights.

All participants provided blood samples following at least 8 hours of fasting. Laboratory biochemical parameters, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT), fasting triglycerides, and fasting blood glucose, were evaluated by an automated analyzer following standard methods. To calculate the TyG index, the following formula was used: ln (fasting triglycerides [mg/dL] × fasting blood glucose [mg/dL]/2).[10]

For the Chinese participants, NAFLD was diagnosed through abdominal ultrasound.[32,33] For the American participants, NAFLD was defined using the USFLI. The USFLI was developed based on the NHANES III dataset and has demonstrated relatively higher accuracy than the fatty liver index within the NHANES population.[27] This index has been validated and widely applied in several previous studies.[34,35] NAFLD was defined as a USFLI score exceeding 30, which has been shown to achieve good diagnostic accuracy in NHANES, with an AUC of 0.80, a sensitivity of 62%, and a specificity of 88%.[27]

Covariates

Covariates with potential modifying effects on the associations between OSA and NAFLD were selected. For the Chinese participants, age and gender information were gathered using self-reported questionnaires. Body mass index (BMI) was computed as weight (kg) per height squared (m^2), and participants were classified into obesity (BMI ≥ 28) and non-obesity (BMI < 28) groups. Smoking status was determined according to their response to the question, "Have you ever smoked in your lifetime?". A diagnosis of hypertension was based on a medical history of hypertension, ongoing antihypertensive treatment, or an average blood pressure of ≥140/90 mmHg. Diabetes was determined by a previous diagnosis, active use of oral hypoglycemic drugs or insulin, a fasting blood glucose level reaching ≥7.0 mmol/L, or a glycohemoglobin (HbA1c) level of ≥6.5%.

For the American participants, demographic information was collected through self-reported interviews, including age, gender, race, educational level, marital status, and family income-to-poverty ratio (PIR). Mexican Americans, non-Hispanic white individuals, and non-Hispanic black individuals were included, and their respective USFLI scores were calculated.[27] Educational level was categorized as "high school or less" and "high school graduate or higher." Marital status was identified as either "married/living with a partner" or "alone" (never married, widowed, divorced, or separated). Family PIR was grouped within three categories: ≤130%, >130% to 350%, and >350% of the federal poverty threshold. American participants were categorized into obesity (BMI ≥ 30) and non-obesity (BMI < 30) groups. Smoking status was stratified across three classifications: current smokers, former smokers, and non-smokers, according to answers to two questions: "Have you smoked at least 100 cigarettes in your entire life?" and "Do you now smoke cigarettes?" The definitions of hypertension and diabetes were consistent with those used for the Chinese participants.

Statistical Analysis

Descriptive statistics for baseline characteristics were shown as frequency (percentage) for categorical variables and mean (standard deviation) for continuous variables. Differences between groups were assessed using t-tests, chi-square tests, or Mann–Whitney *U*-tests as appropriate. Mediation analysis was conducted following the method proposed by Professor VanderWeele[36] to examine whether the TyG index mediates the association of OSA with NAFLD. In accordance with the prerequisites for mediation analysis, the research data were required to satisfy the following criteria: (1) OSA and the TyG index must be associated with NAFLD, analyzed using multivariate logistic regression adjusted for covariates; (2) OSA must be associated with the TyG index, evaluated via multivariate linear regression adjusted for covariates; and (3) the correlation between OSA and NAFLD should diminish when the TyG index is included in the regression models. If these aforementioned conditions were satisfied, mediation analysis was performed to determine whether the TyG index mediates the relationship between OSA and NAFLD. The size of the mediation effect was quantified by calculating the ratio of the indirect effect to the total effect, with covariates adjusted to minimize the impact of confounding factors. The significance of the mediation effect was evaluated through bootstrap sampling (times = 1000). Furthermore, based on the mediation analysis results, we investigated the association of the TyG index with NAFLD specifically in patients with OSA using multivariate logistic regression and restricted cubic spline (RCS) regression. For the NHANES data, the sampling design complexity was taken into account. R software (version 4.3.1) was used for all analyses, and statistical significance was set at a two-tailed P-value <0.05.

