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ORIGINAL RESEARCH

Association Between Obstructive Sleep Apnea and Non-Alcoholic Fatty Liver Disease: Epidemiological Cross-Sectional Study and Mendelian Randomization Analysis

Tianqi Yu*, Yongxu Zhou*, Xu Wu, Zhihao Fang, Chang Liu

Department of General Surgery, Fourth Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang Province, People's Republic of China

*These authors contributed equally to this work

Correspondence: Chang Liu; Zhihao Fang, Email 600509@hrbmu.edu.cn; 202301635@hrbmu.edu.cn

Purpose: Obstructive sleep apnea (OSA) is a common condition that is linked to various complications. Despite its prevalence, limited research has explored the association between OSA and non-alcoholic fatty liver disease (NAFLD). The aim of this study was to examine whether individuals at risk for OSA are more likely to develop NAFLD.

Patients and Methods: This study employed a cross-sectional design coupled with Mendelian randomization, using data from the National Health and Nutrition Examination Survey (NHANES) collected between 2017 and 2020. A total of 6215 eligible participants were included. Multivariable logistic regression was performed to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for the relationship between OSA and NAFLD, adjusting for age, sex, ethnicity, education level, body mass index (BMI), diabetes, and hypertension. To assess causal inference and minimize observational bias, five distinct two-sample Mendelian randomization approaches were applied.

Results: After excluding 9345 individuals who did not meet the study criteria, a total of 6215 participants were included. The weighted prevalence of OSA and NAFLD in the cohort was 43.1% and 43.0%, respectively. Compared with individuals without NAFLD, those with NAFLD were older (median age 52.0 vs 44.0 years), and exhibited higher levels of HbA1c (5.70% vs 5.40%), fasting glucose, total cholesterol, triglycerides, and liver enzymes such as ALT. Additionally, NAFLD patients had markedly higher rates of comorbid conditions including hypertension (65% vs 40%), diabetes (29% vs 14%), and OSA (51% vs 36%). After adjusting for potential confounders, multivariable logistic regression demonstrated a significant association between OSA and NAFLD (OR = 1.86, 95% CI: 1.63–2.11, $p < 0.001$). Mendelian randomization analysis further suggested a potential causal effect of genetically predicted OSA on NAFLD risk (IVW OR = 1.066, 95% CI: 1.010–1.125, $p = 0.020$).

Conclusion: These findings suggest a potential association between OSA and the development of NAFLD. While the results provide preliminary evidence for a link, further longitudinal and interventional studies are needed to clarify causality and inform clinical practice.

Keywords: obstructive sleep apnea, NAFLD, national health and nutrition examination survey, Mendelian randomization

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease worldwide. This condition progresses from simple steatosis to irreversible non-alcoholic steatohepatitis (NASH), followed by liver fibrosis, cirrhosis, and ultimately hepatocellular carcinoma.[1] The prevalence of NAFLD ranges from 13.5% in Africa to 31.8% in the Middle East, potentially influenced by variations in caloric intake, physical activity, body fat distribution, socioeconomic factors, and genetic makeup. Recent studies have shown that 90% of individuals with NAFLD also experience metabolic dysfunction, obesity, and related disorders such as type 2 diabetes.[2] As a result, NAFLD is frequently associated with lipotoxicity and metabolic syndrome, including insulin resistance. By 2030, NAFLD is projected to become the most common indication for liver transplantation in Western countries.[3] At present, no approved

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pharmacological treatments exist for NAFLD, highlighting the need for further investigation into the risk factors driving its development.

Obstructive sleep apnea (OSA) is characterized by recurrent upper airway obstruction during sleep, resulting in cycles of hypoxia and reoxygenation known as chronic intermittent hypoxia (CIH). Over 60% of individuals with OSA are obese, and the condition is independently linked to multiple metabolic syndrome components, including visceral obesity, hypertension, insulin resistance, and dyslipidemia.[4–8] These disturbances collectively contribute to increased cardiometabolic morbidity and mortality. CIH has emerged as a key factor in the pathogenesis of non-alcoholic fatty liver disease (NAFLD).[9] Judith Aron-Wisnewsky et al first reported that OSA, particularly its hypoxic burden, is associated with hepatic steatosis and inflammation.[10] Mesarwi et al further demonstrated that OSA contributes to the transition from NAFL to non-alcoholic steatohepatitis (NASH) and liver fibrosis through inflammatory and fibrotic signaling pathways.[11] Li Yang et al revealed that OSA promotes the release of miR-421 from hepatocytes to macrophages, activating M1 polarization via the SIRT3/AMPK-autophagy axis.[12] Recent mechanistic studies have expanded this understanding. CIH induces excessive reactive oxygen species (ROS), leading to mitochondrial dysfunction, oxidative DNA damage, and hepatocellular injury. It also stabilizes hypoxia-inducible factor-1α (HIF-1α), which upregulates lipogenic genes such as SREBP-1c and FASN while suppressing β-oxidation, resulting in intrahepatic triglyceride accumulation.[13] Moreover, CIH promotes selective autophagy-dependent degradation of Eepd1, a critical DNA repair enzyme. Loss of Eepd1 exacerbates genomic instability, necroinflammation, and fibrogenesis, all of which accelerate NASH progression.[14] Together, these findings indicate that OSA contributes to NAFLD not only through traditional metabolic risk factors but also via direct hypoxia-driven molecular mechanisms. Given the growing prevalence of both OSA and NAFLD, further investigation into this relationship is warranted to guide targeted prevention and intervention strategies.

Mendelian randomization (MR) employs genetic instrumental variables (IVs) to examine the potential association between exposures and outcomes.[15] By taking advantage of the random distribution of genetic variations at conception, this approach minimizes confounding factors and reduces the potential for reverse causality.[16] We hypothesized that individuals at higher genetic and clinical risk for OSA would have a greater likelihood of developing NAFLD, mediated by both metabolic comorbidities and hypoxia-induced molecular pathways.

To investigate the potential relationship between obstructive sleep apnea (OSA) and non-alcoholic fatty liver disease (NAFLD), we adopted a dual approach combining observational and genetic analyses. First, we used data from the 2017–2020 National Health and Nutrition Examination Survey (NHANES) to evaluate the association between clinically defined OSA risk and NAFLD prevalence through cross-sectional analysis. Second, we applied a two-sample Mendelian randomization (MR) framework, utilizing genetic variants from large-scale genome-wide association studies (GWAS), to explore potential causality while minimizing confounding and reverse causation. This integrated approach enhances the robustness and interpretability of our findings.

Materials and Methods

Study Population in NHANES

Data for this study were obtained from the National Health and Nutrition Examination Survey (NHANES), administered by the National Center for Health Statistics (NCHS) to evaluate the health and nutritional status of the US population. NHANES employs a rigorous stratified multistage probability sampling design to ensure national representativeness. All NHANES datasets are publicly available for research purposes and can be accessed online through the NCHS website. For our analysis, we utilized data from two NHANES cycles spanning from 2017 to 2020. Participants under 18 years of age, those who tested positive for HBV surface antigen or HCV antibodies, and heavy drinkers were excluded. Further exclusions were made for incomplete or non-compliant elastography assessments, missing CAP data, or incomplete sleep questionnaires. After all exclusions, a final analytic sample was established for the observational analysis (Figure 1). The investigation followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[17] The protocol for the NHANES study was approved by the Institutional Review Board of the National Center for Health Statistics, and informed written consent was obtained from all participants at enrollment.

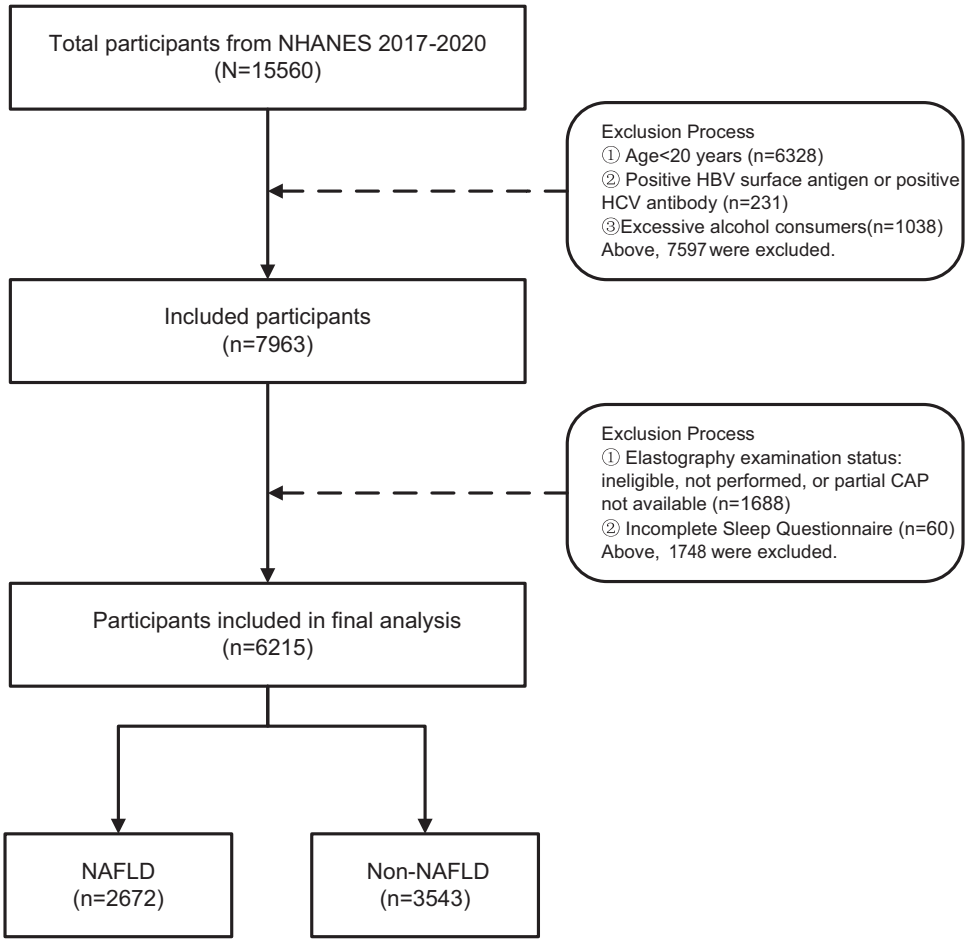

Figure 1 The flowchart of the observational analysis.

