

## Research Article

# Effects of Metabolism-Related Indicators on Nonalcoholic Fatty Liver Disease in Nonobese Population Based on the National Health and Nutrition Examination Survey

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**Objective.** Nonalcoholic fatty liver disease (NAFLD) is becoming more prevalent in the nonobese population. The aim of this study was to investigate the combined effects of metabolism-related mixtures on NAFLD subjects in nonobese populations using four statistical models. **Study Design.** This was a retrospective observational study. **Methods.** Our study included 904 nonobese patients who had taken part in the 2017–2018 National Health and Nutrition Examination Survey (NHANES). We used logistic regression models, Bayesian kernel machine regression (BKMR), and the weighted quantile sum (WQS) regression model to estimate the association between metabolism-related indicators and NAFLD in the nonobese population. Finally, we included several indicators to create nomograms to predict the risk of NAFLD occurrence in the nonobese population. **Results.** Among the 904 participants, 116 (12.83%) had NAFLD. The logistic regression model found that the waist-to-hip ratio (WHR), HDL-c, triglyceride (TG), and HbA1c were positively associated with the outcomes. The WQS regression model showed that the WQS index was significantly associated with the occurrence of NAFLD in the nonobese population (OR: 5.789, 95% CI: 3.933–8.520), and WHR, TC, and TG had the largest weight. The BKMR model's WHR and TG increased from the 25th percentile to the 75th percentile (other metabolite exposure remained fixed at the 75th percentile) and the risk of developing NAFLD increased in the nonobese people. The significant predictors mentioned above were introduced to construct the nomogram. The calibration curve, DCA, and AUROC (0.796) (95% CI: 0.743–0.843) all indicated that the model had a good potential clinical performance. **Conclusions.** By comparing the results of the four models together, WHR and TG were identified as important factors associated with NAFLD in the nonobese population. Further research is warranted to investigate the risk factors and pathogeny of NAFLD in nonobese populations.

## 1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is a metabolic dysfunction related to liver disease characterized by the excessive deposition of fat in the liver ( $\geq 5\%$ ) [1, 2]. Due to lifestyle changes, the incidence of NAFLD has increased significantly over the past few decades [3]. NAFLD usually

presents as obesity or overweight, but NAFLD also occurs in nonobese subjects with similar pathologic severity as obese NAFLD patients [4]. Studies showed that NAFLD in the nonobese population accounts for 5%–20% of the total prevalence, including Asia (38.6%), Europe (51.3%), and America (56.6%) [5–8]. NAFLD includes nonalcoholic simple fatty liver, nonalcoholic steatohepatitis and its

associated cirrhosis, and hepatocellular carcinoma [9]. Nonalcoholic fatty liver disease has become the second leading cause of liver transplantation in the United States [10, 11]. In the future, NAFLD may become a major cause of end-stage liver disease, seriously affecting public health globally [12].

Previous studies revealed that obesity is a critical factor in the development and progression of NAFLD [13, 14]. NAFLD is often neglected in the nonobese population, and there is no clear definition of “nonobese-NAFLD.” Weight is not a diagnostic criterion for NAFLD, and multiple factors cause the occurrence of NAFLD. Therefore, it is inaccurate to describe this disease with nonobese NAFLD. So, we use NAFLD in nonobese individuals to describe this disease in the paper [15]. There is a lack of research on nonobese patients. The risk factors and clinical characteristics of NAFLD in the nonobese population remain unclear, though BMI, advanced age, and lipid levels may be involved [16, 17]. The pathogenesis of NAFLD in nonobese individuals is not fully understood. It may be related to metabolic dysfunction (e.g., insulin resistance and hyperandrogenemia), dietary habits (e.g., sugary drinks and high-fat diet), gut microbiota changes, cytokines (e.g., IL-1 and IL-6), genetic predisposition, and other changes [18–20]. Furthermore, some studies have found that non-obese patients with NAFLD have a higher risk of cardiovascular disease, type 2 diabetes mellitus (T2DM), and hepatocellular carcinoma [21–23]. Past researchers have claimed that early weight loss or dietary modification in nonobese patients with NAFLD can improve or even eliminate steatosis [24–26]. Therefore, more studies are needed to conduct early diagnosis and intervention of this disease. This will have important implications for the prevention of NAFLD-related end-stage disease and death [27].

