



Sex-Specific Basal Metabolic Rate and NAFLD Risk: The Multi-Population Observational and Mendelian Randomization Study

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Background: The impact of basal metabolic rate (BMR) on non-alcoholic fatty liver disease (NAFLD) is still not fully understood, particularly regarding potential sex differences. We aimed to explore population-specific associations using data from health examinations, NHANES 2017–2020, and genome-wide association studies (GWASs).

Methods: 30,845 Chinese from health examinations and 5019 US adults from NHANES were analyzed. BMR was estimated using the Mifflin-St Jeor equation. Multivariable-adjusted logistic regression and restricted cubic splines (RCS) were applied. To determine the causality, a two-sample MR study was conducted among Europeans using GWASs data for BMR (IEU OpenGWAS) and NAFLD (FinnGen). Odds ratios (ORs) with 95% confidence intervals (CIs) were reported.

Results: In Chinese, ORs (95% CIs) for NAFLD across ascending quartile groups of BMR were 1 (reference), 1.17 (1.03–1.33), 1.83 (1.60–2.09), and 5.98 (4.92–7.28). The corresponding ORs (95% CIs) were 2.00 (1.67–2.39), 2.71 (2.24–3.29), and 4.91 (3.97–6.10) for males, and 1.64 (1.41–1.92), 1.93 (1.64–2.27), and 4.04 (3.41–4.81) for females. In the NHANES, weighted ORs (95% CIs) for NAFLD across quartile groups were 1 (reference), 1.84 (0.95–3.54), 4.98 (2.28–10.89), and 16.10 (6.69–38.72), with similar associations across sexes. Significant sex differences in BMR-NAFLD associations (P for interaction <0.05) were observed in the Chinese, but not in the US population. RCS revealed nonlinear dose-response relationships in both sexes within the Chinese population. Two-sample MR confirmed a causal effect with OR (95% CI) of 1.59 (1.24–2.03).

Conclusion: A higher BMR is an independent and causally relevant risk factor for NAFLD. The observed sex effect modification in the Chinese population suggests that population-specific management strategies may be warranted.

Keywords: basal metabolic rate, non-alcoholic fatty liver disease, sex-specific, Mendelian randomization

Introduction

As one of the most common causes of chronic liver disease, non-alcoholic fatty liver disease (NAFLD) has affected about 30% of the population worldwide.¹ The characteristic of NAFLD is excessive lipid accumulation in liver cells, accompanied by insulin resistance (IR), and it occurs without excessive alcohol consumption.² NAFLD is influenced by energy metabolism and closely associated with metabolic diseases such as obesity, type 2 diabetes (T2DM), and dyslipidemia.³ Notably, the magnitude of the role of these factors in NAFLD development varies by sex.⁴ NAFLD can progress from isolated hepatic steatosis to hepatocellular carcinoma and is an independent risk factor for cardiovascular disease (CVD).^{5,6} Early identification and effective control of NAFLD risk factors are beneficial for reducing its global burden and promoting population health.⁷

Abnormal energy metabolism is detrimental to the liver system and critical in human health and physiology throughout the life course.⁸ Basal metabolic rate (BMR) is the daily energy expenditure needed to maintain essential bodily functions while at rest and awake.⁹ In humans, BMR typically accounts for about 60% to 70% of total daily energy expenditure and plays a crucial role in maintaining energy balance.¹⁰ Energy expenditure is directly linked to

T2DM, with a noticeable increase in BMR accompanying the progression of IR,^{11,12} even in relatively healthy (non-T2DM) obese US adults.¹³ Hypertension is also associated with elevated BMR.¹⁴ Additionally, BMR is regarded as a predictor of mortality¹⁵ and has garnered attention in the context of metabolic diseases, CVDs, and cancers.^{16,17} Given the complex interplay between metabolic syndrome and NAFLD, further clarification of the association between BMR and NAFLD is crucial. Elevated BMR may correlate with systemic inflammation, IR, and metabolic stress. Pro-inflammatory cytokines such as TNF- α , IL-6, and IL-1 β induce adaptive thermogenesis to elevate basal energy expenditure.¹⁸ Observational studies showed that IR impairs glucose disposal, disrupts adipose lipolysis, perturbs energy balance, and further modulates BMR.¹⁹ Metabolic stress from IR and inflammation may upregulate BMR as a compensatory mechanism, potentially exacerbating metabolic dysregulation in NAFLD.^{20,21}

Current clinical research on the BMR-NAFLD relationship is limited, with its causal nature remaining unclear. This paucity of studies hinders the development of metabolism-driven risk stratification and targeted preventive strategies for NAFLD. Moreover, the impact of BMR on NAFLD risk may exhibit sexual dimorphism owing to differences in body composition and lifestyle. In terms of body composition, the Chinese population exhibits a higher prevalence of abdominal obesity at lower body mass index (BMI) compared to Western cohorts, a trait linked to altered energy metabolism and heightened NAFLD susceptibility.²² Additionally, higher muscle mass tends to elevate BMR while potentially reducing NAFLD risk, whereas increased adiposity may exacerbate NAFLD.^{23,24} Regarding lifestyle factors, disparities in dietary fat intake patterns and physical activity levels further modulate basal energy expenditure and hepatic lipid accumulation, with sedentary habits worsening NAFLD risk via the mediation of inflammatory markers.²⁵ Collectively, these factors shape the potential interplay between BMR and NAFLD, underscoring the value of our multi-population analysis and the role of lifestyle interventions in NAFLD management.

Mendelian randomization (MR) analyses, as a complementary approach to randomized controlled trials (RCTs), have been widely implemented to evaluate the causal nature using genetic variables as instrumental variables (IVs). Due to the random assignment of genetic variation during gametogenesis, the MR approach minimizes biases from confounding and reverse causality that often affect observational studies.²⁶ Leveraging large-scale genome-wide association study (GWAS) summary statistics, MR design provides a time- and resource-efficient alternative to RCTs.