Results

Baseline Characteristics

This study included two cross-sectional analyses: 920 participants representative of the Chinese population, recruited from the Fifth Affiliated Hospital of Sun Yat-sen University, and 1,603 participants representative of the US population, derived from NHANES data. Participants were categorized according to whether NAFLD was present or absent. Baseline characteristics are presented in Table 1 and Supplementary Table S1 for Chinese and American participants, respectively. Except for marital status and family PIR in the American participants, significant differences were observed across

Table 1 Baseline Characteristics of the Chinese Population

Characteristic	Total	Non-NAFLD	NAFLD	P Value
Total	N=920	N=505	N=415	
Age, year	52.03 (13.01)	53.41 (13.34)	50.36 (12.42)	0.008
Sex, n (%)				<0.001
Male	579 (62.93)	298 (59.01)	281 (67.71)	
Female	341 (37.07)	207 (41.99)	134 (32.29)	
BMI, n (%)				<0.001
Non-obesity	577 (62.72)	396 (78.42)	181 (43.61)	
Obesity	343 (37.28)	109 (21.58)	234 (56.39)	
Smoking status, n (%)				0.007
No	690 (75.00)	397 (78.61)	293 (70.60)	
Yes	230 (25.00)	108 (21.39)	122 (29.40)	
Hypertension, n (%)				<0.001
No	520 (56.52)	315 (62.38)	205 (49.40)	
Yes	400 (43.48)	190 (37.62)	210 (50.60)	
Diabetes, n (%)				0.002
No	779 (84.67)	445 (88.12)	334 (80.48)	
Yes	141 (15.33)	60 (11.88)	81 (19.52)	
OSA, No. (%)				<0.001
No	197 (21.41)	149 (29.50)	48 (11.57)	
Mild	189 (20.55)	111 (21.98)	78 (18.80)	
Moderate	184 (20.00)	86 (17.03)	98 (23.61)	
Severe	350 (38.04)	159 (31.49)	191 (46.02)	
ALT, U/L	28.98 (44.95)	22.33 (23.38)	37.02 (60.74)	<0.001
AST, U/L	22.49 (16.88)	20.18 (15.19)	25.28 (18.36)	<0.001
GGT, U/L	38.67 (41.16)	32.35 (32.50)	46.34 (48.64)	<0.001
Triglyceride, mg/dL	176.62 (188.78)	147.03 (132.12)	212.62 (235.57)	<0.001
Fasting glucose, mg/dL	108.30 (38.66)	101.99 (31.12)	115.99 (45.06)	<0.001
TyG index	8.90 (0.70)	8.69 (0.65)	9.15 (0.68)	<0.001
TyG index				<0.001
T1 (≤ 8.57)	304 (33.04)	229 (45.35)	75 (18.07)	
T2 (8.57–9.13)	311 (33.81)	157 (31.09)	154 (37.11)	
T3 (> 9.13)	305 (33.15)	119 (23.56)	186 (44.82)	

Notes: Values were presented as the mean (standard errors) or sample numbers (percentages). Group differences were assessed using the *t*-test or the chi-square test (P value <0.05 indicates statistical significance).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; GGT, gamma-glutamyl transferase; NAFLD, nonalcoholic fatty liver disease; OSA, obstructive sleep apnea; TyG index, triglyceride-glucose index; T, tertile.

demographic, anthropometric, comorbidities, and serum biomarker parameters between non-NAFLD and NAFLD groups in both populations. Notably, the NAFLD group showed significantly increased OSA prevalence and TyG index compared to the non-NAFLD group in both populations. Among Chinese participants, those with NAFLD also exhibited higher OSA severity compared to their non-NAFLD counterparts.