NAFLD is associated with metabolic disorders, and the liver is a key factor in metabolic abnormalities [21, 28]. It is generally accepted that, like obese NAFLD, subjects with NAFLD in the nonobese population have altered glycolipid metabolism and metabolic profiles [29, 30]. A study found that several lipid metabolism-related protein markers have a high diagnostic value for NAFLD in the nonobese population by proteomic profiling of plasma in nonobese subjects with or without NAFLD [31]. NAFLD in the nonobese population may have a steatosis-like phenotype, characterized by impaired lipogenesis, hypertriglyceridemia, and hepatic steatosis [32]. NAFLD in the nonobese subjects tended to have less metabolic disturbances than obese NAFLD subjects. However, NAFLD in the nonobese population was associated with a higher risk of metabolic disease than obese NAFLD [33]. Therefore, it is of great significance to further study the correlation between metabolism and the risk of NAFLD in nonobese people.

Metabolic disorders are a significant risk factor affecting NAFLD development [34, 35]. We collected data from the National Health and Nutrition Examination Survey (NHANES) during 2017–2018 to discover the role of metabolic-related indicators coexposure in NAFLD and nonobese individuals using WQS and BKMR models. Therefore, the aim of this study was to identify metabolically relevant indicators associated with the development of

NAFLD in nonobese individuals for reducing the incidence of NAFLD.

## 2. Methods

**2.1. Study Sample.** NHANES is a cross-sectional survey of the health status of the United States population performed by the National Center for Health Statistics of the Centers for Disease Control and Prevention. The study randomly selected about 5,000 people each year who live in counties in the US to represent national health. The entire survey included a structured interview, followed by standardized health assessments at mobile examination centers (MECs), which included questionnaires, physical examinations, and laboratory tests. Here, we used the data collected from 2017 to 2018. Written informed consent was obtained from all participants, and the protocol was approved by the National Center for Health Statistics.

**2.2. NAFLD Definition.** After excluding hepatitis B or C virus infection and significant alcohol consumption, NAFLD was defined as a CAP of  $\geq 274$  dB/m [36, 37]. Liver ultrasound transient elastography is a noninvasive technique used to objectively assess liver fibrosis and steatosis. In the 2017–2018 survey, technicians performed liver ultrasound transient elastography examinations in participants by using the FibroScan model 502 V2 Touch (Echosens). Exams were considered complete if participants fasted for at least 3 hours prior to the exam, there were 10 or more complete LSM, and the liver stiffness IQR/median was  $< 30\%$ . CAP values ranged from 100 to 400 dB/m, with higher values indicating higher amounts of fat in the liver. The device can record CAP as an evaluation index of hepatic fat deposition, and for steatosis of  $\geq 34\%$ , the area under the receiver operating characteristic curve (AUROC) is 0.80, with a sensitivity and specificity of 79% and 71% [38, 39]. For quality assurance, NHANES health technicians completed a two-day training program with survey staff and an expert FibroScan technician.

**2.3. Study Design.** For this analysis, patients aged  $\geq 18$  years with controlled attenuation parameter (CAP) of  $\geq 274$  dB/m and body mass index (BMI) of  $< 25$  kg/m<sup>2</sup> were selected. Patients with hepatitis B or C virus infection, and excessive alcohol consumption (defined as  $> 21$  standard drinks per week in males and  $> 14$  standard drinks per week in females) were excluded. Among the 9254 patients who participated in NHANES during 2017–2018, we excluded 8350 participants. The exclusion criteria were as follows: (1) participants without available MEC examination information ( $n = 550$ ), those aged  $< 18$  years ( $n = 3171$ ), and those with a BMI of  $\geq 25$  kg/m<sup>2</sup> or missing BMI ( $n = 4062$ ); (2) participants with evidence of viral hepatitis B and C ( $n = 20$ ), those without alcohol intake information ( $n = 117$ ), and those with significant alcohol intake ( $n = 173$ ); (3) participants with physical limitations for the liver ultrasound transient elastography ( $n = 48$ ); and (4) participants with missing covariates ( $n = 210$ ). Finally, we enrolled 904 patients in our study (Figure 1).