In the present analysis, we conducted an observational study to assess the population-specific relationship between BMR and NAFLD and verify the cross-ethnic generalizability using data from the Chinese health examinations and the National Health and Nutrition Examination Survey (NHANES) 2017–2020. Subsequently, we performed a two-sample MR analysis to investigate its causal association.

Materials and Methods

Study Population

A total of 58,040 Chinese participants who underwent health check-ups and completed abdominal ultrasonography via online appointments between 2015 and 2023 were initially accessed through the electronic health record database from the Department of Health Management. The study was approved by the Ethics Committees of the First Affiliated Hospital of Army Medical University (No. [A]KY202227). All participants provided written informed consent. Exclusion criteria were as follows: (1) age <18 years ($n = 48$); (2) pregnancy ($n=1563$); (3) multiple records (retaining only the first, $n=3205$); (4) presence of serious diseases (chronic hepatitis, cirrhosis, cancer, or cardiovascular diseases) ($n=3354$); (5) daily alcohol consumption ($n = 16,852$); (6) missing BMR information ($n = 2173$).

NHANES, organized by the National Center for Health Statistics (NCHS), employs a stratified, multistage probability cluster design to evaluate the health status of individuals living in communities across the United States. The program includes cross-sectional surveys that gather data on socio-demographics, anthropometric measurements, health and nutrition questionnaires, and laboratory tests. A total of 15,560 individuals from the 2017–March 2020 cycle were initially considered. NHANES protocols were approved by the NCHS Research Ethics Review Board, with informed consent obtained from all participants. The study included participants who were enrolled in the NHANES Mobile Examination Center ($n = 14,300$) and authorized for elastography measurements using FibroScan 502 Touch (Echosens, Paris, France).²⁷ Exclusion criteria were as follows: (1) age <20 years ($n = 5756$); (2) pregnancy ($n = 87$); (3) hepatitis B (hepatitis B surface antigen positive) or hepatitis C (positive for

hepatitis C antibodies or RNA) ($n = 229$); (4) serious diseases (cancer or cardiovascular diseases) ($n = 1685$); (5) high-risk alcohol use (≥ 3 drinks/day for females, ≥ 4 drinks/day for males)²⁸ ($n = 1164$); (6) missing BMR information ($n = 82$); (7) ineligible or partial elastography results ($n = 232$); and (8) cryptogenic cirrhosis ($n = 46$).

Finally, 30,845 Chinese participants (9856 males and 20,989 females) from health examination data (Figure 1A) and 5019 US participants (2350 males and 2669 females) from NHANES (Figure 1B) were included for subsequent analysis.

BMR Assessment

BMR refers to the amount of energy expended by the body at rest, both physically and psychologically, after a night's sleep, measured in an awake state without prior physical activity, 10 hours after the last meal, and in a neutral environment.^{13,29} Measurement via indirect calorimetry requires strict control of pre- and intra-test factors (eg, medication, food intake, temperature, time of day), limiting its practical use.³⁰ Consequently, predictive equations based on individual characteristics (height, weight, sex) have been developed, with the Mifflin-St Jeor equation³¹ demonstrating high accuracy and widespread use in clinical and research settings. Body weight (kg) and height (cm) of physical