The Mediating Role of the TyG Index in the Association Between OSA and NAFLD

Relationship Between OSA and NAFLD

The association between OSA and NAFLD among Chinese and American participants is presented in Table 2. In Chinese participants, Models 1–3 revealed a robust and statistically significant association between OSA and NAFLD. In Model 3, after adjusting for potential confounders, the odds ratio (OR) for this association was 2.17 [95% confidence interval (CI): 1.47–3.24]. Similarly, in American participants, OSA was identified as a significant risk factor for NAFLD, with an OR of 1.96 (95% CI: 1.25–3.07) in Model 3. Furthermore, in Chinese participants, stratified analysis revealed significant associations between moderate and severe OSA and NAFLD, while the correlation between mild OSA and NAFLD was not statistically significant. Importantly, in Model 4, when the TyG index was included, the correlation of OSA with NAFLD was attenuated, with the OR decreasing to 1.68 (95% CI: 1.12–2.54) in Chinese participants and to 1.92 (95% CI: 1.19–3.08) in American participants. Additionally, the correlations between mild, moderate, and severe OSA and NAFLD in Chinese participants were similarly weakened after adjusting for the TyG index. These findings suggest that the TyG index may act as a mediator in the relationship between OSA and NAFLD.

Relationship Between the TyG Index and NAFLD

Multivariate logistic regression analyses indicated a positive correlation of the TyG index with NAFLD in both populations (Supplementary Table S2). In Chinese participants, the association between the TyG index and NAFLD was consistently observed across Models 1–3, with ORs of 2.85 (95% CI: 2.29–3.59), 2.77 (95% CI: 2.21–3.50), and 2.29 (95% CI: 1.81–2.92), respectively. Similarly, in American participants, the TyG index demonstrated a positive correlation with NAFLD, with ORs of 10.31 (95% CI: 7.39–14.37), 9.46 (95% CI: 6.67–13.42), and 5.99 (95% CI: 4.21–8.53), respectively.

Relationship Between OSA and the TyG Index

Using multivariate linear regression analyses, this study explored the relationship between OSA and the TyG index. The results demonstrated that, in both Chinese and American participants, OSA was significantly correlated with an increase in TyG index levels (Table 3, Models 1–3). In Model 3, after adjusting for potential confounders, the regression coefficient (β) for the association between OSA and the TyG index was 0.37 (95% CI: 0.26–0.48) in Chinese participants

Table 2 Relationship Between OSA and NAFLD

Characteristic	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 4 OR (95% CI)
Fifth Affiliated Hospital of Sun Yat-sen University				
OSA	3.20 (2.26–4.61)***	3.51 (2.43–5.14)***	2.17 (1.47–3.24)***	1.68 (1.12–2.54)*
OSA Severity				
Mild	2.18 (1.42–3.39)***	2.18 (1.39–3.45)***	1.45 (0.88–2.40)	1.21 (0.72–2.03)
Moderate	3.54 (2.30–5.50)***	3.99 (2.52–6.41)***	2.54 (1.53–4.24)***	2.10 (1.24–3.57)**
Severe	3.73 (2.55–5.53)***	3.59 (2.41–5.44)***	2.07 (1.32–3.27)**	1.65 (1.04–2.65)*
National Health and Nutrition Examination Survey				
OSA	2.96 (2.03–4.31)***	2.73 (1.83–4.06)***	1.96 (1.25–3.07)**	1.92 (1.19–3.08)**

Notes: Model 1: crude model; Model 2: adjusted for age, sex, and race; Model 3: adjusted for Model 2 + BMI, education level, smoking status, hypertension, and diabetes; Model 4: adjusted for Model 3 + the TyG index. *** $P < 0.001$. ** $P < 0.01$. * $P < 0.05$.
Abbreviations: BMI, body mass index; CI, confidence interval; NAFLD, nonalcoholic fatty liver disease; OSA, obstructive sleep apnea; OR, odds ratio; TyG index, triglyceride-glucose index.

Table 3 Relationship Between OSA and the TyG Index

Characteristic	Model 1 β (95% CI)	Model 2 β (95% CI)	Model 3 β (95% CI)
Fifth Affiliated Hospital of Sun Yat-sen University			
OSA	0.49 (0.38–0.60)***	0.47 (0.37–0.58)***	0.37 (0.26–0.48)***
OSA Severity			
Mild	0.39 (0.26–0.53)***	0.37 (0.23–0.51)***	0.27 (0.13–0.40)***
Moderate	0.52 (0.38–0.66)***	0.50 (0.36–0.64)***	0.35 (0.21–0.49)***
Severe	0.53 (0.41–0.64)***	0.48 (0.36–0.59)***	0.37 (0.25–0.50)***
National Health and Nutrition Examination Survey			
OSA	0.24 (0.16–0.31)***	0.19 (0.12–0.26)***	0.09 (0.03–0.15)**