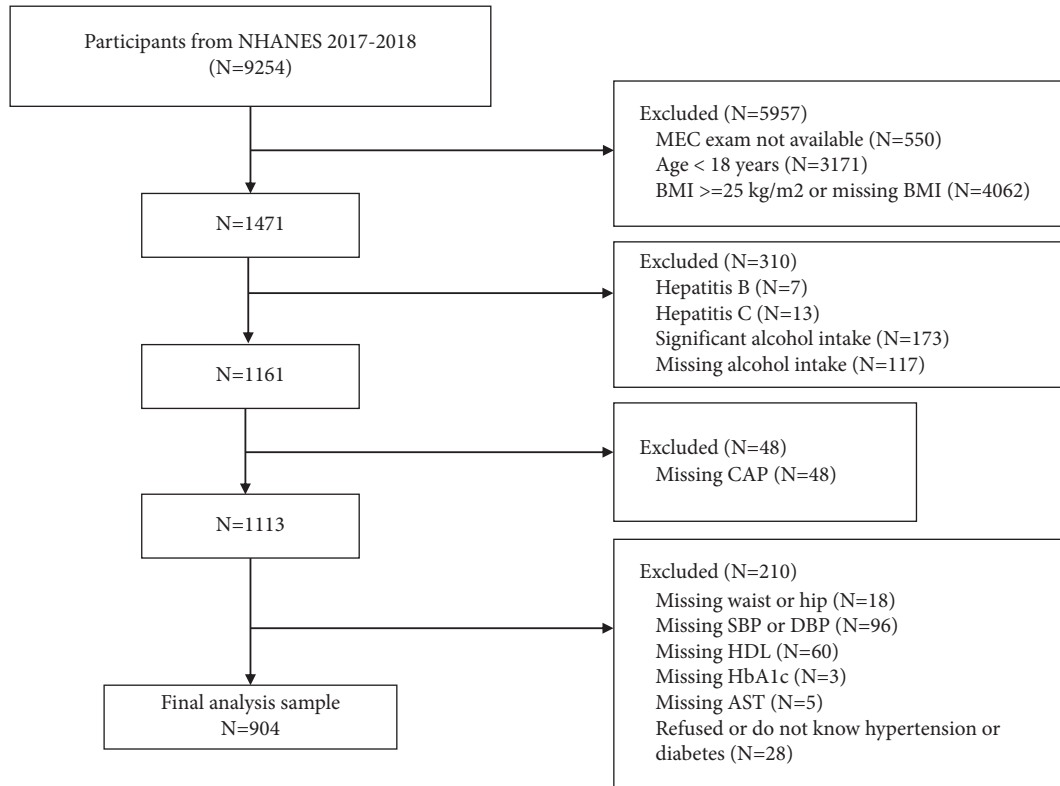


FIGURE 1: Flowchart of the study participant. CAP: controlled attenuation parameter.

**2.4. Laboratory and Clinical Characteristics.** Race, age, sex, BMI, waist-to-hip ratio, blood pressure, glycated hemoglobin (HbA1c), triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), and uric acid were considered in the current study. Information regarding race, age, and sex was collected based on demographic data. During the MEC visit, NHANES staff measured the patient's height, weight, waist circumference, and blood pressure, and the waist-to-hip ratio (WHR) was computed by dividing the waist circumference by the hip circumference and weight in kilograms divided by height in meters squared was used to calculate BMI. Covariates include age, sex, race, smoking, hypertension, and diabetes. HbA1c, TG, TC, HDL-c, and uric acid were obtained from laboratory tests in the MEC. CAP was determined by highly trained medical personnel in the MEC by using a standard protocol. Standard tests for all factors are described at the following website: <https://wwwn.cdc.gov/nchs/nhanes/Default.aspx>.

Based on a self-report, we assessed health conditions such as hypertension, diabetes, smoking, and alcohol consumption. "Did you smoke 100 and more cigarettes in your lifetime?" and "Are you currently smoking cigarettes?" Nonsmokers were classified as those who replied "no" to question 1; ex-smokers were classified as those who said "yes" to question 1 but "not at all" to question 2; and current smokers were classified as those who replied "yes" to question 1 and "every day" or "someday" to question 2. An interview was used to acquire the participants' history of hypertension and T2DM. Hypertension was diagnosed

based on the information provided by a doctor or other healthcare professional. A history of T2DM was considered for those with a self-reported history of diabetes or HbA1c above 6.4%. Alcohol consumption of >3 alcoholic drinks a day for men and >2 alcoholic drinks a day for women was considered excessive drinking. Hepatitis C virus (HCV) infection was diagnosed by hepatitis C antibody or RNA, while viral hepatitis B virus (HBV) infection was diagnosed by hepatitis B surface antigen.

**2.5. Statistical Methods.** Categorical variables were expressed as numbers and proportions, and continuous variables were expressed as mean  $\pm$  standard error (SE). Comparisons between non-NAFLD and NAFLD were performed by using the Rao-Scott chi-square test or *t*-tests. The multivariate logistic regression models were used to explore the relationship between the metabolism-related indicators and NAFLD in nonobese patients. The BKMR and WQS regression models were used to identify the associations of metabolism-related indicators with NAFLD in nonobese patients. BKMR (R package BKMR) is characterized by the exposure-response function modeling and facilitates the visualization of the effect of a single or combined exposure. WQS regression (R package gWQS) integrated the metabolism-related indicators into one index. The contribution of a single metabolism-related indicator level was weighted according to its relevance to the overall association with the outcome. The weights were constrained to sum to 1, with higher numbers indicating a larger contribution. The

associations between the metabolism-related indicators and NAFLD in nonobese patients were analyzed by WQS regression.