Definition of Exposure and Outcomes

In our study, obstructive sleep apnea (OSA) risk was considered the exposure variable. OSA risk was assessed using responses to three yes/no questions: (1) frequent snoring (three or more nights per week), (2) snoring, gasping, or episodes of breathing cessation (three or more nights per week), and (3) experiencing excessive daytime sleepiness (16–30 times per month), despite averaging at least 7 hours of sleep on work nights. Participants reporting any of these symptoms were considered to be at risk for OSA.[18]

The outcome variable of the study was non-alcoholic fatty liver disease (NAFLD). The NHANES staff utilized the FibroScan 502 Touch device to perform vibration-controlled transient elastography (VCTE) on participants from 2017 to 2020. The FibroScan 502 Touch device measures ultrasound attenuation, which is related to the severity of NAFLD, and records the controlled attenuation parameter (CAP) as an indicator of liver fat content. The CAP value is positively correlated with the severity of NAFLD. According to prior studies, NAFLD was diagnosed when the CAP value was ≥ 274 dB/m.[19]

Covariates

Our study employed a multivariable adjustment model that included potential confounders influencing the relationship between obstructive sleep apnea (OSA) and non-alcoholic fatty liver disease (NAFLD). The covariates considered in the model were age (in years), sex (male/female), poverty-to-income ratio (PIR), race, education level, smoking status (never smoked/former smoker/current smoker), marital status, waist circumference, hypertension, diabetes and body mass index (BMI). BMI was categorized into four groups: <18.5, 18.5 to <25, 25 to <30, and ≥30 kg/m², representing underweight,

normal weight, overweight and obese populations, respectively. Laboratory variables included alanine aminotransferase (ALT), aspartate aminotransferase (AST), LDL, HDL, albumin (Alb), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), hemoglobin A1c (HbA1c), fasting blood glucose, total cholesterol (TC), and triglycerides (TG). Measurement protocols for these variables were sourced from the literature.[20,21] For participants, BMI classifications were applied to all groups. Additionally, detailed information on the measurement procedures for the study variables can be accessed publicly at www.cdc.gov/nchs/nhanes/.

Statistical Analysis

In accordance with the NHANES analysis guidelines, this study accounted for the complex sampling design and sampling weights.[22] T-tests and chi-square tests were employed to analyze the associations between non-alcoholic fatty liver disease (NAFLD) and continuous and categorical variables, respectively. Multivariable logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (95% CI) to assess the impact of obstructive sleep apnea (OSA) on NAFLD. In the logistic regression models, Model 1 was unadjusted. Model 2 adjusted for age, sex, education level, and race. Model 3 further adjusted for sex, age, race, education level, waist circumference, hemoglobin A1c, blood glucose, total cholesterol, high-density lipoprotein (HDL), triglycerides, low-density lipoprotein (LDL), marital status, poverty-to-income ratio, smoking status, body mass index (BMI), hypertension and diabetes. Stratified analyses were conducted to evaluate the association between OSA and NAFLD across different subgroups. Furthermore, likelihood ratio tests were employed to identify potential interactions. All analyses were performed using R version 4.3.3 (http://www.r-project.org), with a two-sided significance level set at 0.05.

Selection of Genetic Instruments for Mendelian Randomization Analysis

To ensure the accuracy and robustness of causal inference, the selection of genetic instruments must satisfy the three key assumptions of Mendelian randomization. The study was conducted in accordance with the 2013 revision of the Declaration of Helsinki, and the methods adhered to the STROBE-MR checklist.[23,24] Figure 2 illustrates the overall

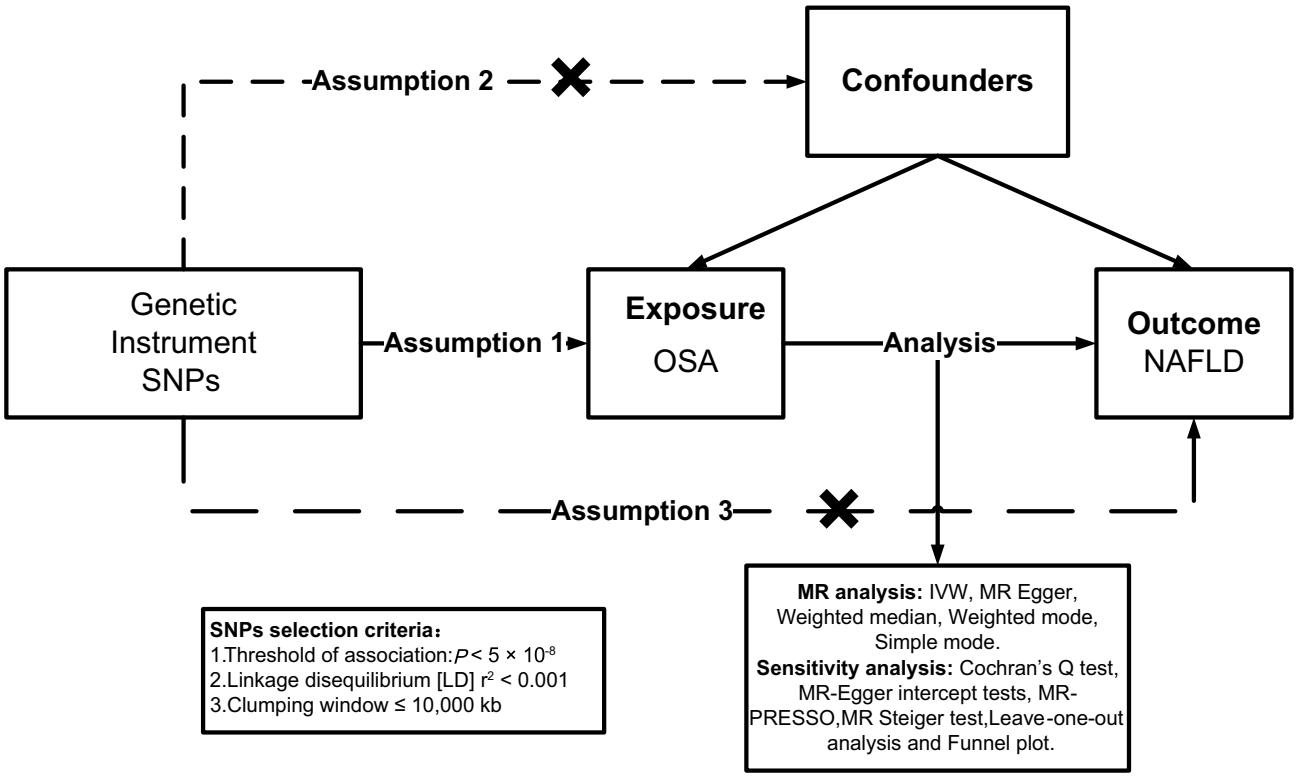

Figure 2 The flowchart of the Mendelian randomization analysis.

design process of this Mendelian randomization analysis. The assumptions are as follows: (a) genetic variants are significantly associated with the exposure of obstructive sleep apnea (OSA); (b) genetic variants are not influenced by potential confounders; and (c) genetic variants affect non-alcoholic fatty liver disease (NAFLD) solely through their effect on OSA, with no direct effect on the outcome.[25,26] Additionally, the following selection criteria were applied: First, single nucleotide polymorphisms (SNPs) were chosen based on the genome-wide significance threshold and an F-statistic > 10.[27] Second, independent SNPs, determined by linkage disequilibrium (LD), were retained, with LD measured using an r^2 threshold of <0.001 and a clustering distance of ≤ 10,000 kb. Finally, SNPs associated with the outcome or potential confounders ($p < 5 \times 10^{-8}$) were excluded, and SNPs with intermediate allele frequencies were removed during the harmonization of exposure and outcome data.[28,29]

