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Hypertension and NAFLD risk: Insights from the NHANES 2017–2018 and Mendelian randomization analyses

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Abstract

Background: Hypertension and non-alcoholic fatty liver disease (NAFLD) share several pathophysiologic risk factors, and the exact relationship between the two remains unclear. Our study aims to provide evidence concerning the relationship between hypertension and NAFLD by analyzing data from the National Health and Nutrition Examination Survey (NHANES) 2017–2018 and Mendelian randomization (MR) analyses.

Methods: Weighted multivariable-adjusted logistic regression was applied to assess the relationship between hypertension and NAFLD risk by using data from the NHANES 2017–2018. Subsequently, a two-sample MR study was performed using the genome-wide association study (GWAS) summary statistics to identify the causal association between hypertension, systolic blood pressure (SBP), diastolic blood pressure (DBP), and NAFLD. The primary inverse variance weighted (IVW) and other supplementary MR approaches were conducted to verify the causal association between hypertension and NAFLD. Sensitivity analyses were adopted to confirm the robustness of the results.

Results: A total of 3144 participants were enrolled for our observational study in NHANES. Weighted multivariable-adjusted logistic regression analysis suggested that hypertension was positively related to NAFLD risk (odds ratio [OR] = 1.677; 95% confidence interval [CI], 1.159–2.423). SBP ≥130 mmHg and DBP ≥80 mmHg were also significantly positively correlated with NAFLD. Moreover, hypertension was independently connected with liver steatosis (β = 7.836 [95% CI, 2.334–13.338]). The results of MR analysis also supported a causal association between hypertension (OR = 7.203 [95% CI, 2.297–22.587]) and NAFLD. Similar results were observed for the causal exploration between SBP (OR = 1.024 [95% CI, 1.003–1.046]), DBP (OR = 1.047 [95% CI, 1.005–1.090]), and NAFLD. The sensitive analysis further confirmed the robustness and reliability of these findings (all P >0.05).

Conclusion: Hypertension was associated with an increased risk of NAFLD.

Keywords: Hypertension; Non-alcoholic fatty liver disease; National Health and Nutrition Examination Survey; Mendelian randomization analysis; Causality

Introduction

Non-alcoholic fatty liver disease (NAFLD) is currently the most prevailing etiology of chronic liver disease.[1] NAFLD is a disease that progresses from steatosis to irreversible steatohepatitis, liver fibrosis, cirrhosis, and finally liver cancer.[2] Although less than 10% of NAFLD patients develop cirrhosis and liver cancer within 10–20 years of diagnosis, this remains a great concern for the medical community given the high prevalence of the disease.[3]

Hypertension is one of the main risk factors for cardiovascular disease, affecting an estimated 30% of the global population.[4] It is worth noting that a cross-sectional multicenter study found that compared to normotensive youth, hypertensive youth had an increased body mass index (BMI), insulin resistance (IR), and liver steatosis.[5] Therefore, the 2016 joint guidelines from the European

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Association for the Study of Liver (EASL), Diabetes (EASD), and Obesity (EASO) recommend that non-alcoholic steatohepatitis patients with fibrosis associated with hypertension should receive closer monitoring.[6] However, hypertension and NAFLD often co-exist in the same individual in a complex two-way relationship as they share common metabolic risk factors, such as age, obesity, and IR.[7] Existing observational studies are also subject to a few limitations, such as small sample sizes, and are usually influenced by confounding and reverse causation. Therefore, it is difficult to obtain definitive proof of an independent association between hypertension and NAFLD.[8]

The National Health and Nutrition Examination Survey (NHANES) is a continuing cross-sectional study carried out by the National Center for Health Statistics (NCHS) that aims to evaluate the nutritional status and emerging public health conditions of the American population.[9] Therefore, NHANES can provide high-quality, large-sample, and nationally representative data to evaluate the correlation between hypertension and NAFLD risk.

Mendelian randomization (MR) analyses have been recognized as a complementary approach to randomized controlled trials (RCTs) and have been widely regarded as an emerging epidemiology method that evaluates the causal effects of exposure on a particular outcome using genetic variables.[10,11] Furthermore, the results of the MR approach are less susceptible to residual confounding and reverse causality bias as the genetic variants are randomly allocated during meiosis and are not correlated with environmental factors.[12]

In this study, we combined a large-scale observational study in the NHANES 2017–2018 and a two-sample MR analysis to comprehensively assess the relationship between hypertension and NAFLD.