To construct the nomogram, factors with significant predictive value were utilized in the multivariate analysis. By using the R caret package, 904 NAFLD in nonobese patients were randomized into two cohorts, a development cohort of 633 participants and a validation cohort of 271 participants with a ratio of 7.5:2.5, which reached the theoretical ratio of 3:1. This increased the robustness and dependability of our results. The validation of the nomogram was conducted by using the AUROC, calibration curve, and decision curve analysis (DCA). 1000 bootstrap resamples were applied to the AUC value and calibration curve.  $P < 0.05$  was considered statistically significant. Data analyses were performed using SAS software (version 9.4) and R software (version 4.1.4).

### 3. Results

**3.1. Baseline Characteristics of Participants.** Table 1 and supplementary Table 1 show the characteristics of the study population of 904 US adults, including 788 non-NAFLD participants and 116 NAFLD participants. There was no difference in biological sex between NAFLD and non-NAFLD. The difference in age distribution was statistically significant between the two groups. The age of the NAFLD group was  $57.70 \pm 1.59$  years ( $41.27 \pm 0.88$  years for non-NAFLD). Diabetes and hypertension distribution was significantly different between the two groups. Although diabetes or hypertension was more common among non-NAFLD participants, most 116 NAFLD participants suffered from both diseases (72/116 and 93/116). In nonobese population, there may be a potential association between NAFLD, diabetes, and hypertension. Metabolic-related indicators such as TC, TG, HDL-c, HbA1c, uric acid, BMI, and WHR were statistically significant between the NAFLD and non-NAFLD groups ( $P < 0.05$ ), and indicator levels were higher in NAFLD than in non-NAFLD participants.

**3.2. Associations between Metabolism-Related Indicators and NAFLD in Nonobese Population.** Table 2 presents logistic regression results to show the relationship between nine metabolic-related indicators and NAFLD in nonobese patients. We found that the waist-to-hip ratio (2.264 (1.535–3.338)) and TG (1.009 (1.005–1.013)) were associated with the onset of NAFLD in the nonobese population. Higher levels of TG and WHR in nonobese people can increase the risk of developing NAFLD (2.264 and 1.0009-fold). Elevated HDL-c levels (1.016 (1.002–1.031)) and HbA1c (1.296 (1.028–1.634)) also increase the risk of NAFLD in nonobese people. In the model, we found that the risk of NAFLD increased by 29.6% with each increment unit of serum HbA1c. No statistical difference was observed with the other indicators.

**3.3. Association of Metabolism-Related Indicators with NAFLD in a Nonobese Population using WQS regression model and BKMR model.** In the covariate-adjusted model, the WQS index was statistically significant ( $P < 0.05$ ) and significantly associated with the occurrence of NAFLD in the

nonobese population (OR: 5.789, 95% CI: 3.933–8.520). The weighting of all WQS indices is shown in Figure 2. The weighting of WHR (0.373) is the most important among all metabolic-related indicators. WHR is the main factor driving the occurrence of NAFLD in the nonobese population. After WHR, TC, TG, and BMI weights were higher in this population (0.162, 0.127, and 0.096, respectively). SBP had the lowest weight (0.003).

The BKMR model analyzed the relationship between metabolic-related indicators and NAFLD in nonobese people. In the model, biological sex, age, smoking, race, hypertension, and T2DM were adjusted. Figure 3(a) shows the cumulative effect of metabolic-related indicators on NAFLD risk in non-obese people. Nine common metabolic-related markers were used to assess their association with NAFLD risk in nonobese people. The results showed that the risk of NAFLD increased with increased exposure to metabolic-related markers. When other metabolites were fixed at the median concentration, each metabolite was analyzed in relation to NAFLD (Figure 3(b)). We found that WHR, TG, HDL-c, and HbA1c were positively associated with developing NAFLD. WHR (PIP = 1.0000) and TG (PIP = 1.0000) contributed the most to developing NAFLD (Figure 3(c)). WHR and TG increased from the 25th to the 75th percentile (other metabolic exposures remained fixed at the 75th percentile), and the risk of developing NAFLD increased in nonobese people (Figure 3(d)). The bivariate exposure-response function suggests a potential interaction between WHR and TG, synergistically furthering NAFLD in nonobese populations (Figure 4).

**3.4. Prediction Model Development.** The significant predictors (Supplementary Table 2) mentioned above were introduced to construct the nomogram (Figure 5(a)). The vertical line is drawn from the variable value to the vertical scale to calculate the number of points specified for the variable value. The points are added up for every variable. The sum is calculated on the total numerical scale and projected vertically on the bottom axis to assess a person's risk of developing NAFLD in the nonobese population. The predictive models' ability was evaluated by using the AUROC, which revealed that the combined model had the best AUROC value. In the training cohort, the AUROC value for this prediction model was 0.794 (95% CI: 0.761–0.825) (Figure 5(b)), with a sensitivity and specificity of 84.0 and 61.6%, respectively. The AUROC value for this prediction model in the validation cohort was 0.796 (95% CI: 0.743–0.843) (Figure 5(c)), with a sensitivity and specificity of 82.9 and 66.9%, respectively. DCA shows a satisfactory positive net benefit for most threshold probability, either in the training or validation cohorts (Figures 5(d) and 5(e)). DCA indicates that the model has good potential clinical effects. According to the calibration curve for this dataset, there is a good agreement between the prediction and the actual results for NAFLD and non-NAFLD (Figures 5(f) and 5(g)).