GWAS Summary Data for OSA and NAFLD

Genetic instruments for sleep apnea were obtained from the IEU OpenGWAS database (https://gwas.mrcieu.ac.uk/), specifically the dataset ebi-a-GCST90018916, which includes 13,818 cases and 463,035 controls. The phenotype is defined by ICD-10 code G47.3, encompassing all types of sleep apnea. In this dataset, OSA diagnosis is based on ICD codes recorded in the Finnish National Hospital Discharge Registry and the Causes of Death Registry. The diagnosis integrates subjective symptoms, clinical examination, and objective sleep registration, typically using an Apnea-Hypopnea Index (AHI) ≥ 5 events/hour or a Respiratory Event Index (REI) ≥ 5 events/hour. Although the phenotype is not exclusive to obstructive sleep apnea (OSA), this dataset has been used as a proxy for OSA in prior Mendelian randomization studies.[30,31] We acknowledge the potential heterogeneity introduced by this broad definition and address it as a study limitation. Summary statistics for non-alcoholic fatty liver disease (NAFLD) were obtained from a meta-analysis of four European cohorts (eMERGE, UK Biobank, Estonian Biobank, FinnGen), comprising 8434 cases and 770,180 controls. The data, adjusted for age, sex, and 10 ancestry principal components, included 6,797,908 SNPs with MAF ≥ 0.01 and are available via the GWAS Catalog: http://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90091001-GCST90092000/GCST90091033/. Given UK Biobank is included in both datasets, some sample overlap is possible. However, previous simulations suggest MR remains robust with strong instruments (F > 10). Sensitivity analyses including MR-Egger and MR-PRESSO were applied to assess potential bias.[32]

Statistical Analysis

In this Mendelian randomization analysis, the inverse variance weighted (IVW) method was utilized as the primary approach to determine the potential association between the exposure and the outcome. The Cochran Q test was employed to assess potential heterogeneity among the instrumental variables (IVs). When P ≥ 0.05, a fixed-effects model was applied; otherwise, a random-effects IVW technique was used.[33] Additionally, MR-Egger, weighted median, simple mode, and weighted mode tests were conducted to assess the stability of the data.[34,35] In MR-Egger regression, the intercept term was used to identify potential horizontal pleiotropy, with a P value less than 0.05 indicating the presence of pleiotropic effects. Furthermore, the MR-Pleiotropy Residual Sum and Outlier (PRESSO) test was employed to detect outliers associated with horizontal pleiotropy.[36] Finally, leave-one-out analysis was performed to evaluate the robustness of the Mendelian randomization estimates and determine whether any single variant significantly influenced the potential association between the exposure and the outcome. All Mendelian randomization analyses were performed using the "TwoSampleMR" and "MRPRESSO" packages in R version 4.3.3, with forest plots generated using the ggplot2 package.

Results

Population Characteristics of NHANES

After excluding 9345 individuals who did not meet the study criteria, a total of 6215 participants were included in this analysis. The weighted mean age of the participants was 47.00 years (95% CI, 44.00–52.00 years), with females comprising 54% of the sample. Participants were categorized based on the presence or absence of non-alcoholic fatty liver disease (NAFLD), and the baseline characteristics are summarized as follows. Among all participants, 42% had

NAFLD, while 58% did not. Compared to individuals without NAFLD, those with NAFLD were significantly older (52.00 years vs 44.00 years), with higher levels of glycated hemoglobin (HbA1c) (5.70% vs 5.40%), blood glucose (108.00 mg/dL vs 101.00 mg/dL), total cholesterol (4.86 mmol/L vs 4.71 mmol/L), triglycerides (1.54 mmol/L vs 0.95 mmol/L), and alanine aminotransferase (ALT) (22.00 U/L vs 16.00 U/L). Additionally, a higher proportion of NAFLD patients were female, and they had elevated rates of hypertension (65% vs 40%), diabetes (29% vs 14%), and obstructive sleep apnea (OSA) (51% vs 36%). These findings suggest significant baseline differences between NAFLD patients and non-NAFLD individuals, particularly in terms of age, metabolic and liver function markers, and comorbidities, highlighting a potential association between NAFLD and health issues such as hypertension, diabetes, and OSA. The full results are presented in Table 1.

The Positive Association Between the Risk of OSA and NAFLD

The results of the weighted logistic regression analysis revealed a significant positive association between obstructive sleep apnea (OSA) and non-alcoholic fatty liver disease (NAFLD) in Model 1, which did not adjust for any covariates (OR = 1.86, 95% CI: 1.63–2.11, $p < 0.001$). In Model 2, after adjusting for age, sex, education level, and race, the association between OSA and NAFLD remained significant (OR = 1.69, 95% CI: 1.49–1.91, $p < 0.001$). However, in Model 3, which adjusted for nearly all relevant factors, the association was no longer significant (OR = 1.07, 95% CI: 0.89–1.22, $p = 0.61$). The full results are presented in Table 2.

Subgroup Analysis

We performed a subgroup analysis to evaluate the stability of the association between obstructive sleep apnea (OSA) and non-alcoholic fatty liver disease (NAFLD) across various population subgroups based on age, BMI, race, marital status, education level, smoking status, diabetes, and hypertension (Figure 3). All covariates were adjusted for in each subgroup analysis model, with the exception of the stratifying variable itself. The results showed a positive association between

Table 1 Baseline Characteristics of Participants Categorized by Non-Alcoholic Fatty Liver Disease

Characteristic (weighted %)	Overall (N = 6215) 100%)	Non-NAFLD (N = 3543) 58%)	NAFLD (N = 2672) 42%)	*P* value
Age(years)	47.00 (32.00, 61.00)	44.00 (30.00, 60.00)	52.00 (37.00, 63.00)	<0.001
HbA1c (%)	5.50 (5.20, 5.90)	5.40 (5.20, 5.70)	5.70 (5.30, 6.10)	<0.001
Glucose (mg/dL)	103.00 (96.00, 113.00)	101.00 (95.00, 109.00)	108.00 (99.00, 122.00)	<0.001
TC (mmol/L)	4.76 (4.14, 5.48)	4.71 (4.11, 5.40)	4.86 (4.19, 5.56)	0.008
HDL (mmol/L)	1.34 (1.11, 1.63)	1.45 (1.24, 1.73)	1.19 (1.01, 1.45)	<0.001
TG (mmol/L)	1.17 (0.60, 2.45)	0.95 (0.53, 2.07)	1.54 (0.82, 2.82)	<0.001
LDL (mmol/L)	2.59 (2.02, 3.18)	2.51 (1.99, 3.08)	2.72 (2.10, 3.31)	<0.001
ALT(U/L)	18.00 (13.00, 26.00)	16.00 (12.00, 21.00)	22.00 (16.00, 32.00)	<0.001
AST(U/L)	19.00 (16.00, 23.00)	18.00 (16.00, 22.00)	20.00 (17.00, 25.00)	<0.001
ALB(g/dL)	4.10 (3.90, 4.30)	4.10 (3.90, 4.30)	4.10 (3.90, 4.30)	<0.001
ALP(IU/L)	71.00 (58.00, 85.00)	68.00 (56.00, 82.00)	74.00 (63.00, 90.00)	<0.001
GGT(IU/L)	20.00 (14.00, 29.00)	16.00 (12.00, 24.00)	24.00 (17.00, 37.00)	<0.001
SBP (mmHg)	119.33 (109.67, 130.33)	117.00 (108.00, 128.67)	121.67 (112.67, 132.33)	<0.001
DBP (mmHg)	73.33 (66.67, 80.67)	71.67 (65.00, 78.33)	75.67 (69.00, 83.00)	<0.001
WC (cm)	98.20 (87.80, 110.20)	91.50 (82.40, 100.50)	108.90 (99.40, 119.30)	<0.001
Gender, n (%)				<0.001
Female	3407 (54%)	2082 (60%)	1325 (47%)	
Male	2808 (46%)	1461 (40%)	1347 (53%)	
Race, n (%)				<0.001
Mexican American	745 (8.4%)	317 (6.3%)	428 (11%)	
Non-Hispanic Black	1626 (11%)	1054 (13%)	572 (8.8%)	
Non-Hispanic White	2063 (62%)	1129 (62%)	934 (62%)	

(*Continued*)

Table 1 (Continued).

Characteristic (weighted %)	Overall (N = 6215) 100%)	Non-NAFLD (N = 3543) 58%)	NAFLD (N = 2672) 42%)	*P* value
Other	1781 (18%)	1043 (18%)	738 (18%)	
Education, n (%)				0.178
Below high school	1079 (10.0%)	576 (9.5%)	503 (11%)	
High School or above	5136 (90%)	2967 (91%)	2169 (89%)	
Marital, n (%)				<0.001
No	2548 (37%)	1576 (41%)	972 (31%)	
Yes	3667 (63%)	1967 (59%)	1700 (69%)	
PIR, n (%)				0.742
Not poor (≥1)	5105 (88%)	2892 (88%)	2213 (88%)	
Poor (< 1)	1110 (12%)	651 (12%)	459 (12%)	
Smoke, n (%)				0.062
Current	897 (13%)	543 (14%)	354 (13%)	
Former	1314 (23%)	663 (22%)	651 (26%)	
Never	4004 (63%)	2337 (64%)	1667 (61%)	
BMI (kg/m^2), n (%)				<0.001
Underweight (<18.5)	84 (1.4%)	82 (2.4%)	2 (<0.1%)	
Normal (18.5 to <25)	1532 (26%)	1336 (40%)	196 (6.3%)	
Overweight (25 to <30)	2032 (32%)	1251 (36%)	781 (27%)	
Obese (30 or greater)	2567 (41%)	874 (22%)	1693 (67%)	
Hypertension, n (%)				<0.001
No	2641 (49%)	1790 (60%)	851 (35%)	
Yes	3574 (51%)	1753 (40%)	1821 (65%)	
Diabetes, n (%)				<0.001
No	4669 (80%)	2907 (86%)	1762 (71%)	
Yes	1546 (20%)	636 (14%)	910 (29%)	
OSA, n (%)				<0.001
No	3536 (58%)	2222 (64%)	1314 (49%)	
Yes	2679 (42%)	1321 (36%)	1358 (51%)	

Notes: The data are presented as median (interquartile range) or n (%). Continuous variables were analyzed using the Mann–Whitney *U*-test, while categorical variables were analyzed using Pearson's chi-square test.