Notes: Model 1: crude model; Model 2: adjusted for age, sex, and race; Model 3: adjusted for Model 2 + BMI, education level, smoking status, hypertension, and diabetes. *** $P < 0.001$. ** $P < 0.01$. * $P < 0.05$.
Abbreviations: β, regression coefficient; BMI, body mass index; CI, confidence interval; OSA, obstructive sleep apnea; TyG index, triglyceride-glucose index.

and 0.09 (95% CI: 0.03–0.15) in American participants. Furthermore, among Chinese participants, the study revealed the positive relationships between different severities of OSA (mild, moderate, and severe) and the TyG index. It was also observed that the β values increased progressively with the severity of OSA.

Mediation Analysis

Mediation analysis was preformed to assess the mediating role of the TyG index in the association of OSA with NAFLD (Figure 1). The analyses revealed significant mediating effects of the TyG index in both Chinese and American participants. Specifically, the TyG index accounted for 35.33% of the association between OSA and NAFLD in Chinese participants and 20.06% in American participants (both P < 0.001). Notably, in Chinese participants, we demonstrated that the mediating effect of the TyG index increased with the severity of OSA. Significant mediation

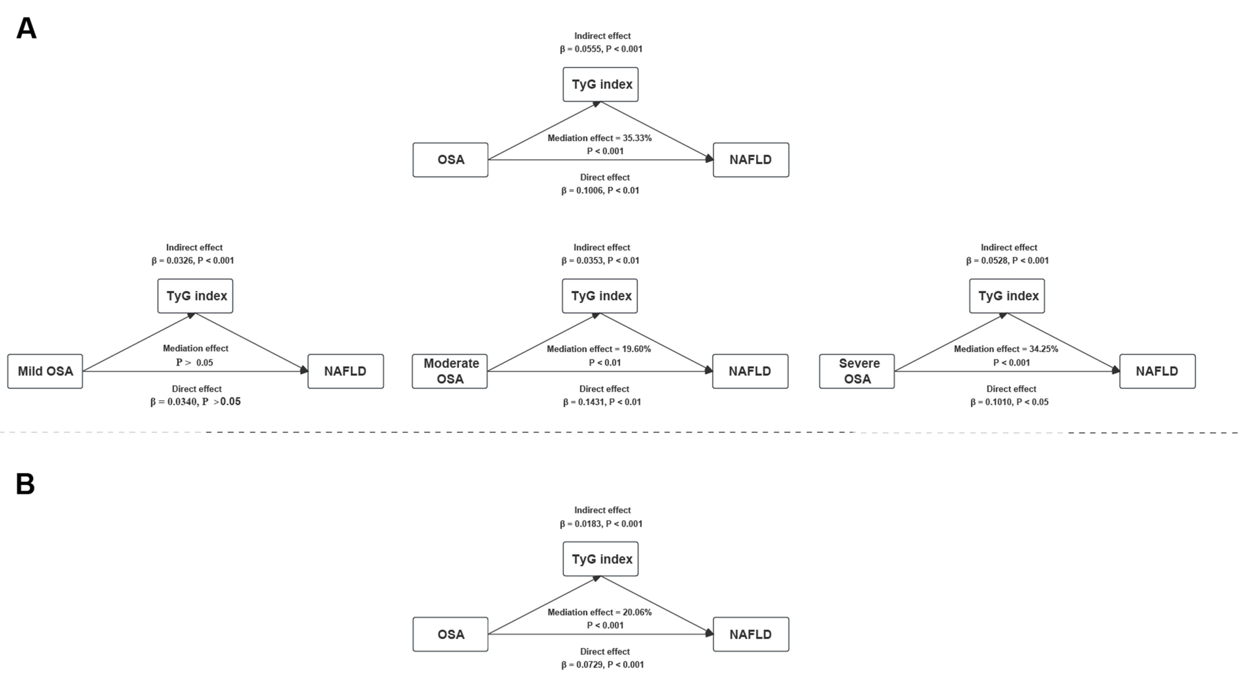

Figure 1 Mediation models of the TyG index in the association between OSA and NAFLD in Chinese (**A**) and American (**B**) participants. Adjusted for age, sex, race, BMI, education level, smoking status, hypertension, and diabetes.
Abbreviations: β, regression coefficient; BMI, body mass index; NAFLD, nonalcoholic fatty liver disease; OSA, obstructive sleep apnea; TyG index, triglyceride-glucose index.