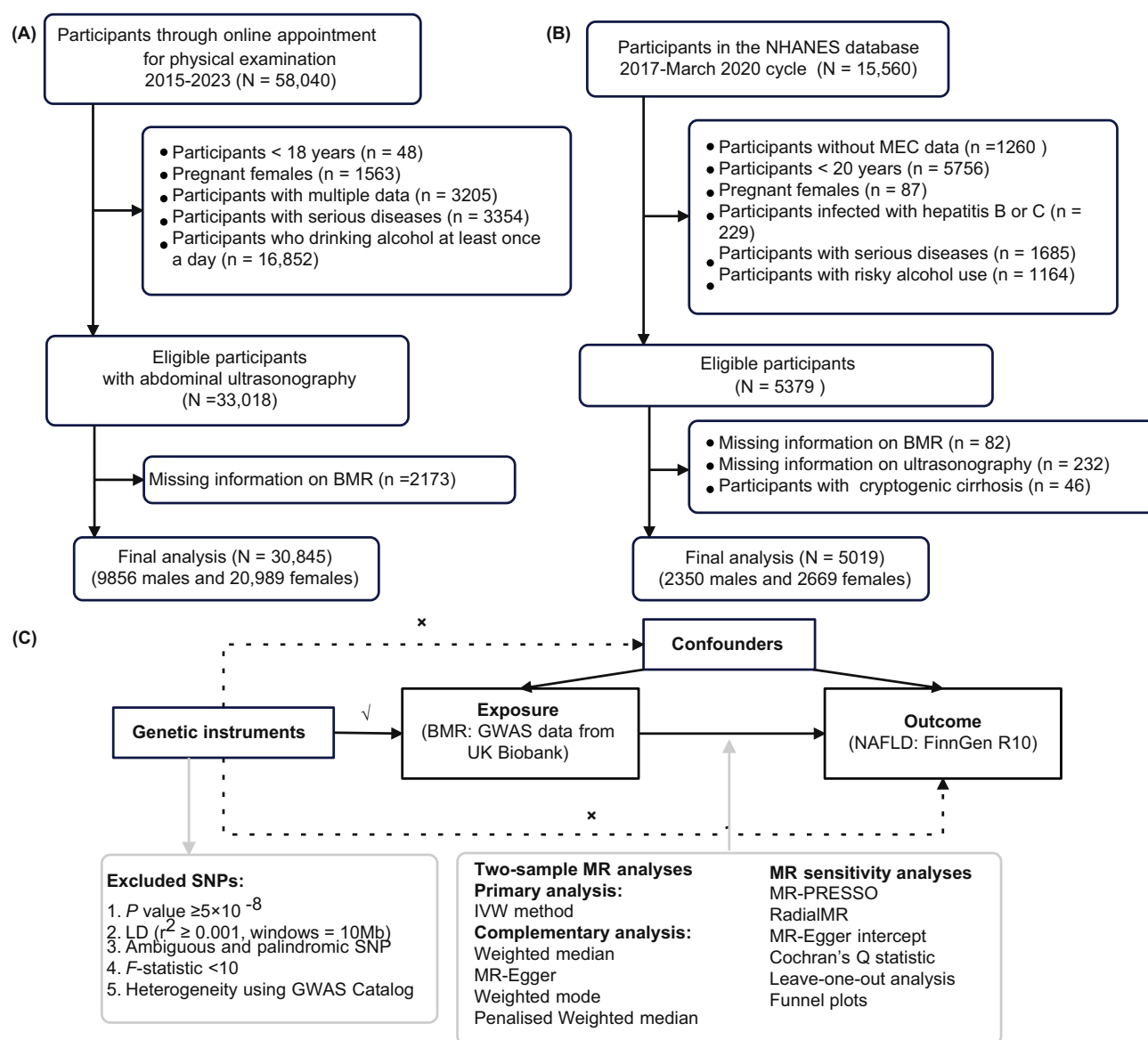


Figure 1 Study flow diagram. **(A)** Participant selection from health examination datasets; **(B)** Inclusion and exclusion criteria for NHANES 2017–2020 participants; **(C)** Schematic overview of the Mendelian randomization (MR) study design.

examination participants were measured using an automatic weighing scale (SK-X80). Weight was measured with participants in light clothing and barefoot, and recorded to the nearest 0.1 kg; height was measured with participants standing upright, heels together, and recorded to the nearest 0.1 cm. BMR in this study was subsequently calculated using the equation, with separate formulas for males and females.

$$\text{Male : BMR} = 10 \times \text{weight}(\text{kg}) + 6.25 \times \text{height}(\text{cm}) - 5 \times \text{age}(\text{y}) + 5$$

$$\text{Female : BMR} = 10 \times \text{weight}(\text{kg}) + 6.25 \times \text{height}(\text{cm}) - 5 \times \text{age}(\text{y}) - 161$$

BMR was then stratified into quartile groups, with the lowest quartile as the reference.

NALFD Ascertainment

For the Chinese health examination population, NAFLD was diagnosed by experienced sonographers via abdominal ultrasonography, excluding individuals with excessive alcohol consumption. Diagnosis followed 2002 criteria from the Fatty Liver and Alcoholic Liver Disease Group of the Chinese Medical Association's Hepatology Branch:³² (1) punctate hyperechogenicity of liver parenchyma; (2) echo attenuation in deep liver tissue; (3) indistinct intrahepatic blood vessels. A confirmed diagnosis required criterion (1) plus either (2) or (3). For the NHANES population, NAFLD was evaluated using vibration-controlled transient elastography (VCTE), which measures ultrasound attenuation and records the controlled attenuation parameter (CAP) as an indicator of hepatic fat content. NAFLD was defined according to the criteria reported in recent epidemiological studies.^{33,34} Briefly, NAFLD was defined as CAP scores of ≥ 302 dB/m.^{33,34} Participants with CAP between 274 and 302 dB/m were considered non-NAFLD, unless their liver stiffness measurement (LSM) exceeded 8.2 kPa (borderline steatosis). Individuals with cryptogenic cirrhosis (LSM >13.6 kPa but CAP <302 dB/m) were excluded.³⁵

Covariates Definition

Covariates considered varied slightly between the two populations owing to differences in data availability and population-specific attributes. For the Chinese health examination data, current smokers are described as those who have smoked at least one cigarette daily for ≥ 12 months. Work-related physical activity was categorized into sedentary (prolonged sitting/typing/reading), light (standing/walking without strenuous exertion), or moderate-to-vigorous (regular heavy labor, eg, lifting/carrying) levels based on self-report questionnaires. Overweight/obesity was defined as BMI ≥ 24 kg/m². Individuals with systolic/diastolic blood pressure (SBP/DBP) $\geq 140/90$ mmHg or those who use antihypertensive medication are divided as patients with hypertension. Diabetes is diagnosed with a fasting blood glucose level ≥ 126 mg/dL, or if the patient is currently undergoing antidiabetic treatment. Dyslipidemia is established by one or more of the following criteria: total cholesterol (TC) ≥ 240 mg/dL, triglycerides (TG) ≥ 200 mg/dL, low-density lipoprotein cholesterol (LDL-C) ≥ 160 mg/dL, high-density lipoprotein cholesterol (HDL-C) <40 mg/dL, or the use of lipid-lowering medication.

For NHANES, participants who had smoked ≥ 100 cigarettes in their lifetime were classified as current smokers if they reported smoking "some days" or "every day," as former smokers if they reported smoking "not at all," and as never smokers otherwise. Physical activity levels were calculated by summing the weekly duration of each work and recreational activity multiplied by each metabolic equivalent (MET), then categorized into <600 , 600–1200, and ≥ 1200 MET-min/week.³⁶ Overweight/obesity was defined as BMI ≥ 25 kg/m². Diabetes was diagnosed as fasting plasma glucose ≥ 126 mg/dL or HbA1c $\geq 6.5\%$. SBP and DBP were calculated as the mean of all available measurements, with hypertension and dyslipidemia defined using the same criteria as in the health examination data.

GWAS Sources and IVs Selection

To explore the causality between BMR and NAFLD, we obtained summary statistics from public databases (Figure 1C). All original studies were approved by the respective institutional review boards with informed consent of all participants. No additional ethical approval was required. The study was reported following the STROBE-MR.³⁷

GWAS data of BMR (534,045 European participants) were accessed via the IEU OpenGWAS project (ebi-a-GCST90029025),³⁸ with BMR measured on a standard deviation (SD) scale. GWAS summary statistics for NAFLD

were from the FinnGen Biobank (Release 10), including 412,181 participants (2568 cases and 409,613 controls). BMR and NAFLD datasets had no overlapping samples to avoid bias and ensure a low type 1 error rate.