Methods

Study population in NHANES

The data used in the current analysis are publicly available through the NHANES database (https://www.cdc.gov/nchs/nhanes/index.htm). The protocols of the NHANES study were authorized by the Research Ethics Review Board of NCHS. Informed consent was obtained from all the NHANES participants. The study was exempt from the approval of the institutional review board as it used de-identified, publicly available data.

The study's inclusion criteria comprised participants who were enrolled in the NHANES Mobile Examination Center in 2017–2018 and met the following conditions: age of 20 years or above, and authorization for elastography measurements using FibroScan 502 Touch (Echosens, Paris, France).[13] The study sample consisted of 5569 individuals who fulfilled these eligibility criteria. Exclusion criteria were as follows: (1) individuals with ineligible, not performed, or partial elastography examination status ($N = 1059$); (2) missing controlled attenuation parameter (CAP, which can quantify the steatosis degree) data ($N = 1$); (3) individuals who were infected with hepatitis B (defined by the presence of hepatitis B surface antigen) or hepatitis C (positive for hepatitis C antibodies or hepatitis C RNA) ($N = 118$); (4) individuals with significant alcohol consumption (individuals who drink an average of one to two or more standardized drinks per day, respectively) or missing information about alcohol consumption ($N = 938$); (5) taking steatogenic drugs (such as amiodarone, methotrexate, and tamoxifen) for at least 3 months before study recruitment ($N = 24$); and (6) missing information regarding blood pressure values ($N = 285$). Finally, this study consisted of 3144 participants [Supplementary Figure 1, http://links.lww.com/CM9/B606].

Definition and assessment of hypertension and NALFD in NHANES

Protocols used for blood pressure measurements followed procedures established by the American Heart Association. After measuring blood pressure thrice under quiescent conditions, the average values of systolic blood pressure (SBP) and diastolic blood pressure (DBP) were calculated. The 2017 American Heart Association/American College of Cardiology (AHA/ACC) guideline recommended that individuals with an SBP ≥130 mmHg and/or DBP ≥80 mmHg should be defined as having hypertension.[14] Meanwhile, participants who answered "yes" to the question: "Ever told you had high blood pressure?" are also classified as having hypertension.

NAFLD is traditionally diagnosed by either imaging or histological pathways to determine the presence of hepatic steatosis. NHANES staff used the FibroScan 502 Touch device to evaluate participants for vibration-controlled transient elastography (VCTE) from 2017 to 2018. The FibroScan 502 Touch device can be used to measure the ultrasound attenuation related to the degree of NAFLD and record the CAP as the indicator for levels of fat in the liver. The CAP value is positively associated with the severity of NAFLD. We utilized a cutoff value of 285 dB/m for CAP as the marker for NAFLD status. This cutoff value, which exhibits an 80% sensitivity and 77% specificity, has been developed and validated in the United States population for detecting hepatic steatosis in individuals.[15]

Other covariates used in NHANES

To control the potential confounding effects, the following demographic characteristics were adjusted: sex, age, race, educational levels, BMI, waist circumference, smoking and diabetes status, total cholesterol, triglycerides, high-density lipoprotein (HDL)-cholesterol, glycosylated hemoglobin (HbA1c), and physical activity. We selected these confounders based on their associations with the outcomes of interest or a change in effects estimate of more than 10%. The smoking status of participants was categorized into never, former, and current smokers. It is distinguished on the condition of whether they have smoked less than 100 cigarettes during their lifetime and whether they do so now. Diabetes was defined as a history of previous diabetes, HbA1c

level ≥6.5%, or fasting blood glucose level ≥126 mg/dL. Physical activity was classified into low (<600 min/week), moderate (≥600 min/week and <8000 min/week), and high levels (≥8000 min/week) according to the metabolic equivalent of the task.