Abbreviations: HbA1c, Glycosylated Hemoglobin; TC, Total Cholesterol; HDL, High-Density Lipoprotein; TG, Triglycerides; LDL, Low-Density Lipoprotein; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; ALB, Albumin; ALP, Alkaline Phosphatase; GGT, Gamma-Glutamyl transferase; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; WC, Waist Circumference; PIR, Income-poverty ratio; BMI, Body Mass Index; OSA, Obstructive Sleep Apnea.

Table 2 Association Between Obstructive Sleep Apnea and Non-Alcoholic Fatty Liver Disease in Participants From NHANES 2017–2020

	OR (95% CI), *p* value		
	Model 1	**Model 2**	**Model 3**
OSA NAFLD Without With	 Reference 1.86 (1.63, 2.11), <0.001	 Reference 1.69 (1.49, 1.91), <0.001	 Reference 1.07 (0.89, 1.22), 0.61

Notes: Model 1 was unadjusted. Model 2 adjusted for age, sex, education level, and race. Model 3 further adjusted for sex, age, race, education level, waist circumference, hemoglobin A1c, blood glucose, total cholesterol, high-density lipoprotein (HDL), triglycerides, low-density lipoprotein (LDL), marital status, poverty-to-income ratio, smoking status, body mass index (BMI), hypertension, and diabetes.

Abbreviations: NAFLD, Non-alcoholic fatty liver disease; OR, Odds ratio; OSA, Obstructive Sleep Apnea.

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Variable	Group	OR (95% CI)	pvalue	Interaction_pvalue
Gender	Female	1.780 (1.397 to 2.269)	<0.001	0.805
	Male	1.855 (1.577 to 2.181)	<0.001	
Age	<=60	2.267 (1.912 to 2.689)	<0.001	<0.001
	>60	1.052 (0.777 to 1.424)	0.747	
Race	Mexican American	1.511 (1.029 to 2.218)	0.049	0.486
	Non−Hispanic Black	2.154 (1.635 to 2.839)	<0.001	
	Non−Hispanic White	1.917 (1.561 to 2.354)	<0.001	
	Other	1.677 (1.267 to 2.221)	0.001	
Education	Below high school	1.918 (1.386 to 2.655)	<0.001	0.830
	High School or above	1.847 (1.603 to 2.128)	<0.001	
Marital	No	1.913 (1.496 to 2.445)	<0.001	0.604
	Yes	1.773 (1.529 to 2.056)	<0.001	
PIR	Not poor	1.836 (1.581 to 2.134)	<0.001	0.592
	Poor	2.021 (1.510 to 2.704)	<0.001	
Smoke	Never	1.940 (1.638 to 2.298)	<0.001	0.440
	Current	1.520 (1.145 to 2.018)	0.008	
	Former	1.792 (1.342 to 2.394)	<0.001	
BMI	Normal	1.776 (1.075 to 2.934)	0.034	0.504
	Obese	1.242 (0.955 to 1.616)	0.119	
	Overweight	1.354 (1.034 to 1.772)	0.037	
	Underweight	0.000 (0.000 to 0.000)	<0.001	
Hypertension	No	1.965 (1.650 to 2.341)	<0.001	0.029
	Yes	1.487 (1.220 to 1.813)	<0.001	
Diabetes	No	1.902 (1.651 to 2.192)	<0.001	0.041
	Yes	1.388 (1.075 to 1.793)	0.019	

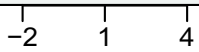

Figure 3 Subgroup analysis (forest plots).

OSA and NAFLD, except in individuals with lower BMI. No significant interactions were observed between subgroups, with the exception of those based on age, diabetes, and hypertension, indicating that the positive association between OSA and NAFLD was not influenced by interactions across different subgroups (all interaction p-values > 0.05).

Results of Two-Sample MR Analysis

Initially, we performed a linkage disequilibrium (LD) test and excluded SNPs with an F-statistic below 10. The remaining SNPs were then utilized as genetic instruments in our Mendelian randomization (MR) analysis, with the detailed data provided in Supplementary Table 1. The results revealed a potential association between obstructive sleep apnea (OSA) and an increased risk of non-alcoholic fatty liver disease (NAFLD), as confirmed by the inverse variance weighted (IVW) method (OR: 1.066, 95% CI: 1.010–1.125, p = 0.020), as depicted in Figure 4. The scatter plot results are shown in Figure 5. Notably, statistical heterogeneity among SNPs in relation to the effect of OSA on NAFLD was observed (IVW: P = 0.044, MR Egger: P = 0.046, I^2 = 17.94%), as outlined in Supplementary Table 2. Additionally, the MR-PRESSO global test identified 19 potential outliers; however, most SNPs did not exhibit significant bias. While the results were no longer significant after removing the outliers, the combined findings from the MR-PRESSO global test, outlier test, and distortion test suggest that a potential association between OSA and NAFLD may still exist.

Subsequently, we employed the multiplicative random effects inverse variance weighted (IVW) method to assess the potential association between obstructive sleep apnea (OSA) and non-alcoholic fatty liver disease (NAFLD), accounting for measured heterogeneity. To examine whether SNPs associated with OSA might influence NAFLD through alternative pathways, we conducted a horizontal pleiotropy analysis. The MR-Egger test did not provide evidence of pleiotropic effects (all P > 0.05). (Supplementary Table 3) This conclusion was further supported by the symmetry of the funnel plot, as shown in Figure 6. The leave-one-SNP-out analysis confirmed that the potential association between OSA and

Method	pval	OR(95% CI)
MR Egger	0.905	0.992 (0.863 to 1.139)
Weighted median	0.304	1.038 (0.967 to 1.113)
Inverse variance weighted	0.020	**1.066 (1.010 to 1.125)**
Simple mode	0.752	1.037 (0.828 to 1.299)
Weighted mode	0.961	0.995 (0.817 to 1.213)

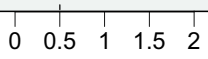

Figure 4 Results of Mendelian Randomization Analysis (forest plots).

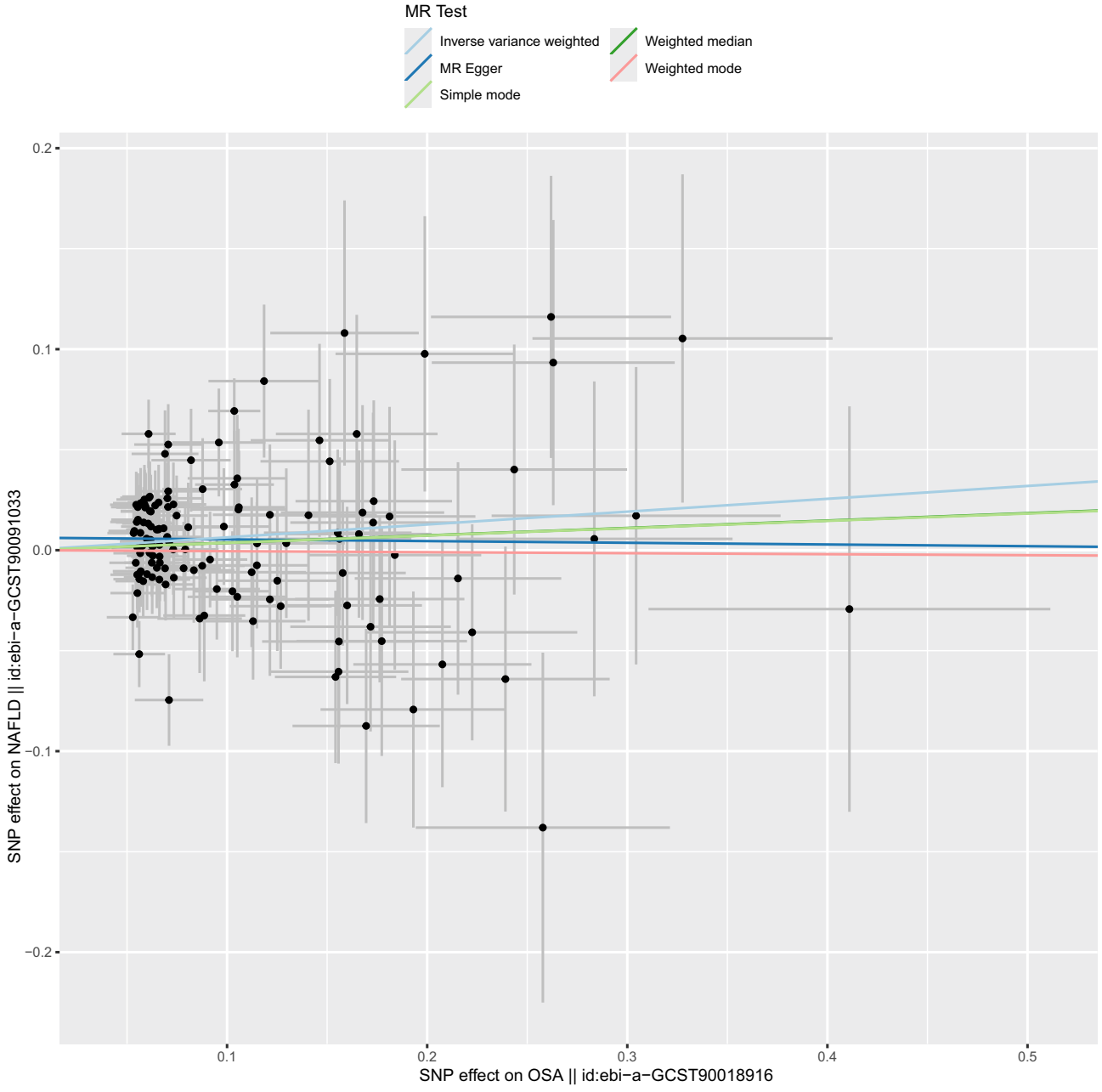

Figure 5 Scatter plot depicting the Mendelian randomization analysis of causal links between OSA SNPs and NAFLD.