In two-sample MR, genetic variants must fulfill three core assumptions: (1) robust association with exposure (relevance); (2) independence from confounders (independence); (3) no effect on outcome except via exposure pathway (exclusion restriction).²⁶ We selected single-nucleotide polymorphisms (SNPs) strongly associated with BMR ($P < 5 \times 10^{-8}$), ensured their independence through clumping ($r^2 < 0.001$, window = 10 Mb), and excluded weak instruments (F -statistic < 10). F -statistics were calculated as $F = R^2 \times (N - 2) / (1 - R^2)$, where $R^2 = 2 \times MAF \times (1 - MAF) \times (\beta / (SE \times \sqrt{N}))^2$ represents the proportion of the variability of the exposure explained by IVs.³⁹ MAF means minor allele frequency, and N represents the sample size of the GWAS for BMR. β and SE represent the effect size and standard error of the SNP-BMR association, respectively. Additionally, the GWAS Catalog⁴⁰ was screened to exclude SNPs ($P < 5 \times 10^{-8}$) significantly related to potential confounders (drinking, smoking, coronary artery disease, stroke) and other NAFLD-related traits. Ambiguous and palindromic SNPs were removed during harmonization. For the outcome dataset lacking specific SNPs, proxies in strong LD ($r^2 = 0.8$) were used.

Statistical Analysis

The basic characteristics of the overall population were outlined separately by sex. For health examination data, continuous variables were analyzed using ANOVA or t-tests, while categorical variables were examined with Chi-squared tests or Fisher's exact tests. In the NHANES data, weighted generalized linear regression and weighted Chi-squared tests were utilized to compare subjects with non-NAFLD and those with NAFLD. Mean BMR (with standard error) across age groups was calculated and plotted for the overall population and sex subgroups to illustrate distribution and trends.

Logistic regression models adjusted for multiple variables were employed to calculate sex-specific odds ratios (ORs) with 95% confidence intervals (CIs) for the relationship between BMR and NAFLD in both populations. To explore potential nonlinearity, trend P -values were calculated using group medians as a continuous variable. Three models were used in this study. For the health examination data, Model 1 adjusted for age, sex, and year of physical examination, as appropriate. Model 2 added race/ethnicity (Han Chinese or others), marital status (married/cohabiting or divorced/single), smoking status (never, former, or current smoking), and work-related physical activity (sedentary, light, or moderate-to-vigorous categories). Model 3 further adjusted for cardiometabolic factors, including overweight/obesity, hypertension, diabetes, and dyslipidemia. In the NHANES analysis, appropriate weights were applied. Model 1 was adjusted for age and sex; Model 2 further considered race (Hispanic, Non-Hispanic White, Non-Hispanic Black, Non-Hispanic Asian, or others), marital status, education level (high school or above, others), smoking status, physical activity level, and poverty income ratio; Model 3 additionally added the above-mentioned cardiometabolic factors. To further investigate the nonlinear and dose-response relationships, we employed restricted cubic spline (RCS) logistic regression. Subgroup analyses were conducted, utilizing likelihood ratio tests to compare models with and without multiplicative interaction terms.

Sensitivity analyses were conducted to bolster the robustness of the results. The analyses included: (1) regrouping BMR by tertiles; (2) calculating BMR using the Harris-Benedict equation. For male, $BMR = 88.362 + 13.397 \times weight(kg) + 4.799 \times height(cm) - 5.677 \times age(y)$; for female, $BMR = 447.593 + 9.247 \times weight(kg) + 3.098 \times height(cm) - 4.330 \times age(y)$; and (3) defining NAFLD with a CAP cutoff of 285 dB/m, which has 80% sensitivity and 77% specificity, and was validated to detect hepatic steatosis in the US population.⁴¹

In two-sample MR analysis, we applied inverse variance weighted (IVW) as the principal method to assess the causal association of genetically predicted BMR and NAFLD risk. Four complementary MR analysis methods were used, including weighted median, MR Egger, weighted mode, and penalised weighted median, to validate the results. If heterogeneity exists, IVW with the outliers correction was used as the primary result. MR-PRESSO,⁴² RadialMR method,⁴³ MR-Egger intercept, Cochran's Q statistic, and leave-one-out analysis were used for sensitivity analyses. We obtained estimates without evidence of horizontal pleiotropy bias (MR-PRESSO global $P > 0.05$, also MR-Egger intercept $P > 0.05$). We utilized Cochran's Q test to assess IV heterogeneity, with a P -value > 0.05 indicating no heterogeneity. Scatter, forest, and funnel plots were depicted to determine whether the results were driven by individual variants. The statistical power of the MR estimates was calculated using the online tool (<https://sb452.shinyapps.io/power/>).⁴⁴

All analyses were accomplished using R software, version 4.2.1 (R Foundation for Statistical Computing). A 2-tailed $P < 0.05$ was regarded as statistically significant.

Results

Basic Characteristics

Basic characteristics of participants from different populations were presented separately. Among the 30,845 Chinese participants included in the study, 9856 (32.0%) were male, with a mean age of 40.1 years. The overall prevalence of NAFLD was 17.1%, with rates of 31.4% in males and 10.4% in females. Those with NAFLD were older, predominantly male, had higher smoking rates (males only), and poorer cardiometabolic health (higher rates of overweight/obesity, hypertension, diabetes, dyslipidemia) ([Table S1](#)).

In NHANES, 1,431 participants had NAFLD (using a CAP cutoff of 302 dB/m), and 3,588 did not. NAFLD individuals were older, mostly male (weighted 57.30%), with lower high-intensity physical activity, higher BMI, SBP, fasting glucose, TG, and elevated liver markers (GGT, AST, ALT, ALP, median stiffness, median CAP) ([Table S2](#)). NAFLD prevalence was higher in males, and those with NAFLD had higher BMR across both populations.

BMR trends across 10-year age groups (stratified by sex and NAFLD status) showed that NAFLD individuals had higher BMR (especially males) in both populations ([Figure 2A](#) and [B](#)). BMR decreased with age; the Chinese population had lower BMR overall, with an earlier age of decline.