Genome-wide association study (GWAS) sources and single nucleotide polymorphisms (SNPs) selection

The genetic variants strongly related to hypertension were derived from the MRC Integrative Epidemiology Unit (MRC-IEU) consortium, which enrolled 462,933 Europeans (119,731 cases and 343,202 controls) in total. Data for SBP and DBP were collected from a meta-analysis of GWAS, which included 757,601 participants from the UK Biobank and the International Consortium of Blood Pressure (ICBP) consortium.[16] Moreover, we obtained a summary of data for genetic associations with NAFLD from the FinnGen GWAS, which enrolled 894 cases and 217,898 controls. NAFLD used in the Finngen cohort referred to the fatty replacement of the hepatic parenchyma that was not related to alcohol use and was diagnosed according to the International Classification of Diseases (ICD) -10 K76.0 (both hospital discharge and cause of death). These GWAS data were downloaded from the Integrative Epidemiology Unit (IEU) OpenGWAS database (https://gwas. mrcieu. ac. uk/).[17] All studies were reviewed and approved by local institutional review boards, and all participants provided informed consent.

To identify the genetic variations that can be used for the estimation of causal effects between exposures (hypertension, SBP, and DBP, respectively) and NAFLD, the genome-wide significance level was set at $P < 5\times10^{-8}$ to screen the genetic variant that strongly associated with the exposure. Furthermore, we excluded those SNPs with linkage disequilibrium (r^2 <0.001, 10,000 kb). Then, the PhenoScanner database was used to check each SNP to eliminate the SNPs that were significantly related to the potential confounders and other NALFD-related characteristics. Finally, 144, 286, and 302 SNPs for hypertension, SBP, and DBP, respectively, were extracted for the subsequent causality analysis [Supplementary Table 1, http://links.lww.com/CM9/B606]. Considering the effect of metabolic factors on NAFLD, we excluded potential confounders including BMI, waist circumference, other cardiovascular diseases, diabetes, dyslipidemia, drinking, and smoking.[18] Details information about data downloading and screening are displayed in Table 1.

Statistical analysis

When performing NHANES analysis, we implemented multivariate-adjusted logistic regression to assess the relationship between hypertension, SBP, DBP, and NAFLD. Three models adjusted for covariates were assessed: Model 1 was not adjusted; Model 2 included gender, age, race, and education level; Model 3 was additionally adjusted for age, gender, race, education level, BMI, waist circumference, total cholesterol, triglycerides, HDL-cholesterol, diabetes, HbA1c, smoking status, and physical activity class. Results are presented as odds ratios (ORs) or β coefficients (95% confidence interval [CI]). Given the complex probabilistic clustering design of NHANES, weights were considered in statistical analyses in this study.

As for the two-sample MR analysis, we applied inverse variance weighted (IVW) as the principal method to assess the causal association of genetically predicted hypertension, SBP, DBP, and NAFLD risk. Furthermore, four complementary MR analysis methods were used, including MR Egger, weighted median, weighted mode, and MR-Pleiotropy residual sum and outlier (MR-PRESSO), to validate the results from IVW. Since the IVW estimates may be biased by introducing pleiotropic instrumental variables, the pleiotropic effects in the causal estimates were resolved by sensitivity analyses. Cochrane's Q test was used to evaluate the potential heterogeneity. A random-effects IVW analysis was used to adjust the measured heterogeneity (P <0.05). Next, the intercept of MR-Egger was adopted to estimate the horizontal pleiotropy of the genetic variants (P <0.05 was considered as the potential presence of horizontal pleiotropy). MR-PRESSO was also used to assess the presence of pleiotropy by comparing the observed residual sum of squares with the expected residual sum of squares. Moreover, the leave-one-out analysis was performed to determine whether the results were driven by individual variants.

R software, version 4.1.3 (R Foundation, Vienna, Austria) and EmpowerStats software (X&Y Solutions Inc., Boston, MA, USA) were used to perform all statistical analyses.

Table 1: Characteristics of GWAS enrolled in the MR study.

Items	GWAS ID	Consortium	Sample size	No. of strongly related SNPs	No. of enrolled SNPs	Population
Hypertension	ukb-b-14057	MRC-IEU	462,933	225	144	Europeans
SBP	ieu-b-38	ICBP	757,601	461	286	Europeans
DBP	ieu-b-39	ICBP	757,601	460	302	Europeans
NAFLD	finn-b-NAFLD	FinnGen	218,792	–	–	Europeans

DBP: Diastolic blood pressure; GWAS: Genome-wide association study; ICBP: International Consortium of Blood Pressure; MR: Mendelian randomization; MRC-IEU: MRC Integrative Epidemiology Unit; NAFLD: Non-alcoholic fatty liver disease; SBP: Systolic blood pressure; SNPs: Single nucleotide polymorphisms.