### 4. Discussion

In this population-based study, we applied logistic regression, WQS, and BKMR models to evaluate the effects of

TABLE 1: Characteristics of the study population by nonobese NAFLD status.

Variables	Total	Non-NAFLD	NAFLD	P value
N	904	788 (87.16%)	116 (12.83%)	
Age (years)	42.85 ± 0.86	41.27 ± 0.88	57.70 ± 1.59	<0.001
BMI (Kg/m <sup>2</sup> )	22.07 ± 0.08	21.96 ± 0.08	23.06 ± 0.18	<0.001
WHR	0.86 ± 0.01	0.85 ± 0.01	0.92 ± 0.01	<0.001
SBP (mmHg)	117.49 ± 0.84	116.76 ± 0.83	124.39 ± 1.82	<0.001
DBP (mmHg)	69.48 ± 0.52	69.18 ± 0.54	72.23 ± 0.82	<0.001
<i>Comorbidity</i>				
Hypertension				<0.001
Yes	738	666 (80.04%)	72 (5.94%)	
No	166	122 (10.35%)	44 (3.66%)	
T2DM				<0.001
Yes	845	752 (88.59%)	93 (7.81%)	
No	59	36 (1.80%)	23 (1.78%)	
TC (mg/dl)	182.09 ± 2.08	180.60 ± 2.45	196.17 ± 6.52	<0.001
HDL-c (mg/dl)	61.73 ± 0.77	61.63 ± 0.84	62.75 ± 2.65	<0.001
TG (mg/dl)	98.25 ± 2.38	93.54 ± 2.15	142.56 ± 12.31	<0.001
HbA1c (%)	5.38 ± 0.03	5.32 ± 0.01	5.98 ± 0.19	<0.001
Uric acid (μmol/L)	278.67 ± 3.50	274.80 ± 3.34	315.19 ± 10.20	<0.001

Weighted mean ± SE for continuous variables or *n* and weighted proportion for categorical variables. BMI, body mass index; WHR, waist-to-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; TC, total cholesterol; BMI, body mass index; T2DM, type 2 diabetes mellitus; HDL-c, high-density lipoprotein cholesterol; NAFLD, nonalcoholic fatty liver disease.

TABLE 2: Risk of NAFLD in nonobese population associated with metabolism-related indicators.

Variables	OR (95% CI)	P value
BMI (kg/m <sup>2</sup> )	1.012 (0.962–1.261)	0.160
WHR	2.264 (1.535–3.338)	<0.001
SBP (mmHg)	0.990 (0.975–1.006)	0.228
DBP (mmHg)	1.013 (0.987–1.040)	0.324
TC	1.003 (0.997–1.009)	0.345
HDL-c	1.016 (1.002–1.031)	0.028
TG	1.009 (1.005–1.013)	<0.001
Uric acid	1.002 (0.999–1.004)	0.292
HbA1c (%)	1.296 (1.028–1.634)	0.028

BMI, body mass index; WHR, waist-to-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; TC, total cholesterol.

nine metabolic-related indicators in the general population on the occurrence of NAFLD in nonobese populations and established a clinical prediction model. For the logistic regression model, there were positive correlations of WHR, HDL-c, TG, and HbA1c with outcomes. The results of the WQS model showed the association of WHR, TC, TG, and BMI with the occurrence of NAFLD in the nonobese population. In the BKMR model, we found that mixed metabolic markers were significantly associated with the development of NAFLD in the nonobese population. The univariate exposure-response function showed a positive relationship between WHR, HbA1c, and TG. The bivariate exposure-response function suggested a potential interaction between WHR and TG. From the results of the three models, we found that the WHR and TG were strong risk factors for predicting the development of NAFLD in a nonobese population.