Sex-Specific Association Between BMR and NAFLD

BMR was evaluated as both a continuous and categorical variable to assess its association with NAFLD risk ([Figure 3](#)). In Chinese health examination data, BMR was positively linked to NAFLD in the total population and by sex. Multivariable-adjusted ORs (95% CIs) for ascending BMR quartiles (vs lowest) were 1.17 (1.03–1.33), 1.83 (1.60–2.09), and 5.98 (4.92–7.28) (P for trend <0.05). Each 1-SD increase in BMR correlated with a 217% higher NAFLD risk, with the OR (95% CI) of 3.17 (2.93–3.43). In males, the corresponding ORs (95% CIs) were 2.00 (1.67–2.39), 2.71 (2.24–3.29), and 4.91 (3.97–6.10). In females, the corresponding ORs (95% CIs) were 1.64 (1.41–1.92), 1.93 (1.64–2.27), and 4.04 (3.41–4.81). Sensitivity analyses had no substantial influence on the original results ([Table S3](#)). Notably, the magnitude of association between BMR and NAFLD showed significant sex differences (P for interaction <0.05) when BMR was divided into tertile groups but not quartile groups, indicating a modification effect of sex. The RCS analysis revealed nonlinear dose-response relationships in both sexes (P for nonlinear <0.05 , [Figure 4A](#) and [B](#)).

In NHANES 2017–2020, the results mirrored those of the health examination data. Weighted ORs (95% CIs) for BMR quartiles (vs lowest) were 1.84 (0.95–3.54), 4.98 (2.28–10.89), and 16.10 (6.69–38.72) (P for trend <0.05). Per 1-SD BMR increase, the OR (95% CI) was 4.69 (3.66–6.02). Sensitivity analyses, including the use of an alternative CAP cutoff of 285 dB/m to define NAFLD, did not significantly alter these results ([Table S4](#)). In the top quartile group of BMR, the risk of NAFLD was the highest, with OR (95% CI) of 11.26 (4.21–30.10) in males and 12.88 (5.13–32.30) in females, with no significant sex discrepancies (P for interaction >0.05). No evidence of nonlinear dose-response relationships was found between BMR and NAFLD in either sex (P for nonlinear >0.05 , [Figure 4C](#) and [D](#)).

In the sex-specific subgroup, BMR-NAFLD associations were consistent across hypertension, diabetes, and dyslipidemia subgroups for the Chinese health examination population. A notable interaction effect was observed between BMR and overweight/obesity (P for interaction <0.05). In females but not males, a significant interaction effect between BMR and age was noted ([Table S5](#)). In US participants, associations were consistent across age, diabetes, and dyslipidemia subgroups. There was also a marked interaction effect between BMR and overweight/obesity (P for interaction <0.05). In females but not males, a significant interaction effect between BMR and hypertension was observed ([Table S6](#)).

Causal Association Between BMR and NAFLD

Given the significant positive correlation between BMR and NAFLD risk observed in multivariable regression analyses, we further conducted MR analysis to infer causal effects ([Figure 3](#)). After excluding ambiguous, palindromic, unavailable

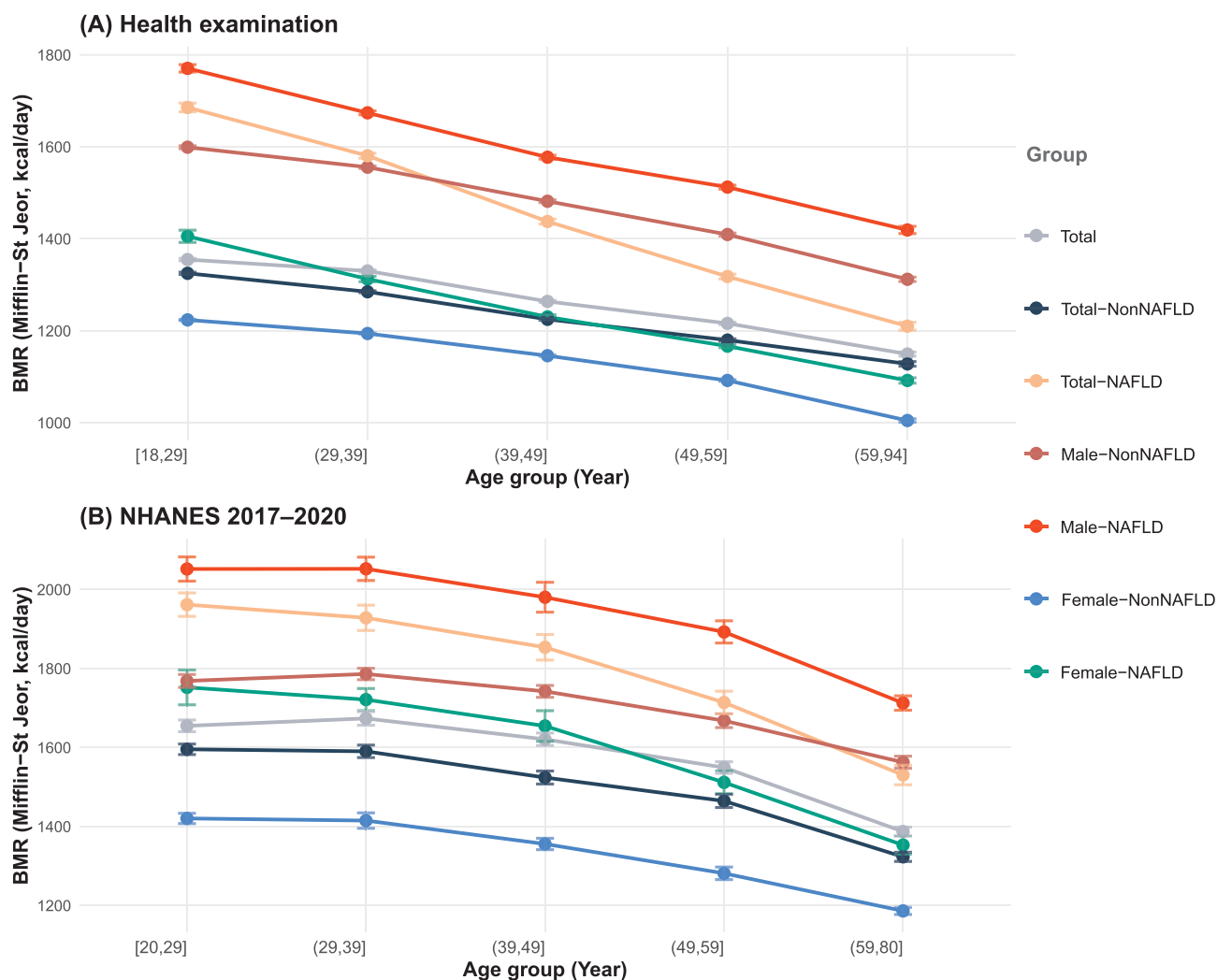


Figure 2 Trends of mean BMR values by gender and NAFLD status among Chinese (A) and US adults (B) across different age groups.