Results

Population characteristics of study subjects according to NAFLD

Table 2 shows the clinical and laboratory features of the study participants. Participants were classified into 1929 individuals with NAFLD and 1215 individuals without NAFLD according to the cutoff value of 285 dB/m for CAP. Patients with NAFLD were older, predominantly male, and of a non-Hispanic white ethnicity; additionally, they demonstrated a lower level of education and a higher prevalence of smoking, diabetes, and hypertension. Furthermore, as expected, they had significantly higher median stiffness, median CAP, BMI, waist circumference, SBP, DBP, alanine aminotransferase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), γ-glutamyltransferase (GGT), uric acid, total cholesterol, triglycerides, high-sensitivity C-reactive protein (HS-CRP), HbA1c, and fasting glucose, while high-density lipoprotein (HDL)-cholesterol was lower.

Observational associations between hypertension and NAFLD in NHANES

The result of multivariate regression analysis depicted that there was a significant relationship between hypertension (OR = 1.677 [95% CI, 1.159–2.423]) and NAFLD risk [Table 3]. After adjustment for potential confounding, 130 mmHg ≤SBP <140 mmHg (OR = 1.802 [95% CI, 1.184–2.743]), SBP ≥140 mmHg (OR = 1.648 [95% CI, 1.073–2.531]), 80 mmHg ≤DBP <90 mmHg (OR = 1.397 [95% CI, 1.072–1.820]), and DBP ≥90 mmHg (OR = 1.513 [95% CI, 1.036–2.210]) were also significantly positively correlated with NAFLD. However, the significant correlation between 120 mmHg ≤SBP<130 mmHg and NAFLD becomes insignificant after adjusting for the covariates in Model 3 (OR = 1.564 [95% CI, 0.988–2.478]). Additionally, Table 4 depicts that hypertension was positively linked with CAP (*β* 7.836 [95% CI, 2.334–13.338]). Hypertension also exhibited a significant positive association with liver stiffness in Model 1 (*β* 1.142 [95% CI, 0.913–1.572]) and Model 2 (*β* 0.985 [95% CI, 0.411–1.559]). However, this significant relationship becomes insignificant after adjusting for the covariates in Model 3 (β –0.031 [95% CI, –0.761 to 0.699]).

Causal relationships between hypertension and NAFLD risk in MR

As the significantly positive correlation between hypertension and NAFLD risk was observed in the multivariable regression analysis mentioned above, we further conducted MR analysis to deduce the causal effects of hypertension on NAFLD risk. As shown in Table 5, results suggested that there were positive causal relationships between hypertension (OR = 7.203 [95% CI, 2.297–22.587]), SBP (OR = 1.024 [95% CI, 1.003–1.046]), and DBP (OR = 1.047 [95% CI, 1.005–1.090]) and NAFLD using the IVW method. Additionally, these results were consistent with other supplementary MR methods in terms of the direction of causal estimation and the magnitude of the causal effect, thus indicating that these findings are reliable and robust. Figure 1 depicted the effect estimates of exposure on NAFLD that were measured by different MR methods. The forest diagram was used to show the estimated effect of each SNP on NAFLD [Supplementary Figure 2, http://links.lww.com/CM9/B606].

Notably, potential statistical SNP heterogeneity was observed in the effects of DBP on NAFLD (IVW: $P = 0.041$ and MR Egger: $P = 0.041$, respectively, Table 5). Therefore, we then applied the multiplicative random-effects IVW method to assess the causal association between DBP and NAFLD by adjusting the measured heterogeneity. To evaluate whether the three exposures associated SNPs can lead to NAFLD through other potential ways, we further conducted horizontal pleiotropic analyses. The results showed that no evidence of pleiotropic effects was found in any of the three exposures using the MR-Egger test (all $P > 0.05$). Moreover, the MR-PRESSO global test also did not detect the horizontal pleiotropic effect and any outlier SNPs (all $P > 0.05$). The symmetry of the funnel plot also indicated the same result [Supplementary Figure 3, http://links.lww.com/CM9/B606]. The leave-one-SNP-out analysis further confirmed that the causal relationship between hypertension, SBP, DBP, and NAFLD was not driven by any single SNP [Supplementary Figure 4, http://links.lww.com/CM9/B606]. Therefore, the above result showcases that our results were robust and reliable.