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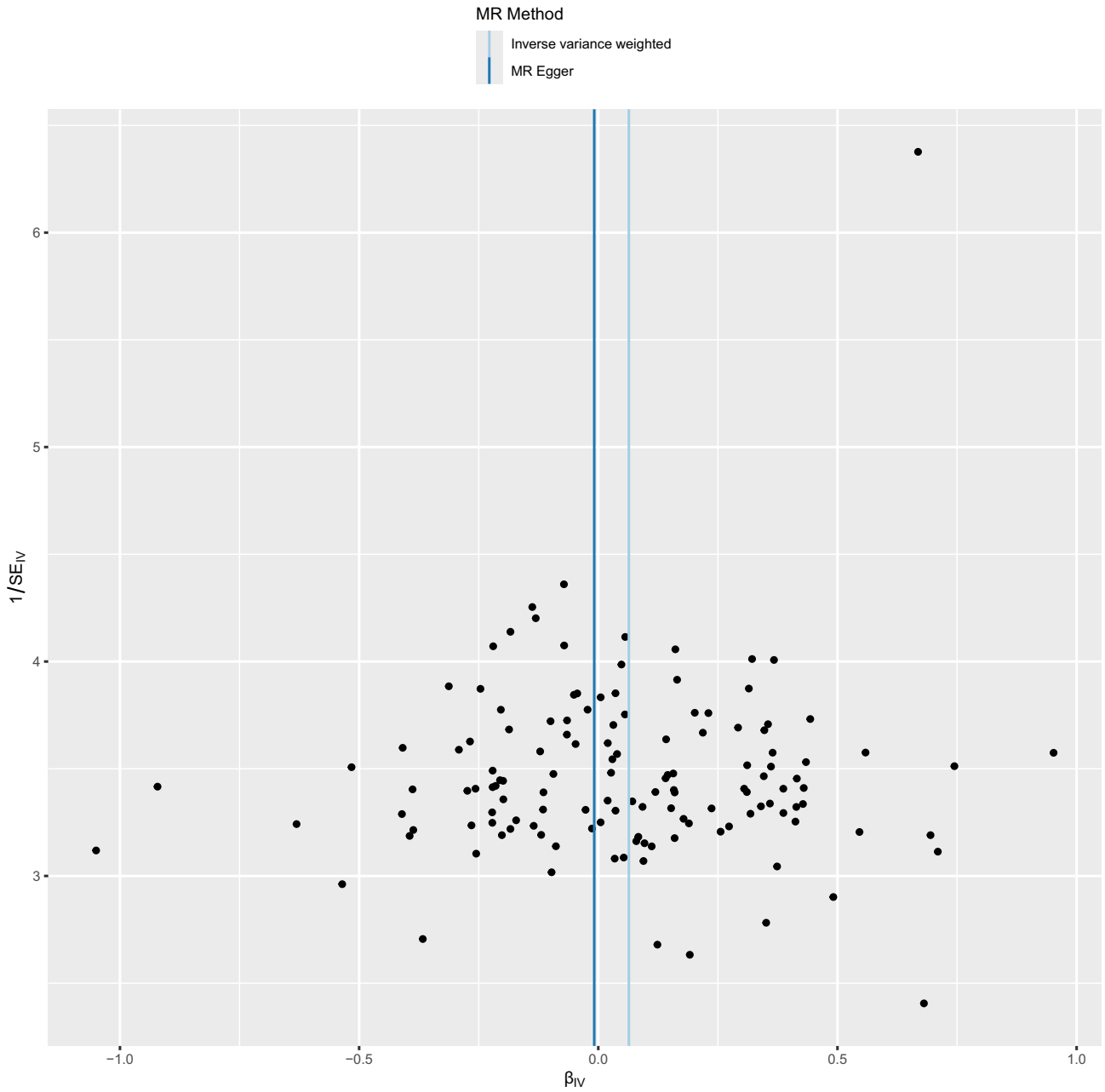

Figure 6 Funnel plot showing the Mendelian randomization analysis of causal relationships between SNPs associated with OSA and NAFLD.

NAFLD was not driven by any individual SNP (Figure 7). Taken together, these results suggest that our findings are both robust and reliable.

Discussion

This study examined data from 6215 eligible participants in the NHANES 2017–2020 cycle. After adjusting for potential confounders, our results demonstrated a positive association between the risk of obstructive sleep apnea (OSA) and non-alcoholic fatty liver disease (NAFLD). Moreover, Mendelian randomization analysis of comprehensive genetic data provides suggestive evidence of a potential link between these two conditions.

The global rise in obesity prevalence has contributed to an increased incidence of obesity-related chronic conditions, particularly metabolic syndrome, insulin resistance, type 2 diabetes (T2D), obstructive sleep apnea (OSA), and non-

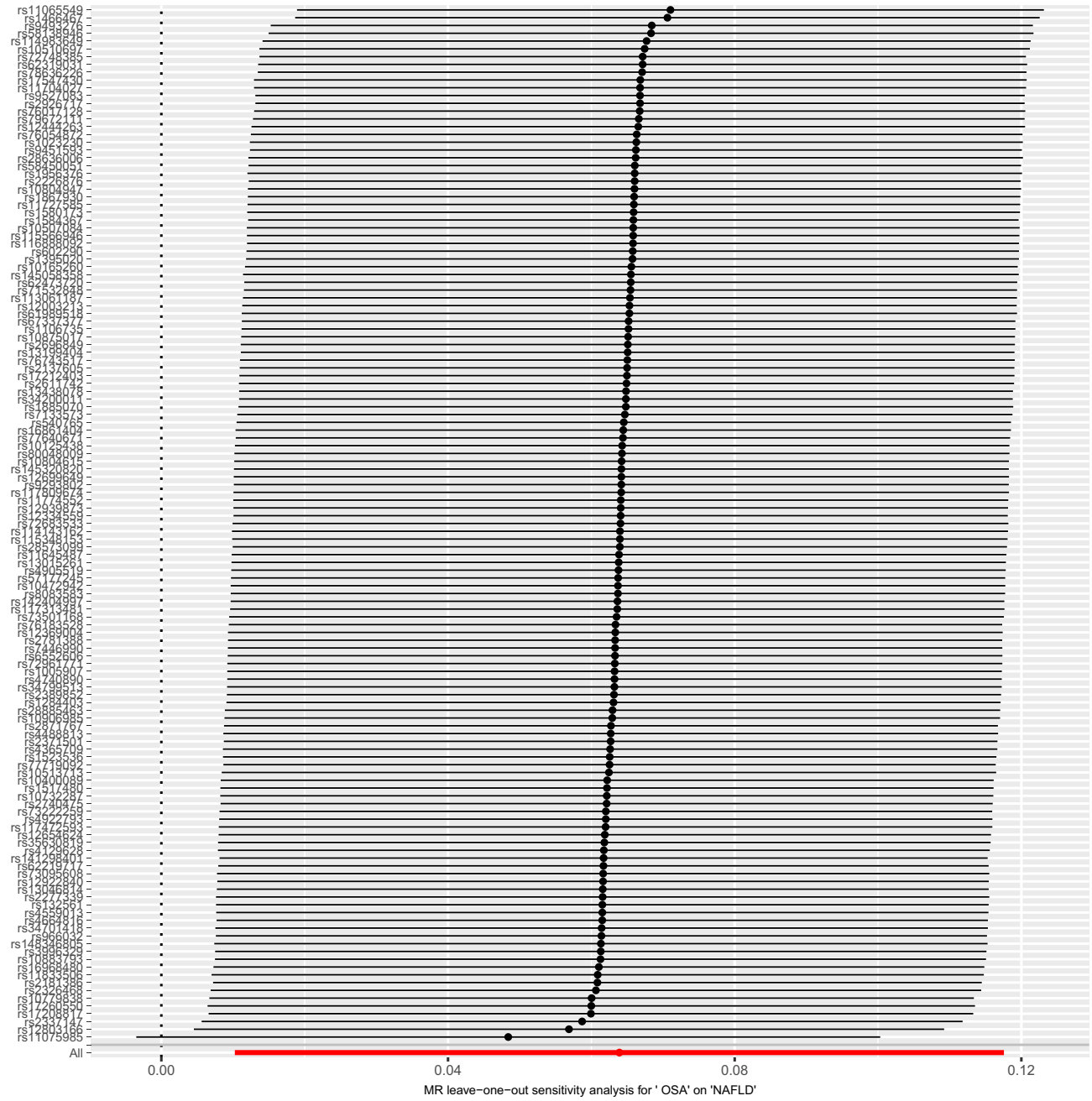

Figure 7 Leave-one-out sensitivity analysis for NAFLD using SNPs associated with OSA.