Previous studies have reported BMI and waist circumference as traditional indicators of NAFLD. Xu et al. reported that BMI was associated with the presence and development of NAFLD in nonobese subjects [40, 41]. Ding et al. claimed that weight loss reduces the risk of NAFLD in

a nonobese population, and a lower weight reduction target may suffice in this population [42, 43]. However, in our study, BMI played a small role in driving the development of NAFLD in nonobese people. The phenomenon is consistent with Janssen et al.'s findings that waist circumference is associated with obesity-related health risks compared to BMI [43]. Johanna et al. reported that NAFLD in nonobese people occurs in association with an increase in visceral adiposity, independent of BMI [44]. Approximately 20% of adults are classified in the incorrect BMI category on the basis of self-reported height and weight [45]. This may also account for the difference. BMI is not an accurate indicator of the degree of lipid accumulation in the body, and some of the subjects with a BMI of <25 also had elevated TG levels in our study.

In our study, WHR was identified as a significant risk factor influencing the occurrence of NAFLD in the nonobese population. A higher WHR was demonstrated in participants with NAFLD due to increased waist circumference than healthy subjects in the nonobese population. According to Shao et al., waist circumference is strongly associated with the development of moderate to severe hepatic steatosis and

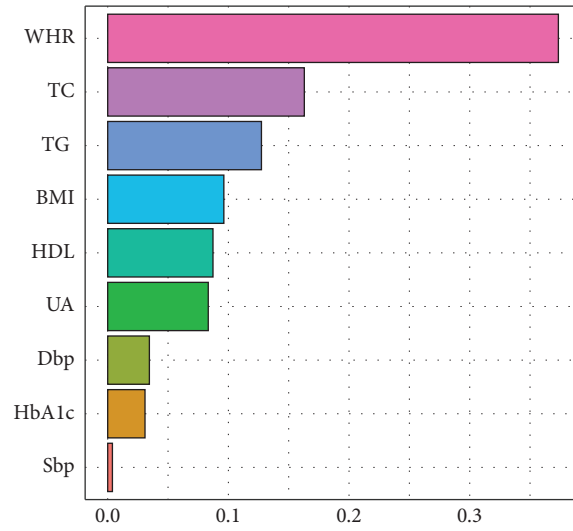


FIGURE 2: WQS regression model weights of each metabolism-related indicator. The figure shows the weights of each individual metabolism-related indicator contributing to the overall effect. The models were adjusted for sex, age, smoking, race, hypertension, and T2DM.