Discussion

In the present research, we integrated the observational study using the nationally representative NHANES 2017–2018 cohort and a two-sample MR analysis to investigate the relationship between hypertension and NAFLD. Our finding suggested that compared with non-NAFLD patients, NAFLD patients have a higher proportion of hypertension. Meanwhile, the two-sample MR method further confirmed the causal effect of hypertension on NAFLD, suggesting that hypertension would be a candidate modifiable factor for NAFLD.

NAFLD is characterized by an excessive accumulation of lipids within hepatocytes accompanied by IR in the absence of heavy alcohol consumption.[19] As a hepatic manifestation of a metabolic syndrome, NAFLD is associated with metabolic comorbidities, such as obesity, hyperlipidemia, type 2 diabetes, and cardiovascular diseases.[18,20] With the deepening of the research on metabolic diseases, we continue to gain a better understanding of the relationship between hypertension and NAFLD risk.[21,22] A large-scale cohort study involving over 5000 participants and a meta-analysis that included 11 observational cohort studies both concluded that the presence of hypertension was significantly associated with an increased risk of incident NAFLD.[23,24] Moreover, the increased level of SBP within the normal range was also correlated with a significantly increased risk of NAFLD.[25] Our findings from the nationally representative NHANES 2017–2018 also suggested that NAFLD patients presented a significantly higher proportion of hyperten-

Table 2: Demographic and clinical characteristics of the participants with and without NAFLD.

Items	Non-NAFLD	NAFLD	Statistics	*P* value
Age (years)	48 (32, 62)	55 (41, 66)	–7.052	<0.001*
Gender			30.855	<0.001†
Male	920 (47.7%)	703 (57.9%)		
Female	1009 (52.3%)	512 (42.1%)		
Race			60.735	<0.001†
Mexican American	198 (10.3%)	222 (18.3%)		
Other Hispanic	519 (26.9%)	224 (18.4%)		
Non-Hispanic White	678 (35.1%)	456 (37.5%)		
Non-Hispanic Black	186 (9.6%)	113 (9.3%)		
Other race	348 (18.0%)	200 (16.5%)		
Education level‡			14.784	0.001†
High school	754 (39.1%)	526 (43.3%)		
Some college or AA degree	632 (32.8%)	422 (34.7%)		
College graduate or above	541 (28.1%)	267 (22.0%)		
Unknown	2 (0%)	0 (0%)		
Ratio of family income to poverty‡	2.4 (1.2, 4.3)	2.2 (1.2, 4.3)	–0.134	0.894*
Physical activity‡			5.607	0.061†
Low level (<600 min/week)	212 (11.0%)	159 (13.1%)		
Moderate level (≥600 and <8000 min/week)	928 (48.1%)	529 (43.5%)		
High level (≥8000 min/week)	365 (18.9%)	211 (17.4%)		
Unknown	424 (22.0%)	316 (26.0%)		
Smoker status			25.011	<0.001†
Never	1134 (58.8%)	642 (58.8%)		
Former	442 (22.9%)	376 (30.9%)		
Current	353 (18.3%)	197 (16.2%)		
BMI‡	26.3 (23.2, 30.2)	32.7 (28.6, 37.6)	–25.817	<0.001*
Waist circumference (cm)‡	92.7 (83.7, 102.7)	110.7 (100.0, 120.6)	–28.052	<0.001*
SBP	118.0 (108.8, 131.0)	124.3 (112.7, 138.7)	–7.714	<0.001*
DBP	71.3 (65.3, 79.0)	75.7 (68.3, 83.7)	–9.598	<0.001*
Median stiffness (kPa)	4.6 (3.8, 5.6)	5.6 (4.5, 7.0)	–17.818	<0.001*
Median CAP (dB/m)	230.0 (200.0, 258.0)	327.0 (302.0, 351.3)	–47.284	<0.001*
Hypertension			132.150	<0.001†
No	978 (50.7%)	363 (29.9%)		
Yes	951 (49.3%)	852 (70.1%)		
Diabetes			201.289	<0.001†
No	1697 (88.0%)	816 (67.2%)		
Yes	232 (12.0%)	399 (32.8%)		
Laboratory features‡				
ALT (U/L)	16.0 (12.0, 23.0)	22.0 (16.0, 34.0)	–16.732	<0.001*
AST (U/L)	19.0 (16.0, 22.0)	20.0 (16.0, 27.0)	–7.246	<0.001*
ALB (g/dL)	4.0 (3.9, 4.3)	4.0 (3.8, 4.2)	–2.406	0.016*
ALP (IU/L)	71.0 (60.0, 86.0)	78.5 (65.0, 96.0)	–8.842	<0.001*
GGT (IU/L)	18.0 (13.0, 27.0)	25.0 (18.0, 38.0)	–16.668	<0.001*
Total bilirubin (mg/dL)	6.8 (5.1, 10.3)	6.8 (5.1, 10.2)	–0.760	0.447
Uric acid (mg/dL)	5.1 (4.3, 6.0)	5.9 (4.9, 7.0)	–12.692	<0.001*
Total cholesterol (mmol/L)	4.7 (4.0, 5.4)	4.7 (4.1, 5.6)	–3.208	0.001*
Triglycerides (mmol/L)	1.0 (0.8, 1.5)	1.5 (1.2, 2.0)	–19.664	<0.001*
HDL-cholesterol (mmol/L)	1.4 (1.2, 1.7)	1.2 (1.0, 1.4)	–17.134	<0.001*
LDL-cholesterol (mmol/L)	2.7 (2.2, 3.4)	2.8 (2.3, 3.5)	–1.051	0.293*
HS-CRP (mg/L)	1.5 (0.7, 3.3)	2.9 (1.3, 5.9)	–14.288	<0.001*
HbA1c (%)	5.5 (5.2, 5.8)	5.9 (5.5, 6.5)	–16.792	<0.001*
Fasting glucose (mg/dL)	100.0 (95.0, 109.0)	112.0 (102.0, 130.0)	–13.897	<0.001*