SNPs, and those with potential confounding, as well as F -statistics <10 , 466 SNPs for BMR were retained for causality analysis (Table S7).

Genetically predicted BMR showed a positive relationship with the NAFLD risk, with the OR (95% CI) of 1.51 (1.17–1.96), corresponding to a 51% increase in NAFLD risk per 1-SD increment in BMR. Little evidence of pleiotropy was found ($P = 3.11E-01$), but some heterogeneity among the individual SNP effects was observed ($P = 9.32E-04$). We therefore used causal effects after correcting outliers as final estimates. After removing 33 outliers identified by RadialMR (Table S7 and Figure S1), genetically predicted BMR remained positively associated with NAFLD risk, with the OR (95% CI) of 1.59 (1.24–2.03). These results aligned with other complementary MR methods in both direction and magnitude of causal estimates (Figure S2). Notably, no significant evidence of horizontal pleiotropy (MR-Egger test, MR-PRESSO global test) or heterogeneity was detected in individual instrument effects after outlier corrections (all $P > 0.05$). Funnel plot symmetry supported this finding (Figure S3). Leave-one-out analysis further confirmed that no single SNP drove the causal relationship between BMR and NAFLD (not depicted). The statistical power of MR estimates for BMR and NAFLD based on the IVW methods was 96%. These results thus affirm the robustness and trustworthiness of our findings.

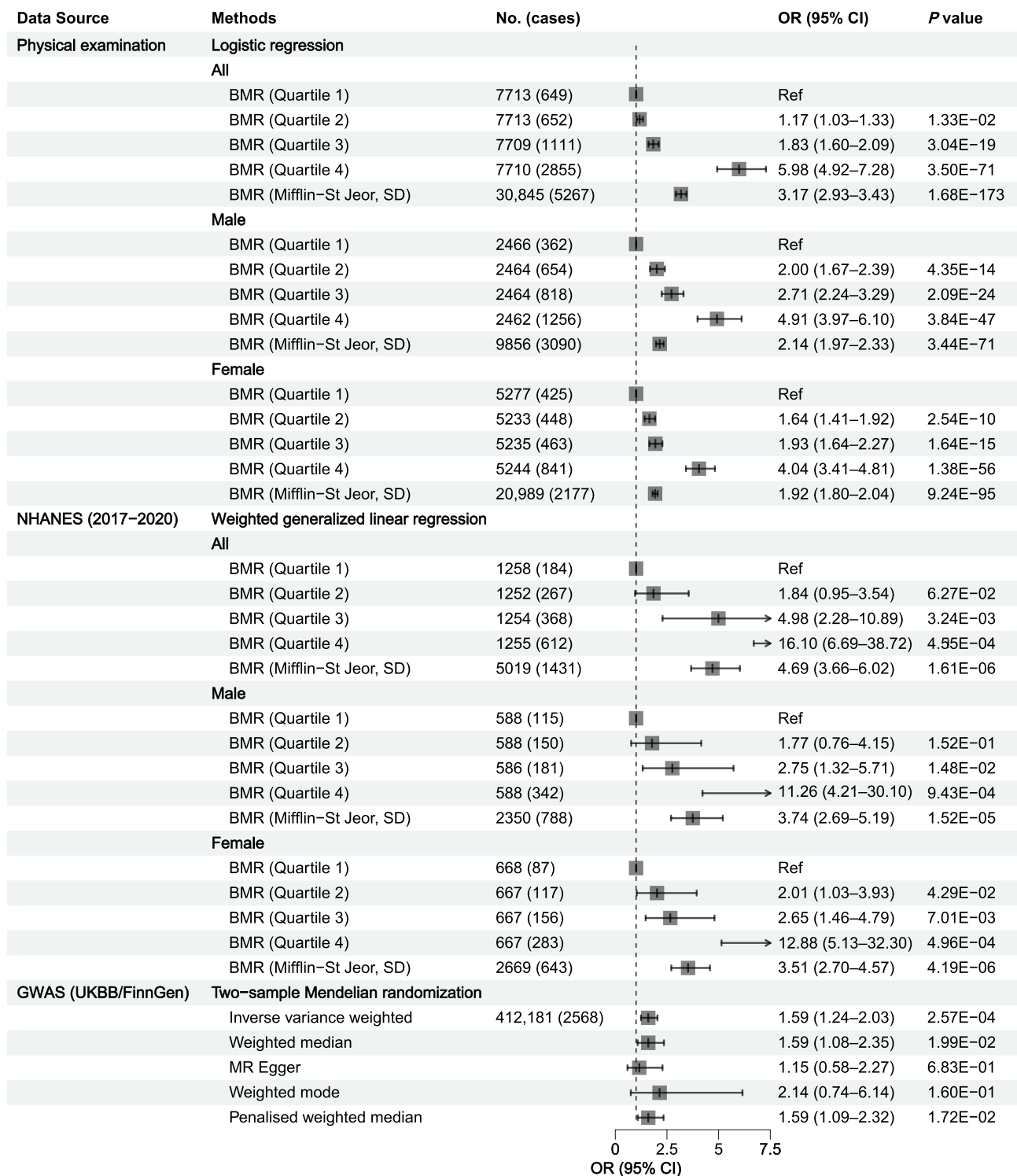


Figure 3 Association between BMR and NAFLD using the observational study and two-sample MR analysis. Effect sizes are on the OR per 1-SD unit increase in BMR for MR analysis.