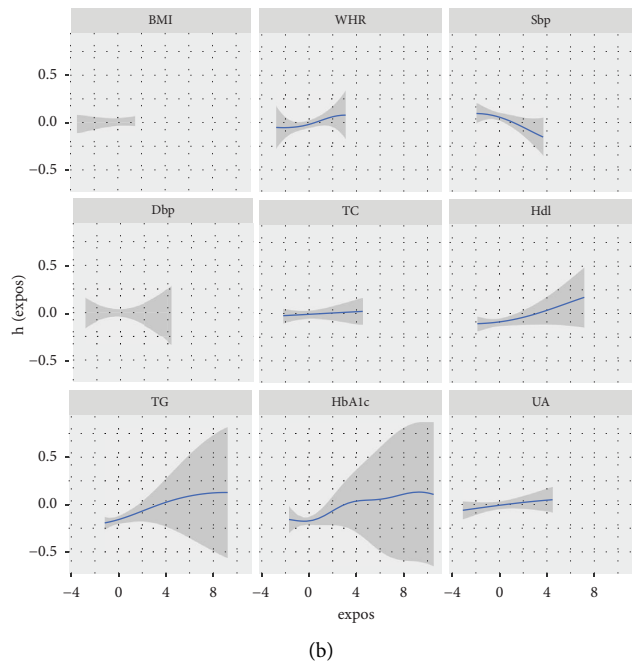
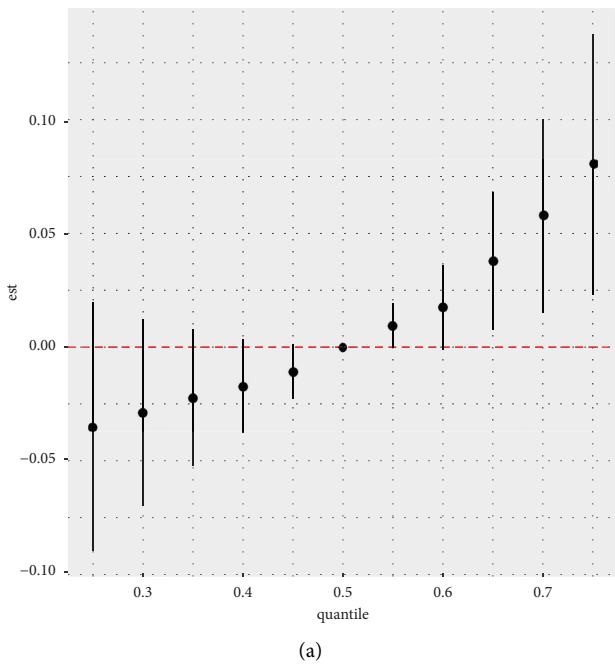
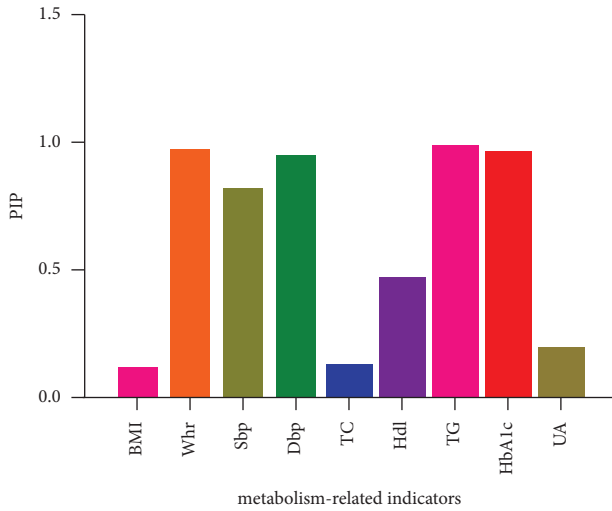
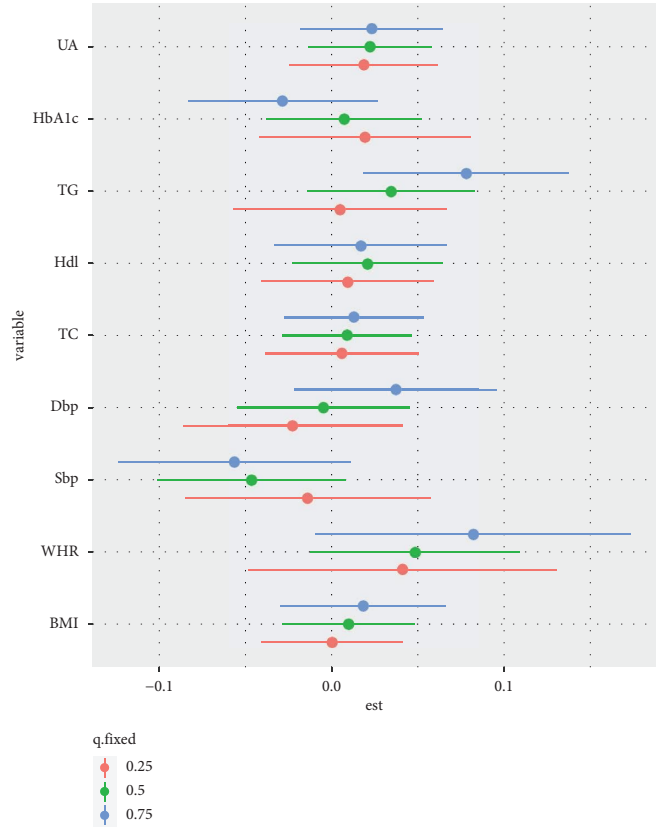


FIGURE 3: Continued.



(c)



(d)

FIGURE 3: BKMR model to assess the association between metabolism-related indicators and NAFLD in nonobese patients. (a) Cumulative effect of metabolism-related indicators. (b) Univariate exposure-response functions for each metabolism-related indicator, with other metabolites fixed at their median concentrations. (c) Posterior inclusion probabilities (PIPs) for NAFLD in nonobese population, using BKMR model. (d) The single-exposure effect of metabolism-related indicators.

fibrosis in people with a normal BMI [46]. WHR is an important predictor for NAFLD cutoff points as WHR varies in different populations [47, 48]. WHR is one of the indicators to assess visceral fat accumulation [49]. Compared with healthy nonobese participants, nonobese participants with NAFLD had more visceral fat [50]. Accumulation of visceral fat exposes the liver to high levels of free fatty acids, thus exacerbating the accumulation of TG in the liver [51]. Therefore, maintaining a normal WHR is essential to prevent the development of NAFLD in nonobese participants.

Dyslipidemia is a known risk factor for NAFLD [52]. Leung et al. found that high serum triglyceride levels were a risk factor for developing NAFLD in nonobese people and a risk factor for advanced NAFLD-related liver disease [23]. This is consistent with our study that TG levels are associated with the development of NAFLD. Elevated serum TG levels increase free fatty acids, producing excessive hepatic triglyceride deposition. Studies have reported that NAFLD is associated with dyslipidemia and dysglycemia, and fat deposition, including visceral fat, is an independent risk factor [52]. Insulin resistance (IR) may be a potential mediator of the relationship between TG levels and the development and progression of NAFLD. On the one hand, IR promotes elevated TG levels, which might further aggravate tissue IR

[53]. On the other hand, IR can boost TG lipolysis in adipose tissue and hepatic TG production from scratch [54]. Although the current evidence makes it difficult to speculate on the role of high TG in developing NAFLD, it is one of the markers for NAFLD progression, especially in nonobese people.