Data were presented as median (interquartile range) or *n* (%). *Mann-Whitney U test for continuous variables. †Pearson's chi-squared test for categorical variables. ‡Presence of missing values. AA: Associate of arts; ALB: albumin; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate transaminase; BMI: Body mass index; CAP: Controlled attenuation parameter; DBP: Diastolic blood pressure; GGT: γ-Glutamyltransferase; HbA1c: glycosylated hemoglobin; HDL: High-density lipoprotein; HS-CRP: High-sensitivity C-reactive protein; LDL: Low-density lipoprotein; NAFLD: Non-alcoholic fatty liver disease; PRESSO: Pleiotropy residual sum and outlier; SBP: Systolic blood pressure.

Table 3: Association between blood pressure categories and NAFLD.

Items	Model 1: OR (95% CI)	Model 2: OR (95% CI)	Model 3: OR (95% CI)
Non-hypertension	Reference	Reference	Reference
Hypertension	3.126 (2.507, 3.898)	2.857 (2.067, 3.948)	1.677 (1.159, 2.423)
SBP			
SBP <120 mmHg	Reference	Reference	Reference
120 mmHg ≤ SBP < 130 mmHg	1.991 (1.493, 2.655)	1.712 (1.071, 2.736)	1.564 (0.988, 2.478)
130 mmHg ≤ SBP < 140 mmHg	1.931 (1.562, 2.386)	1.562 (1.223, 2.173)	1.802 (1.184, 2.743)
SBP ≥140 mmHg	2.197 (1.628, 2.966)	1.661 (1.029, 2.682)	1.648 (1.073, 2.531)
DBP			
DBP <80 mmHg	Reference	Reference	Reference
80 mmHg ≤ DBP < 90 mmHg	2.102 (1.635, 2.702)	2.069 (1.472, 2.907)	1.397 (1.072, 1.820)
DBP ≥90 mmHg	2.704 (1.913, 3.823)	2.609 (1.571, 4.333)	1.513 (1.036, 2.210)

Model 1 adjusted for: none. Model 2 adjusted for: gender, age, race, and education level. Model 3 adjusted for: gender, age, race, education level, BMI, waist circumference, total cholesterol, triglycerides, HDL-cholesterol, diabetes, HbA1c, smoking status, and physical activity class. BMI: Body mass index; CI: Confidence interval; DBP: Diastolic blood pressure; HbA1c: Glycosylated hemoglobin; HDL: High-density lipoprotein; NAFLD: Non-alcoholic fatty liver disease; OR: Odds ratio; SBP: Systolic blood pressure.