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proportions were observed in the relationships between moderate and severe OSA and NAFLD, with mediation proportions of 19.60% and 34.25%, respectively. In contrast, the mediating effect of the TyG index in the relationship between mild OSA and NAFLD was not statistically significant. These findings highlight the increasing contribution of the TyG index as OSA severity progresses.

Association Between the TyG Index and NAFLD in Patients with OSA

Considering the significant mediation effect of the TyG index in the OSA-NAFLD association, we further examined its association with NAFLD in patients with OSA. After adjusting for potential confounders (Table 4, Models 1–3), a significant positive correlation between the TyG index and NAFLD was observed in both Chinese and American patients with OSA. In Model 3, the TyG index showed a significant positive association with NAFLD, with ORs of 2.32 (95% CI: 1.78–3.07) for Chinese patients with OSA and 6.80 (95% CI: 4.42–10.45) for American patients with OSA. Moreover, individuals in the second and third tertiles of the TyG index exhibited significantly higher NAFLD risks than those in the lowest tertile. In Chinese patients, the ORs for the second and third tertiles were 2.26 (95% CI: 1.48–3.47) and 3.28 (95% CI: 2.15–5.04), respectively. In American patients, the ORs were 2.89 (95% CI: 1.73–4.86) and 9.58 (95% CI: 5.06–18.16), respectively. Trend analyses confirmed a statistically significant dose-response correlation of the TyG index with NAFLD in both Chinese and American patients with OSA. RCS regression (Figure 2) further supported the positive correlation of the TyG index with NAFLD in patients with OSA. In both Chinese and American participants, the RCS curves demonstrated a linear rise in NAFLD risk as the TyG index increased in patients with OSA, highlighting its potential utility as a biomarker for NAFLD risk assessment in this population.

Discussion

This study provides the first empirical evidence supporting the hypothesis that the TyG index serves as a key mediator in the association between OSA and NAFLD. Significant mediating effects of the TyG index were observed in both Chinese and American participants, accounting for 35.33% and 20.06% of the relationship, respectively. Furthermore, the mediation effect increased with OSA severity, indicating the progressive role of IR in the pathophysiology of OSA-induced NAFLD. Considering the significant mediating role of the TyG index, further analyses demonstrated a strong correlation of elevated

Table 4 Association of the TyG Index with NAFLD in Patients with OSA

Characteristic	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Fifth Affiliated Hospital of Sun Yat-sen University			
TyG index	2.73 (2.11–3.56)***	2.56 (1.98–3.35)***	2.32 (1.78–3.07)***
TyG index			
T1 (≤ 8.57)	Reference	Reference	Reference
T2 (8.57–9.13)	2.94 (1.98–4.41)***	2.63 (1.76–3.98)***	2.26 (1.48–3.47)***
T3 (> 9.13)	4.44 (2.99–6.66)***	3.95 (2.64–5.97)***	3.28 (2.15–5.04)***
P for trend	<0.001	<0.001	<0.001
National Health and Nutrition Examination Survey			
TyG index	9.49 (6.66–13.51)***	8.82 (6.08–12.79)***	6.80 (4.42–10.45)***
TyG index			
T1 (≤ 8.39)	Reference	Reference	Reference
T2 (8.39–8.94)	3.66 (2.25–5.94)***	3.44 (2.08–5.69)***	2.89 (1.73–4.86)***
T3 (>8.94)	15.64 (9.17–26.68)***	13.88 (7.83–24.60)***	9.58 (5.06–18.16)***
P for trend	<0.001	<0.001	<0.001

Notes: Model 1: crude model; Model 2: adjusted for age, sex, and race; Model 3: adjusted for Model 2 + BMI, education level, smoking status, hypertension, and diabetes. *** $P < 0.001$. ** $P < 0.01$. * $P < 0.05$.
Abbreviations: BMI, body mass index; CI, confidence interval; NAFLD, nonalcoholic fatty liver disease; OSA, obstructive sleep apnea; OR, odds ratio; TyG index, triglyceride-glucose index; T, tertile.