alcoholic fatty liver disease (NAFLD).[37] These obesity-related metabolic comorbidities, particularly OSA and its primary consequence—chronic intermittent hypoxia (CIH)—as well as NAFLD, often exacerbate each other's severity. Emerging clinical evidence underscores a significant association between the onset and severity of OSA and NAFLD, especially in adults.[38–40] In a study involving 334 patients, the severity of OSA, as measured by the AHI index, showed a negative correlation with various biomarkers, including transaminases, HDL, BMI, HOMA-IR index, and FIB-4 index, suggesting these biomarkers' high sensitivity and specificity in assessing liver fibrosis.[41] The same study also indicated that OSA severity, as reflected by the AHI value, serves as an independent predictor of significant fibrosis in NAFLD patients.[42] In individuals with metabolic diseases, the severity of OSA correlates with increased liver stiffness, a critical indicator for evaluating liver fibrosis.[43] Furthermore, a multicenter study revealed a strong association between OSA severity and the increased risk of hepatic steatosis, although no significant relationship with liver fibrosis was observed, even after

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adjusting for confounding factors such as central obesity.[44] A meta-regression analysis further supported that OSA is linked to NAFLD, particularly in terms of steatosis severity, lobular inflammation, ballooning degeneration, and fibrosis, with OSA severity correlating with elevated ALT levels, but not with AST levels.[45] Additionally, another meta-analysis confirmed a close association between OSA and the incidence and severity of NAFLD, NASH, and liver fibrosis, independent of gender, age, BMI, or abdominal obesity.[46] Consistent with the findings of our current study, our logistic regression analysis demonstrated that the association between OSA and NAFLD remains significant after adjusting for age, gender, education level, and ethnicity (OR = 1.69, 95% CI: 1.49–1.91, $p < 0.001$). Subgroup analyses further indicated that the relationship between OSA and NAFLD is not influenced by gender or BMI. Previous research has identified shared risk factors between OSA and NAFLD, such as male gender, older age, and obesity.[47] Even after controlling for these variables, the severity of OSA continues to be positively correlated with the severity of NAFLD, suggesting that OSA may increase the risk of NASH in obese patients, a conclusion that persists even after adjusting for BMI and other factors.[38,48,49]

Cross-sectional studies can only suggest an association between exposure and outcome, without establishing causality. To address this limitation, we conducted a Mendelian Randomization (MR) analysis to investigate the potential association between obstructive sleep apnea (OSA) and non-alcoholic fatty liver disease (NAFLD). This study utilized MR to explore the possible link between OSA and NAFLD, yielding several important findings. Preliminary analysis indicated a potential association between OSA and NAFLD (OR = 1.066, $p = 0.020$), but after applying the MR-PRESSO global test and removing outliers, the result was no longer statistically significant. This suggests that the association between OSA and NAFLD may be influenced by other underlying factors, such as genetic pleiotropy or uncontrolled mediating effects. Nevertheless, using alternative statistical methods, including IVW and MR-Egger regression, we continued to observe some evidence supporting the hypothesis of a potential association between OSA and NAFLD. Clinically, these findings highlight the complexity of the relationship between sleep-disordered breathing and hepatic metabolic dysfunction. Even though the causal inference weakened after outlier correction, the observed trends warrant attention. OSA is highly prevalent and often underdiagnosed in individuals with metabolic syndrome, a population already at elevated risk for NAFLD. Our results suggest that early screening and management of OSA in at-risk populations may contribute to improved liver health outcomes. Furthermore, these findings reinforce the importance of interdisciplinary collaboration between sleep medicine and hepatology in the integrated management of chronic metabolic diseases. Our findings contrast with those of Ding et al,[50] who did not identify a possible link between OSA and NAFLD, proposing that this association may be confounded by factors such as obesity. Although Ding et al excluded obesity-related SNPs (eg, rs9937053 in the FTO gene) from their analysis, they still found no evidence supporting a direct potential association between OSA and NAFLD. The discrepancies between the two studies may be attributed to differences in the genetic tools and analytical techniques employed. We hypothesize that obesity, as a significant confounder, may influence the observed relationship between OSA and NAFLD. Future studies should more comprehensively examine the complex interactions among obesity, genetic susceptibility, and metabolic diseases.

The exact mechanisms underlying the potential link between obstructive sleep apnea (OSA) and non-alcoholic fatty liver disease (NAFLD) remain incompletely understood. However, evidence from our genetic instrument analysis supports several biologically plausible pathways. Multiple SNPs used in this study are located near genes involved in shared metabolic and fibrotic processes. For example, *NEDD1*, near rs10507084, plays a role in airway neuromuscular function and hepatic stellate cell activation, implicating structural and fibrotic mechanisms.[51] *NME7* (rs10732287) and *GCKR* (rs12922840) are involved in glycemic control and lipid metabolism, both of which contribute to insulin resistance—a common feature in both OSA and NAFLD. *COL5A2* (rs10165260) is related to extracellular matrix remodeling, a critical process in airway collapsibility and liver fibrosis. In addition, variants near *FTO, TMEM18, MC4R*, and *PNPLA3* link obesity, appetite regulation, and hepatic triglyceride remodeling to both conditions.[52–54] Together, these findings suggest that dysregulated energy balance, adiposity, insulin resistance, and hepatic fibrogenesis are key overlapping mechanisms through which OSA may contribute to NAFLD development. The connection between OSA and NAFLD is primarily mediated through intermittent hypoxia (IH). Research suggests that intermittent hypoxia induced by OSA may exacerbate the development of NAFLD, particularly in terms of hepatic fat accumulation (hepatic steatosis) and liver fibrosis. Animal studies have demonstrated that chronic intermittent hypoxia leads to increased liver triglyceride levels and histological evidence of hepatic steatosis in obese mice.[48,55] In humans, the severity of OSA correlates with liver fat content, with measures such as the apnea-hypopnea index (AHI), percentage of time with oxygen

saturation below 90%, and the oxygen desaturation index.[44,56–58] However, studies examining the effects of continuous positive airway pressure (CPAP) on hepatic fat accumulation have shown generally disappointing results. For instance, a CPAP-controlled study involving 27 patients with moderate to severe OSA reported no significant changes in liver lipid content following CPAP treatment.[59] Additionally, OSA plays a crucial role in liver inflammation and fibrosis in the progression of NAFLD. Several studies have demonstrated an association between OSA and liver fibrosis, particularly highlighting the role of OSA-induced hypoxic burden in exacerbating fibrosis.[60] Although some studies have failed to confirm a definitive association between OSA and NAFLD progression, the majority suggest that the presence of OSA increases the risk of liver fibrosis.[48] A few studies have examined the effects of CPAP on liver fibrosis; while most findings are negative, some have reported improvements in alternative biomarkers, such as transaminase levels.[61,62] Thus, intermittent hypoxia caused by OSA may worsen liver damage through oxidative stress, mitochondrial dysfunction, and inflammatory responses, facilitating the progression of NAFLD to non-alcoholic steatohepatitis (NASH) and liver fibrosis.[63,64] Research by Omar A. Mesarwi et al has shown that OSA, particularly in relation to NAFLD, is closely associated with metabolic dysfunction, dysregulation of glucose and lipid metabolism, liver inflammation, oxidative stress, and liver fibrosis. This association may be attributed to the intermittent hypoxic burden induced by OSA. Severe nocturnal hypoxemia has been linked to hepatocellular ballooning degeneration and pericellular liver fibrosis, with similar findings observed in OSA patients by another research group.[38] Animal studies also confirm the role of chronic intermittent hypoxia in the progression of obesity-related fatty liver disease.[65] OSA is itself a highly heterogeneous condition, characterized by various physiological changes beyond intermittent hypoxia. Therefore, further research is essential to enhance our understanding of the relationship between OSA and NAFLD and to improve screening and treatment strategies for clinical practice.

The primary strength of this study lies in the integration of observational data from the NHANES 2017–2020 cycle with Mendelian Randomization (MR) methods. The comprehensive evaluation of various factors, combined with the large sample size, allowed for reliable adjustment for multiple confounders simultaneously in multivariable regression models, providing sufficient statistical power to assess the potential association between OSA and NAFLD. Moreover, the MR approach mitigates biases arising from unmeasured confounders and reverse causality.[66] Notably, the results obtained from the two methods used in this study were nearly identical, further enhancing the robustness and reliability of the findings. However, several limitations should be considered. In our study, OSA was assessed using a validated questionnaire rather than polysomnography (PSG), which is considered the gold standard. While this may have introduced recall bias and potential misclassification, such errors are likely to be non-differential with respect to NAFLD, and thus would bias the association toward the null.[67] Therefore, the observed association between OSA and NAFLD may actually underestimate the true magnitude of the effect. Transient elastography was used to assess hepatic steatosis instead of liver biopsy. Although biopsy is the diagnostic gold standard, it is invasive and not feasible for population-based studies. CAP (controlled attenuation parameter) has been validated in clinical cohorts, and is widely used as a reliable non-invasive tool for liver fat quantification. Nevertheless, we acknowledge that this approach may underestimate the prevalence of mild NAFLD and introduce selection bias. In our MR analysis, although the initial IVW results indicated a potential causal relationship, the association lost statistical significance after outlier removal using MR-PRESSO. This may be due in part to a reduction in instrument strength and statistical power, as the number of valid SNPs decreases with the exclusion of outliers. Moreover, residual horizontal pleiotropy cannot be fully ruled out, and future studies with larger, ancestry-specific GWAS datasets are needed to confirm this finding. A limitation of the MR analysis is the use of summary statistics from European ancestry cohorts, while our observational data were derived from a multi-ethnic US sample. Although this may affect generalizability, the consistency of findings across analytical methods enhances internal validity. Future studies should validate our results in more diverse populations, including East Asian and Hispanic cohorts, to improve the global applicability of these findings.