Table 4: Association between hypertension and hepatic steatosis and liver stiffness.

	CAP (dB/m)			Liver stiffness (kPa)		
Items	Model 1: β (95% CI)	Model 2: β (95% CI)	Model 3: β (95% CI)	Model 1: β (95% CI)	Model 2: β (95% CI)	Model 3: β (95% CI)
Non-hypertension	Reference	Reference	Reference	Reference	Reference	Reference
Hypertension	36.386 (29.769, 43.004)	29.324 (21.759, 36.888)	7.836 (2.334, 13.338)	1.142 (0.913, 1.572)	0.985 (0.411, 1.559)	–0.031 (–0.761, 0.699)

Model 1 adjusted for: none. Model 2 adjusted for: gender, age, race, and education level. Model 3 adjusted for: gender, age, race, education level, BMI, waist circumference, total cholesterol, triglycerides, HDL-cholesterol, diabetes, HbA1c, smoking status, and physical activity class. BMI: Body mass index; CAP: Controlled attenuation parameter; CI: Confidence interval; HbA1c: Glycosylated hemoglobin; HDL: High-density lipoprotein.

Table 5: MR estimates from each method of assessing the causal effect of hypertension on the risk of NAFLD.

Exposure	MR method	β	SE	OR (95% CI)	*P* vale for association	*P* value for heterogeneity test	*P* value for MR-Egger intercept	*P* value for MR-PRESSO global test
Hypertension	IVW	1.975	0.583	7.203 (2.297, 22.587)	<0.001	0.780		
	MR-Egger	5.073	1.751	159.677 (5.166, 4935.958)	0.004	0.825	0.063	
	Weighted median	2.515	0.892	12.361 (2.304, 66.306)	0.005			
	Weighted mode	2.922	1.989	18.587 (0.390, 884.793)	0.144			
	MR-PRESSO	1.730	0.542	5.640 (1.949, 16.314)	0.002			0.778
SBP	IVW	0.026	0.012	1.024 (1.003, 1.046)	0.029	0.270		
	MR-Egger	0.057	0.031	1.063 (1.008, 1.122)	0.067	0.273	0.278	
	Weighted median	0.048	0.019	1.051 (1.018, 1.085)	0.011			
	Weighted mode	0.073	0.035	1.073 (1.003, 1.148)	0.040			
	MR-PRESSO	0.027	0.012	1.028 (1.004, 1.051)	0.020			0.306
DBP	IVW	0.045	0.021	1.047 (1.005, 1.090)	0.027	0.041		
	MR-Egger	0.098	0.053	1.103 (0.995, 1.224)	0.064	0.041	0.280	
	Weighted median	0.062	0.030	1.064 (1.003, 1.129)	0.041			
	Weighted mode	0.107	0.066	1.113 (0.978, 1.267)	0.110			
	MR-PRESSO	0.045	0.020	1.046 (1.005, 1.087)	0.026			0.070

CI: Confidence interval; DBP: Diastolic blood pressure; IVW: Inverse variance weighted; MR: Mendelian randomization; NAFLD: Non-alcoholic fatty liver disease; OR: Odds ratio; PRESSO: Pleiotropy residual sum and outlier; SBP: Systolic blood pressure; SE: Standard error.