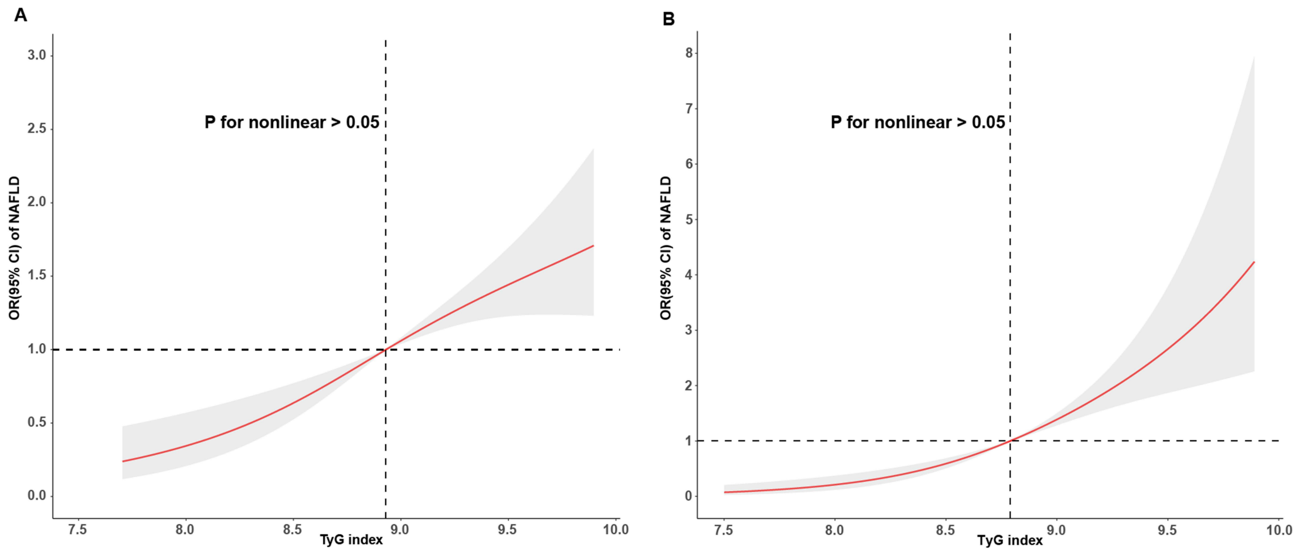

Figure 2 Restricted cubic spline plot of the association between the TyG index and NAFLD in Chinese (**A**) and American (**B**) participants with OSA. Odds ratios (95% confidence intervals) were obtained from the weighted multivariate logistic regression models, adjusted for age, sex, race, BMI, education level, smoking status, hypertension, and diabetes. The solid lines and shaded areas represent the central risk estimates and 95% CIs.

Abbreviations: BMI, body mass index; CI, confidence interval; NAFLD, nonalcoholic fatty liver disease; OSA, obstructive sleep apnea; OR, odds ratio; TyG index, triglyceride-glucose index.

TyG index levels with an increased risk of NAFLD in patients with OSA, reinforcing the clinical relevance of this marker. This study highlights the TyG index as a biologically relevant and effective non-invasive biomarker of IR in the OSA-NAFLD association, with potential for early NAFLD identification and risk stratification in patients with OSA.