Conclusion

Our results highlight a potential link between OSA and NAFLD development. While this association may reflect shared metabolic pathways, the causality and clinical implications remain to be fully elucidated. These findings underscore the importance of continued investigation in at-risk populations.

Data Sharing Statement

The data supporting the findings of this study were obtained from the National Health and Nutrition Examination Survey (NHANES), which is accessible at www.cdc.gov/nchs/nhanes/. The Genome-Wide Association Studies (GWAS) data for obstructive sleep apnea (OSA) can be accessed at https://gwas.mrcieu.ac.uk/. The summary data for non-alcoholic fatty liver disease (NAFLD) from GWAS are available through the GWAS catalog and can be accessed via the following link: (http://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90091001-GCST90092000/GCST90091033/).

Ethics Approval

The Ethics Committee of the Fourth Affiliated Hospital of Harbin Medical University strictly adheres to the principles outlined in the Declaration of Helsinki and the International Ethical Guidelines for Health-related Research Involving Humans, ensuring an independent and thorough ethical review process. As this study utilized legally obtained, publicly available database data, it falls under the exemption criteria for ethical review as specified by the Ethics Committee of the Fourth Affiliated Hospital of Harbin Medical University.

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Author Contributions

TQY: Conceptualization, Methodology, Formal Analysis, Writing - Original Draft. TQY&ZHF: Methodology, Data Curation, Writing - Original Draft, Writing - Review & Editing. YXZ: Investigation, Software, Visualization, Writing - Original Draft. XW: Data curation, Visualization, Writing – original draft. TQY: Formal Analysis, Validation. CL: Conceptualization, Supervision, Writing – review and editing. All authors contributed significantly to the work, drafted or revised the article, approved the final version for publication, and agreed on the journal and to be accountable for all aspects of the work.

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References

1. Powell EE, Wong VW-S, Rinella M. Non-alcoholic fatty liver disease. *Lancet*. 2021;397(10290):2212–2224. doi:10.1016/S0140-6736(20)32511-3
2. Tilg H, Adolph TE, Dudek M, Knolle P. Non-alcoholic fatty liver disease: the interplay between metabolism, microbes and immunity. *Nat Metab*. 2021;3(12):1596–1607. doi:10.1038/s42255-021-00501-9
3. Lazarus JV, Mark HE, Anstee QM, et al. Advancing the global public health agenda for NAFLD: a consensus statement. *Nat Rev Gastroenterol Hepatol*. 2022;19(1):60–78. doi:10.1038/s41575-021-00523-4
4. Baguet J-P, Barone-Rochette G, Tamisier R, Levy P, Pépin J-L. Mechanisms of cardiac dysfunction in obstructive sleep apnea. *Nat Rev Cardiol*. 2012;9(12):679–688. doi:10.1038/nrcardio.2012.141
5. Malhotra A, Patil S, Sands S, Ayas N. Central sleep apnoea in congestive heart failure. *Lancet Respir Med*. 2015;3(7):507–508. doi:10.1016/S2213-2600(15)00235-0
6. Tasali E, Ip MSM. Obstructive sleep apnea and metabolic syndrome: alterations in glucose metabolism and inflammation. *Proc Am Thorac Soc*. 2008;5(2):207–217. doi:10.1513/pats.200708-139MG
7. Jullian-Desayes I, Joyeux-Faure M, Tamisier R, et al. Impact of obstructive sleep apnea treatment by continuous positive airway pressure on cardiometabolic biomarkers: a systematic review from sham CPAP randomized controlled trials. *Sleep Med Rev*. 2015;21:23–38. doi:10.1016/j.smrv.2014.07.004
8. Ip MSM, Lam B, Ng MMT, Lam WK, Tsang KWT, Lam KSL. Obstructive sleep apnea is independently associated with insulin resistance. *Am J Respir Crit Care Med*. 2002;165(5):670–676. doi:10.1164/ajrccm.165.5.2103001
9. Arnaud C, Dematteis M, Pepin J-L, Baguet J-P, Lévy P. Obstructive sleep apnea, immuno-inflammation, and atherosclerosis. *Semin Immunopathol*. 2009;31(1):113–125. doi:10.1007/s00281-009-0148-5

10. Aron-Wisnewsky J, Clement K, Pépin J-L. Nonalcoholic fatty liver disease and obstructive sleep apnea. *Metabolism*. 2016;65(8):1124–1135. doi:10.1016/j.metabol.2016.05.004
11. Mesarwi OA, Loomba R, Malhotra A. Obstructive sleep apnea, hypoxia, and nonalcoholic fatty liver disease. *Am J Respir Crit Care Med*. 2019;199(7):830–841. doi:10.1164/rccm.201806-1109TR
12. Yang L, Liu S, He Y, et al. Exosomes regulate SIRT3-related autophagy by delivering miR-421 to regulate macrophage polarization and participate in OSA-related NAFLD. *J Transl Med*. 2024;22(1):475. doi:10.1186/s12967-024-05283-8
13. Aron-Wisnewsky J, Clement K, Pépin JL. Nonalcoholic fatty liver disease and obstructive sleep apnea. *Metabolism*. 2016;65(8):1124–1135.
14. Xiong J, Xu Y, Wang N, et al. Obstructive sleep apnea syndrome exacerbates NASH progression via selective autophagy-mediated Eepd1 degradation. *Adv Sci*. 2024;11(35):e2405955. doi:10.1002/advs.202405955
15. Sekula P, Del Greco MF, Pattaro C, Köttgen A. Mendelian randomization as an approach to assess causality using observational data. *J Am Soc Nephrol*. 2016;27(11):3253–3265. doi:10.1681/ASN.2016010098
16. Guo Q, Burgess S, Turman C, et al. Body mass index and breast cancer survival: a Mendelian randomization analysis. *Int J Epidemiol*. 2017;46(6):1814–1822. doi:10.1093/ije/dyx131
17. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*. 2007;370(9596):1453–1457. doi:10.1016/S0140-6736(07)61602-X
18. Scinicariello F, Buser MC, Feroe AG, Attanasio R. Antimony and sleep-related disorders: NHANES 2005-2008. *Environ Res*. 2017;156:247–252. doi:10.1016/j.envres.2017.03.036
19. Lu C-F, Cang X-M, Liu W-S, et al. Association between the platelet/high-density lipoprotein cholesterol ratio and nonalcoholic fatty liver disease: results from NHANES 2017-2020. *Lipids Health Dis*. 2023;22(1):130. doi:10.1186/s12944-023-01861-9
20. Min Y, Wei X, Wei Z, Song G, Zhao X, Lei Y. Prognostic effect of triglyceride glucose-related parameters on all-cause and cardiovascular mortality in the United States adults with metabolic dysfunction-associated steatotic liver disease. *Cardiovasc Diabetol*. 2024;23(1):188. doi:10.1186/s12933-024-02287-y
21. Yuan M, He J, Hu X, et al. Hypertension and NAFLD risk: insights from the NHANES 2017-2018 and Mendelian randomization analyses. *Chin Med J*. 2024;137(4):457–464. doi:10.1097/CM9.0000000000002753
22. Li B, Chen L, Hu X, et al. Association of serum uric acid with all-cause and cardiovascular mortality in diabetes. *Diabetes Care*. 2023;46(2):425–433. doi:10.2337/dc22-1339
23. Skrivankova VW, Richmond RC, Woolf BAR, et al. Strengthening the reporting of observational studies in epidemiology using mendelian randomization: the STROBE-MR statement. *JAMA*. 2021;326(16):1614–1621. doi:10.1001/jama.2021.18236
24. Skrivankova VW, Richmond RC, Woolf BAR, et al. Strengthening the reporting of observational studies in epidemiology using mendelian randomisation (STROBE-MR): explanation and elaboration. *BMJ*. 2021;375:n2233. doi:10.1136/bmj.n2233
25. Burgess S, Scott RA, Timpson NJ, Davey Smith G, Thompson SG. Using published data in Mendelian randomization: a blueprint for efficient identification of causal risk factors. *Eur J Epidemiol*. 2015;30(7):543–552. doi:10.1007/s10654-015-0011-z
26. Evans DM, Davey Smith G. Mendelian randomization: new applications in the coming age of hypothesis-free causality. *Annu Rev Genomics Hum Genet*. 2015;16(1):327–350. doi:10.1146/annurev-genom-090314-050016
27. Kuppa A, Tripathi H, Al-Darraji A, Tarhuni WM, Abdel-Latif A. C-reactive protein levels and risk of cardiovascular diseases: a two-sample bidirectional mendelian randomization study. *Int J Mol Sci*. 2023;24(11):9129. doi:10.3390/ijms24119129
28. Yu Z, Coresh J, Qi G, et al. A bidirectional Mendelian randomization study supports causal effects of kidney function on blood pressure. *Kidney Int*. 2020;98(3):708–716. doi:10.1016/j.kint.2020.04.044
29. Bottigliengo D, Foco L, Seibler P, Klein C, König IR, Del Greco MF. A Mendelian randomization study investigating the causal role of inflammation on Parkinson's disease. *Brain*. 2022;145(10):3444–3453. doi:10.1093/brain/awac193
30. Yan W, Jiang M, Hu W, et al. Causality investigation between gut microbiota, derived metabolites, and obstructive sleep apnea: a bidirectional mendelian randomization study. *Nutrients*. 2023;15(21):4544. doi:10.3390/nu15214544
31. Liu Y, Wang L, Bao EH, et al. Link between obstructive sleep apnea and kidney stones: NHANES 2015-2018 and Mendelian randomization. *Nat Sci Sleep*. 2024;16:1557–1568. doi:10.2147/NSS.S483343
32. Burgess S, Davies NM, Thompson SG. Bias due to participant overlap in two-sample Mendelian randomization. *Genetic Epidemiol*. 2016;40(7):597–608. doi:10.1002/gepi.21998
33. Hartwig FP, Davey Smith G, Bowden J. Robust inference in summary data Mendelian randomization via the zero modal pleiotropy assumption. *Int J Epidemiol*. 2017;46(6):1985–1998. doi:10.1093/ije/dyx102
34. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *Int J Epidemiol*. 2015;44(2):512–525. doi:10.1093/ije/dyv080
35. Huang D, Lin S, He J, Wang Q, Zhan Y. Association between COVID-19 and telomere length: a bidirectional Mendelian randomization study. *J Med Virol*. 2022;94(11):5345–5353. doi:10.1002/jmv.28008
36. Burgess S, Thompson SG. Interpreting findings from Mendelian randomization using the MR-Egger method. *Eur J Epidemiol*. 2017;32(5):377–389. doi:10.1007/s10654-017-0255-x
37. Kopelman PG. Obesity as a medical problem. *Nature*. 2000;404(6778):635–643. doi:10.1038/35007508
38. Aron-Wisnewsky J, Minville C, Tordjman J, et al. Chronic intermittent hypoxia is a major trigger for non-alcoholic fatty liver disease in morbid obese. *J Hepatol*. 2012;56(1):225–233. doi:10.1016/j.jhep.2011.04.022
39. Benotti P, Wood GC, Argyropoulos G, et al. The impact of obstructive sleep apnea on nonalcoholic fatty liver disease in patients with severe obesity. *Obesity*. 2016;24(4):871–877. doi:10.1002/oby.21409
40. Minville C, Hilleret MN, Tamisier R, et al. Nonalcoholic fatty liver disease, nocturnal hypoxia, and endothelial function in patients with sleep apnea. *Chest*. 2014;145(3):525–533. doi:10.1378/chest.13-0938
41. Shah AG, Lydecker A, Murray K, Tetri BN, Contos MJ, Sanyal AJ. Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol*. 2009;7(10):1104–1112. doi:10.1016/j.cgh.2009.05.033
42. Agrawal S, Duseja A, Aggarwal A, et al. Obstructive sleep apnea is an important predictor of hepatic fibrosis in patients with nonalcoholic fatty liver disease in a tertiary care center. *Hepatol Int*. 2015;9(2):283–291. doi:10.1007/s12072-015-9615-3