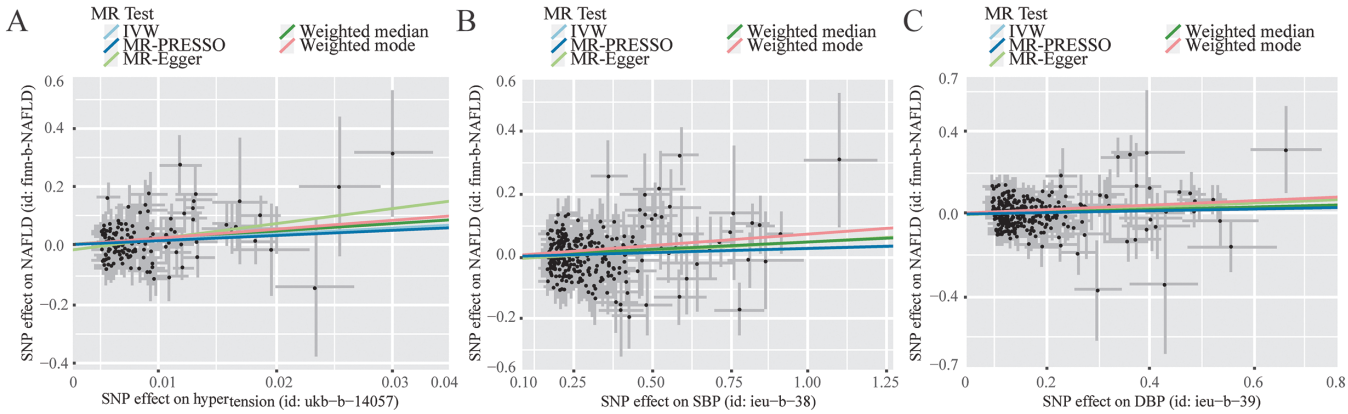

Figure 1: Scatter plot for the associations between hypertension against risk of NAFLD. (A) Hypertension, (B) SBP, and (C) DBP. DBP: Diastolic blood pressure; IVW: Inverse variance weighted; MR: Mendelian randomization; NAFLD: Non-alcoholic fatty liver disease; PRESSO: Pleiotropy residual sum and outlier; SBP: Systolic blood pressure; SNP: Single nucleotide polymorphism.

sion and higher levels of SBP and DBP. Multivariable logistic regression analysis implied a significant positive association between hypertension, SBP, DBP, and NAFLD after adjusting for potential confounders. Furthermore, according to our findings, hypertension was strongly associated with increased odds of CAP, which was consistent with previous studies.[26,27]

However, it is difficult to make causal inferences between hypertension and NAFLD as the association between them is complex.[28] Therefore, apart from using the nationally representative observational study, we further performed the MR method to clarify the causal association between hypertension and NAFLD. Based on the MR results in the European population, our understanding of the positive causal effect of hypertension on NAFLD has been broadened. Except for the primary IVW method, other complementary MR methods provided consistent findings. The sensitivity analysis further affirmed the robustness and reliability of the positive association. In addition, the same results were observed in the causal exploration of SBP, DBP, and NAFLD.

The primary advantage of this study is the use of an observational study from the NHANES 2017–2018 combined with the MR approach. The comprehensive assessment of various factors and large sample size allowed us to reliably adjust our analyses for multiple confounders simultaneously in multivariable regression models and provide sufficient statistical power to evaluate the causality between hypertension and NAFLD. Furthermore, the MR approach can avoid unmeasured confounding as well as reverse causality bias.[29] Against this backdrop, it is noteworthy to mention that both methods obtained nearly consistent results in the present study, which made the findings more reliable. However, our study also has several limitations. First, NAFLD was diagnosed based on VCTE, which may have understated the prevalence of the disease. Second, since many individuals with missing alcohol consumption and blood pressure data were excluded from the observational analysis, there may be a potential selection bias. Third, although we controlled for many covariates that were considered relevant confounders, it is possible that there was still residual and unmeasured confounding (such as dietary factors). Finally, our observations mainly focused on European and American populations, limiting the extrapolation of our findings to other ethnic groups. Further studies in larger sample sizes and other ethnic populations are warranted to validate the present findings.

In conclusion, combining a large observational study in NHANES and MR analysis allowed us to arrive at the finding that hypertension is a strong indicator of an increased risk of NAFLD. Findings highlight the causal effects of hypertension-associated variants on NAFLD, which has significant implications for understanding the relationship between hypertension and NAFLD. However, our findings need to be verified and the underlying mechanisms should be clarified further.

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Conflicts of interest

None.

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