Previous research has extensively studied the association between OSA and NAFLD, demonstrating that OSA is involved in the initiation and progression of NAFLD.[5,7,8] Among the various pathophysiological mechanisms implicated in OSA-induced NAFLD, the OSA/IH-IR-NAFLD pathway has emerged as a key mechanism, providing a plausible explanation for how OSA, through IH-induced IR, contributes to NAFLD pathogenesis.[5,6] During sleep, recurrent upper airway collapse in OSA patients triggers episodes of IH.[2] Basic research has demonstrated that IH can induce a proinflammatory response in visceral adipose tissue,[37] excessive activation of the sympathetic nervous system,[38] increased oxidative stress in the pancreas,[39] and other mechanisms that collectively contribute to IR. Clinical research in patients with OSA has also demonstrated an independent association between OSA and IR,[40,41] with IR severity increasing in parallel with OSA severity.[42–44] Moreover, IR is a pivotal factor in the pathogenesis of NAFLD. It promotes peripheral lipolysis, leading to an increased influx of free fatty acids into the liver, while simultaneously enhancing hepatic de novo lipogenesis.[45,46] IR also contributes to NAFLD through multiple pathways, including impaired mitochondrial fatty acid β-oxidation, activation of hepatic macrophages, altered fat distribution, gut microbiome dysbiosis, dysregulated adipokine secretion, and elevated inflammatory cytokine levels.[47–49] The growing recognition of IR as a therapeutic target for NAFLD further underscores its significance in disease management.[47] Consistent with previous findings, our study confirmed significant associations between OSA and IR, IR and NAFLD, as well as OSA and NAFLD, reinforcing the critical role of IR in this relationship. However, although IR has been widely recognized as a key pathway linking OSA to NAFLD, an effective measure of IR for early identification and risk stratification of NAFLD in OSA patients has yet to be established, limiting its clinical application.

Recognized as the gold standard, the hyperinsulinemic-euglycemic clamp is the most precise test for evaluating IR.[50] However, its clinical application and feasibility in large-scale population research are restricted by its complex procedure and high costs.[51] The homeostasis model assessment of insulin resistance (HOMA-IR), calculated using fasting insulin and fasting blood glucose, has been used in previous studies to quantify IR.[52] However, its applicability varies significantly across populations with different demographic characteristics, leading to inconsistencies in its use as a standardized measure.[52] Recently, the TyG index has emerged as a practical surrogate marker for IR, correlated with the gold-standard clamp method.[11] Offering advantages in convenience, cost-effectiveness, and reliability, the TyG index is highly applicable to large-scale epidemiological research and holds significant potential for clinical application.[15] In this study, the TyG index was demonstrated as a significant mediator in the association of OSA with NAFLD in both Chinese and American populations, exhibiting significant mediating effects in both populations. Additionally, the mediating role of the two constituent components of the TyG index—fasting blood glucose and fasting triglycerides—was individually examined in both populations. The findings revealed that, except for fasting blood glucose in the Chinese population, which exhibited a modest mediating effect (mediation effect = 8.56%, $P < 0.001$), all other components failed to show significant mediation effects (Supplementary Figure S1). Furthermore, our study revealed that elevated TyG index levels were strongly associated with a heightened risk of NAFLD. These results highlight the TyG index as a biologically significant and reliable marker of IR in the association between OSA and NAFLD, further emphasizing its potential clinical implications in patients with OSA for predicting NAFLD.

Our study may also provide potential insights into the treatment strategies for individuals with comorbid OSA and NAFLD. Although continuous positive airway pressure (CPAP) remains the gold-standard treatment for OSA, it has been shown to be ineffective in improving NAFLD in these patients.[53,54] This lack of efficacy may be primarily due to CPAP's inability to address IR.[55] In contrast, lifestyle interventions, including a Mediterranean diet, reduced sedentary behavior, and increased physical activity, have been shown to improve IR[56,57] and have proven effective in managing both OSA and NAFLD.[58–60] These therapeutic approaches may therefore be valuable for patients with comorbid OSA and NAFLD. However, the differential effects of these interventions on individuals with comorbid OSA and NAFLD remain insufficiently understood. Evaluating the TyG index within the context of these interventions could provide novel insights into the mechanisms of action and effectiveness of these treatments, potentially refining therapeutic strategies for this population.