Discussion

We integrated observational data from health examinations and NHANES 2017–2020 with two-sample MR analysis to explore the BMR-NAFLD relationship. Our findings revealed higher BMR in NAFLD patients than in non-NAFLD individuals in both the Chinese and US populations. Moreover, NAFLD risk increased with BMR, with distinct sex

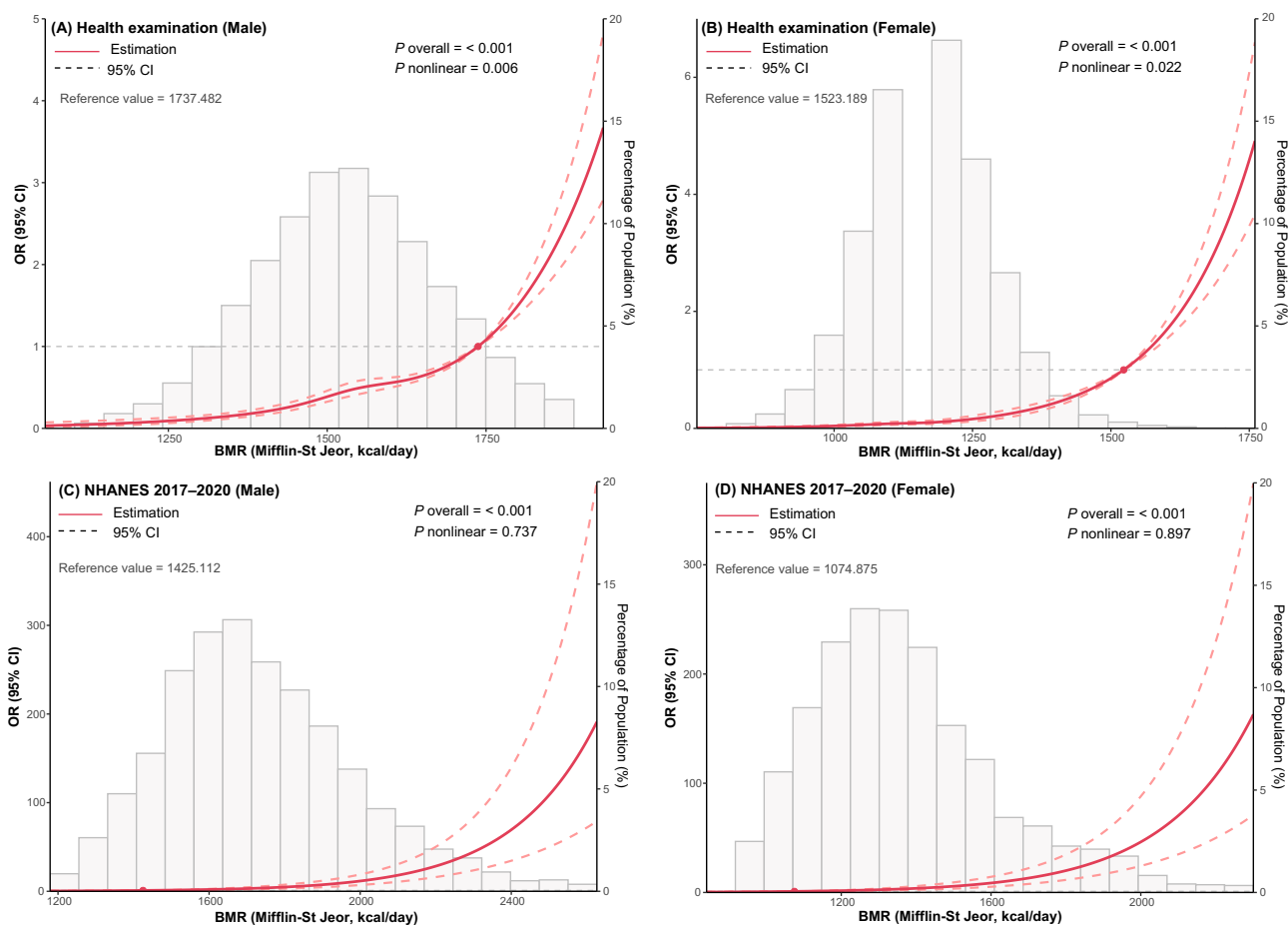


Figure 4 Sex-specific association between BMR and NAFLD in a restricted cubic spline analysis. **(A)** Male participants, Chinese health examination data; **(B)** Female participants, Chinese health examination data; **(C)** Male participants, NHANES 2017–2020 data; **(D)** Female participants, NHANES 2017–2020 data.

differences observed in China but not the US. Among Chinese participants, nonlinear dose-response relationships were depicted in both sexes. Besides, the two-sample MR method further confirmed the causal effect of BMR on NAFLD, suggesting BMR as a candidate modifiable factor for NAFLD.

BMR exhibits distinct population-specific patterns, with lower values observed in the Chinese population compared to the US population (males: 1540.5 vs 1746.25 kcal/day; females: 1169.9 vs 1336.75 kcal/day), likely driven by differences in body composition and metabolic status. In Bangladeshi adult students, males had a higher BMR (1543 kcal/day) than females (1234 kcal/day), due to greater fat-free mass in males.⁴⁵ Similarly, Singaporean adults showed a strong correlation between lean body mass and BMR ($r = 0.87$), linking lean mass energy demand to BMR.⁴⁶ Pathological conditions also alter BMR levels. In patients with T2DM and peripheral neuropathy, BMR showed a positive correlation with insulin resistance (HOMA-IR: $r=0.913$) and visceral fat ($r=0.332$), reflecting metabolic adaptations to hyperglycemia and adipose tissue dysfunction.⁴⁷ In obesity-related NAFLD, BMR was predicted by spleen length and interleukin-16 (both linked to hepatic growth factor), which links immune-metabolic crosstalk to BMR regulation.⁴⁸ Taken together, BMR is not merely affected by body size but is a marker of underlying metabolic perturbations.