43. Trzepizur W, Boursier J, Le Vaillant M, et al. Increased liver stiffness in patients with severe sleep apnoea and metabolic comorbidities. *Europ resp J*. 2018;51(6):1800601. doi:10.1183/13993003.00601-2018
44. Trzepizur W, Boursier J, Mansour Y, et al. Association between severity of obstructive sleep apnea and blood markers of liver injury. *Clin Gastroenterol Hepatol*. 2016;14(11):1657–1661. doi:10.1016/j.cgh.2016.04.037
45. Jin S, Jiang S, Hu A. Association between obstructive sleep apnea and non-alcoholic fatty liver disease: a systematic review and meta-analysis. *Sleep Breathing*. 2018;22(3):841–851. doi:10.1007/s11325-018-1625-7
46. Musso G, Cassader M, Olivetti C, Rosina F, Carbone G, Gambino R. Association of obstructive sleep apnoea with the presence and severity of non-alcoholic fatty liver disease. A systematic review and meta-analysis. *Obesity Rev*. 2013;14(5):417–431. doi:10.1111/obr.12020
47. Chung GE, Cho EJ, Yoo JJ, et al. Nonalcoholic fatty liver disease is associated with the development of obstructive sleep apnea. *Sci Rep*. 2021;11(1):13473. doi:10.1038/s41598-021-92703-0
48. Tanné F, Gagnadoux F, Chazouillères O, et al. Chronic liver injury during obstructive sleep apnea. *Hepatology*. 2005;41(6):1290–1296. doi:10.1002/hep.20725
49. Fu Y, Zhang N, Tang W, et al. Chronic intermittent hypoxia contributes to non-alcoholic steatohepatitis progression in patients with obesity. *Hepatol Int*. 2022;16(4):824–834. doi:10.1007/s12072-022-10347-2
50. Ding X, Zhao L, Cui X, Qi L, Chen Y. Mendelian randomization reveals no associations of genetically-predicted obstructive sleep apnea with the risk of type 2 diabetes, nonalcoholic fatty liver disease, and coronary heart disease. *Front Psychiatry*. 2023;14:1068756. doi:10.3389/fpsyt.2023.1068756
51. Strausz S, Ruotsalainen S, Ollila HM, et al. Genetic analysis of obstructive sleep apnoea discovers a strong association with cardiometabolic health. *Europ resp J*. 2021;57(5):2003091. doi:10.1183/13993003.03091-2020
52. Frayling TM, Timpson NJ, Weedon MN, et al. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. *Science*. 2007;316(5826):889–894. doi:10.1126/science.1141634
53. Thorleifsson G, Walters GB, Gudbjartsson DF, et al. Genome-wide association yields new sequence variants at seven loci that associate with measures of obesity. *Nat Genet*. 2009;41(1):18–24. doi:10.1038/ng.274
54. Romeo S, Kozlitina J, Xing C, et al. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. *Nat Genet*. 2008;40(12):1461–1465. doi:10.1038/ng.257
55. Drager LF, Li J, Shin M-K, et al. Intermittent hypoxia inhibits clearance of triglyceride-rich lipoproteins and inactivates adipose lipoprotein lipase in a mouse model of sleep apnoea. *Eur Heart J*. 2012;33(6):783–790. doi:10.1093/eurheartj/ehr097
56. Chen L-D, Zhang L-J, Lin X-J, et al. Association between continuous positive airway pressure and serum aminotransferases in patients with obstructive sleep apnea. *Eur Arch Otorhinolaryngol*. 2018;275(2):587–594. doi:10.1007/s00405-017-4840-0
57. Minville C, Hilleret M-N, Tamisier R, et al. Nonalcoholic fatty liver disease, nocturnal hypoxia, and endothelial function in patients with sleep apnea. *Chest*. 2014;145(3):525–533.
58. Cakmak E, Duksal F, Altinkaya E, et al. Association between the severity of nocturnal hypoxia in obstructive sleep apnea and non-alcoholic fatty liver damage. *Hepat Mon*. 2015;15(11):e32655. doi:10.5812/hepatmon.32655
59. Qi J-C, Huang J-C, Lin Q-C, et al. Relationship between obstructive sleep apnea and nonalcoholic fatty liver disease in nonobese adults. *Sleep Breath*. 2016;20(2):529–535. doi:10.1007/s11325-015-1232-9
60. Singh S, Allen AM, Wang Z, Prokop LJ, Murad MH, Loomba R. Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. *Clin Gastroenterol Hepatol*. 2015;13(4):643–654.e9. doi:10.1016/j.cgh.2014.04.014
61. Sivam S, Phillips CL, Trenell MI, et al. Effects of 8 weeks of continuous positive airway pressure on abdominal adiposity in obstructive sleep apnoea. *Eur Respir J*. 2012;40(4):913–918. doi:10.1183/09031936.00177011
62. Buttacavoli M, Gruttad'Auria CI, Olivo M, et al. Liver steatosis and fibrosis in OSA patients after long-term CPAP treatment: a preliminary ultrasound study. *Ultrasound Med Biol*. 2016;42(1):104–109. doi:10.1016/j.ultrasmedbio.2015.08.009
63. Mesarwi OA, Shin M-K, Drager LF, et al. Lysyl oxidase as a serum biomarker of liver fibrosis in patients with severe obesity and obstructive sleep apnea. *Sleep*. 2015;38(10):1583–1591. doi:10.5665/sleep.5052
64. Savransky V, Nanayakkara A, Vivero A, et al. Chronic intermittent hypoxia predisposes to liver injury. *Hepatology*. 2007;45(4):1007–1013. doi:10.1002/hep.21593
65. Drager LF, Li J, Reinke C, Bevans-Fonti S, Jun JC, Polotsky VY. Intermittent hypoxia exacerbates metabolic effects of diet-induced obesity. *Obesity*. 2011;19(11):2167–2174. doi:10.1038/oby.2011.240
66. Zuber V, Grinberg NF, Gill D, et al. Combining evidence from Mendelian randomization and colocalization: review and comparison of approaches. *Am J Hum Genet*. 2022;109(5):767–782. doi:10.1016/j.ajhg.2022.04.001
67. Suri TM, Ghosh T, Mittal S, Hadda V, Madan K, Mohan A. Systematic review and meta-analysis of the prevalence of obstructive sleep apnea in Indian adults. *Sleep Med Rev*. 2023;71:101829. doi:10.1016/j.smrv.2023.101829