To the best of our knowledge, this is the first study to explore the role of the TyG index in the association between OSA and NAFLD, while also exploring its clinical significance within this context. The analysis included populations from both China and the US, which are among the countries with the highest global prevalence of OSA. The similar findings across these two populations suggest a high degree of reproducibility and applicability across diverse countries and ethnic groups. However, several limitations must be acknowledged. First, our study, based on cross-sectional datasets from the Chinese population and NHANES, does not allow for definitive conclusions regarding causality. Further longitudinal research is required to confirm the causal relationships and elucidate the mechanisms underlying. Second, while the TyG index significantly mediated the relationship between OSA and NAFLD, it explains only part of the observed association. Additional mechanistic studies are needed to identify other biological mediators and pathways involved in this link. Third, OSA and NAFLD in the NHANES dataset were defined using validated surrogate tools—the STOP questionnaire and the USFLI, respectively. While these proxies have been used in previous large-scale studies,[27,30,31] the absence of polysomnography and imaging-based liver assessment (eg, ultrasound or MRI) may have led to misclassification bias. For example, STOP mis-classifies some mild OSA as negative and may over-call OSA in hypertensive or sleepy individuals, yielding non-differential bias that would attenuate true associations toward the null.[61] Similarly, USFLI mis-classifies advanced fibrotic NAFLD and misses modest steatosis in lean subjects, again diluting effect estimates.[62] Finally, although we adjusted for multiple covariates, several important potential confounders—such as physical activity, dietary intake, socioeconomic status, and family history—were either unavailable or inconsistent across the two datasets. These variables are known to influence insulin resistance, NAFLD, and OSA, and their omission may have introduced residual confounding, thereby affecting the accuracy of the observed associations. Future prospective or intervention-based studies incorporating detailed lifestyle and genetic data are warranted to validate and refine these findings.

Conclusion

This study provides novel evidence supporting the TyG index as a significant mediator in the association between OSA and NAFLD. It underscores the TyG index as a biologically meaningful and effective non-invasive biomarker of IR in this relationship. Moreover, elevated TyG index levels were significantly associated with an increased risk of NAFLD in patients with OSA, suggesting that the TyG index could serve as a valuable tool for identifying individuals at higher risk for NAFLD among those with OSA. The similar results observed across both Chinese and American populations, two countries with the highest prevalence of OSA globally, further highlights the TyG index's potential for broad applicability. However, future research, particularly longitudinal studies, is needed to validate these findings and further elucidate the mechanisms underlying this association.

Abbreviations

AHI, Apnea-Hypopnea Index; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; AUROC, Area under the receiver operating characteristic curve; BMI, Body Mass Index; CI, Confidence interval; CPAP, Continuous positive airway pressure; GGT, Gamma-glutamyltransferase; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; IH, Intermittent hypoxia; IR, Insulin resistance; MEC, Mobile Examination Center; NAFLD, Nonalcoholic fatty liver disease; NHANES, National Health and Nutrition Examination Survey; OR, Odds ratio; OSA, Obstructive Sleep Apnea; TyG, Triglyceride-glucose; USFLI, US Fatty Liver Index.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. The National Health and Nutrition Examination Survey dataset is publicly available at the National Center for Health Statistics of the Centers for Disease Control and Prevention (https://www.cdc.gov/nchs/nhanes/index.htm).

Ethical Approval and Consent to Participate

This study included two independent cross-sectional datasets: the NHANES database from the United States and a retrospective dataset from the Fifth Affiliated Hospital of Sun Yat-sen University in China. The combined use of these two datasets has been reviewed and approved by the Ethics Committee of the Fifth Affiliated Hospital of Sun Yat-sen University (2025K08-1). For the clinical dataset, due to its retrospective nature, the requirement for informed consent was waived. Moreover, the NHANES data are publicly available and fully de-identified. The NHANES study protocol was approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board, and all participants provided written informed consent. The NHANES procedures complied with the Declaration of Helsinki. Further details are available at https://www.cdc.gov/nchs/nhanes/. In accordance with Item 1 and Item 2 of Article 32 of the *Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects* (February 18, 2023, China), and as confirmed by the Ethics Committee, this study is exempt from additional ethical approval.

Consent to Publish

All authors gave their consent for publication.

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Author Contributions

All authors met the ICMJE authorship criteria. Haiyu Hong, Juntao Wu, and Shan Zhu had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Haohong Lai, Haiyu Hong, and Haidi Yang conceived the study and contributed to the study design. Juntao Wu, Haohong Lai, and Jiyuan Yin were involved in data analysis, interpretation, and drafting of the manuscript. All authors participated in critical revision of the manuscript, approved the final version to be published, agreed on the journal to which the article was submitted, and take accountability for all aspects of the work.

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The authors have no relevant financial or non-financial interests to disclose.

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