Subgroup analyses revealed that the associations between BMR and NAFLD were modified by age, overweight/obesity, and hypertension, with population- and sex-specific patterns, underscoring the need for stratified assessment. Specifically, a significant modification effect of overweight/obesity was observed among the Chinese and US populations in both sexes. In Chinese but not US adults, the positive association was more pronounced in elderly females (≥ 60 years) but not males, suggesting a sex-specific effect pattern with advancing age. Similar sex-specific patterns exist for other health outcomes. In Korean adults, a higher energy intake-to-BMR ratio reduced sarcopenia risk across ages, but strength

exercise protected only males under 50 years.⁴⁹ In Southern Chinese adults, the inverse association of BMR with all-cause mortality was restricted to elderly males (≥ 60 years).⁵⁰ The observed sex- and population-specific BMR-NAFLD associations are driven by sex-based and population-level metabolic and epidemiological disparities. Sex differences in the Chinese likely stem from distinct body composition, hormonal regulation of energy metabolism, and age-related NAFLD susceptibility. Population variations derive from basal BMR differences, divergent NAFLD phenotypes, and metabolic risk profiles. Obesity-dominated dysregulation in the US may mask sex-specific patterns, which are more pronounced in the Chinese with distinct anthropometric and epidemiological features. These findings confirm that BMR's clinical relevance is context-dependent, requiring targeted analyses for robust inference.

As research on metabolic diseases advances, our understanding of the BMR-NAFLD risk relationship continues to deepen. An MR analysis revealed a causal link between BMR and cardiometabolic factors.⁵¹ Specifically, genetically determined higher BMR was associated with an increased BMI, lower HDL-C, higher TG, waist circumference, and elevated glycated hemoglobin. Our findings from health examinations and NHANES 2017–2020 complemented the evidence, showing significantly higher BMR in NAFLD patients. Beyond observational data, two-sample MR clarified the causal relationship, broadening our understanding of BMR's positive causal effect on NAFLD based on European population data. The reliability of this association was confirmed by consistent outcomes from complementary MR and sensitivity analyses.

Several mechanisms could explain this association. First, elevated BMR is associated with a pro-inflammatory state,⁵² and chronic inflammation is a key driver of NAFLD progression.^{48,53} Second, a higher BMR necessitates greater energy intake, and dietary patterns that support a high metabolic rate may contribute to liver fat accumulation.^{54–56} Third, at the cellular level, increased energy expenditure can lead to mitochondrial dysfunction and oxidative stress, contributing to the pathogenesis of NAFLD by promoting lipid accumulation and liver cell damage.^{57–59}

The key strength of this study lies in integrating observational studies from the health examination and NHANES 2017–2020 data with the MR approach. Both methods yielded nearly consistent results in this study, which enhances the reliability of our findings. However, several limitations should be noted. First, despite controlling for relevant covariates, residual or unmeasured confounding (eg, energy intake) may persist, though adjustment for proxies (physical activity, BMI) mitigated bias. Second, findings only address the impact of higher BMR on NAFLD, not the potential effect of short-term BMR reduction in clinical practice, requiring further validation via laboratory and clinical research. Third, due to the limited NAFLD-associated significant variants, reverse MR between BMR and NAFLD was not feasible. Finally, potential misclassification and cross-population result comparability issues should be acknowledged. NAFLD diagnosis in the Chinese dataset relies on ultrasound, a qualitative assessment, which may lead to underestimation of mild hepatic steatosis. In contrast, NHANES employs the CAP, a quantitative measure that can be confounded by BMI, thereby introducing population-specific measurement biases. Importantly, the consistent positive BMR-NAFLD association observed across both populations, despite these differential misclassification risks and divergent assessment modalities, further underscores the robustness of our core findings.

Conclusions

This study identifies higher BMR as an independent risk factor for NAFLD in general populations. In Chinese but not US adults, the positive BMR-NAFLD association was more pronounced in elderly females (≥ 60 years) versus males, highlighting the need for stratified management. We further confirm that overweight/obesity is a key modifier of the BMR-NAFLD association, with consistent effects across Chinese and US populations of both sexes. Further research is warranted to elucidate the underlying pathogenic mechanisms.

Abbreviations

BMR, basal metabolic rate; NAFLD, non-alcoholic fatty liver disease; NHANES, National Health and Nutrition Examination Survey; GWAS, genome-wide association studies; MR, Mendelian randomization; IVs, instrumental variables; OR, odds ratio; CI, confidence interval; IR, insulin resistance; T2D, type 2 diabetes; RCTs, randomized controlled trials; VCTE, vibration-controlled transient elastography; CAP, controlled attenuation parameter; CVD, cardiovascular disease; LSM, liver stiffness measurements; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; MET, metabolic equivalent.

Data Sharing Statement

Datasets from the health examinations during the present study are not publicly available but are available from the corresponding author on reasonable request. NHANES datasets (<https://www.cdc.gov/nchs/nhanes/default.aspx>) and the GWAS files (<https://gwas.mrcieu.ac.uk/datasets/>; <https://risteys.finnngen.fi/>) are publicly available for download.

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committees of the First Affiliated Hospital of Army Medical University (No. [A] KY202227). The protocols of the NHANES study were authorized by the Research Ethics Review Board of NCHS. Informed consent was obtained from all participants. All MR analyses were based on publicly available summary statistics, which do not require ethical approval and consent.

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Author Contributions

Chunyu Hu: Software, Methodology, Formal analysis, Visualization, Writing – original draft, Writing – review & editing, Funding acquisition. Yuanling Tao: Methodology, Writing – review & editing. Laixi Zhang: Investigation, Writing – review & editing. Zhen Cheng: Resources, Data curation, Writing – review & editing. Li Sun: Resources, Data curation, Writing – review & editing. Zongtao Chen: Conceptualization, Writing – review & editing, Project administration. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflict of interest.

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