The WQS and BKMR models are recently developed statistical algorithms designed to elucidate metabolic-related indicators' combined effects on NAFLD occurrence in nonobese populations. The WQS regression model was based on weighting determined empirically through bootstrap sampling to examine the whole-body burden of exposure to metabolically relevant indicators. The BKMR model can provide a new perspective on nonlinear exposure-reexposure response and potential interactions between metabolically related indicators. The results were the same for the WQS and BKMR models. WHR and TG are significant contributors to the overall mixture effect. The bivariate exposure-response function revealed a potential interaction between WHR and TG.

Our study has several limitations. First, the included participants may be biased because CAP values rather than biopsy-proven parameters were used to define NAFLD. Second, the data used in this study were extracted from

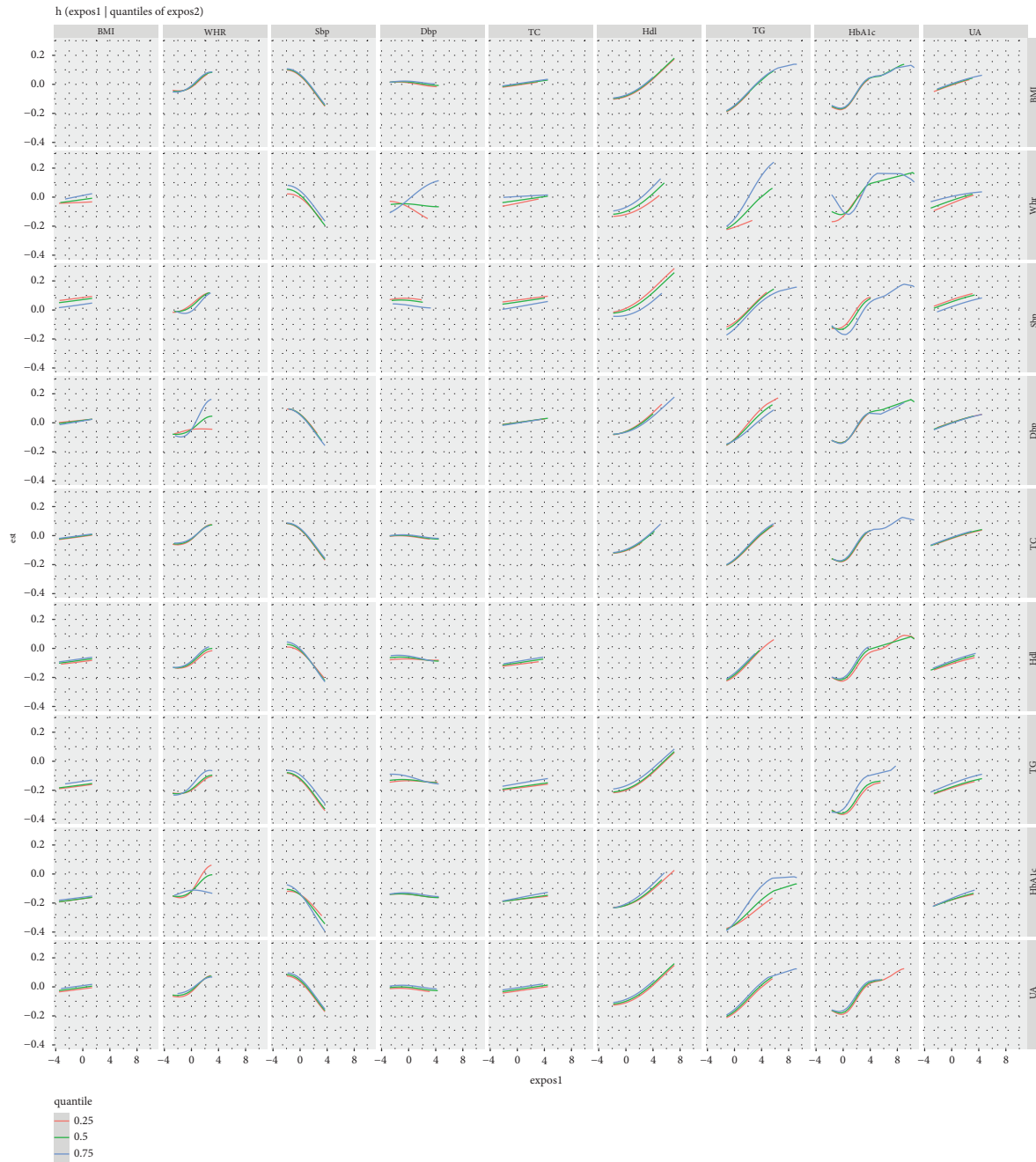
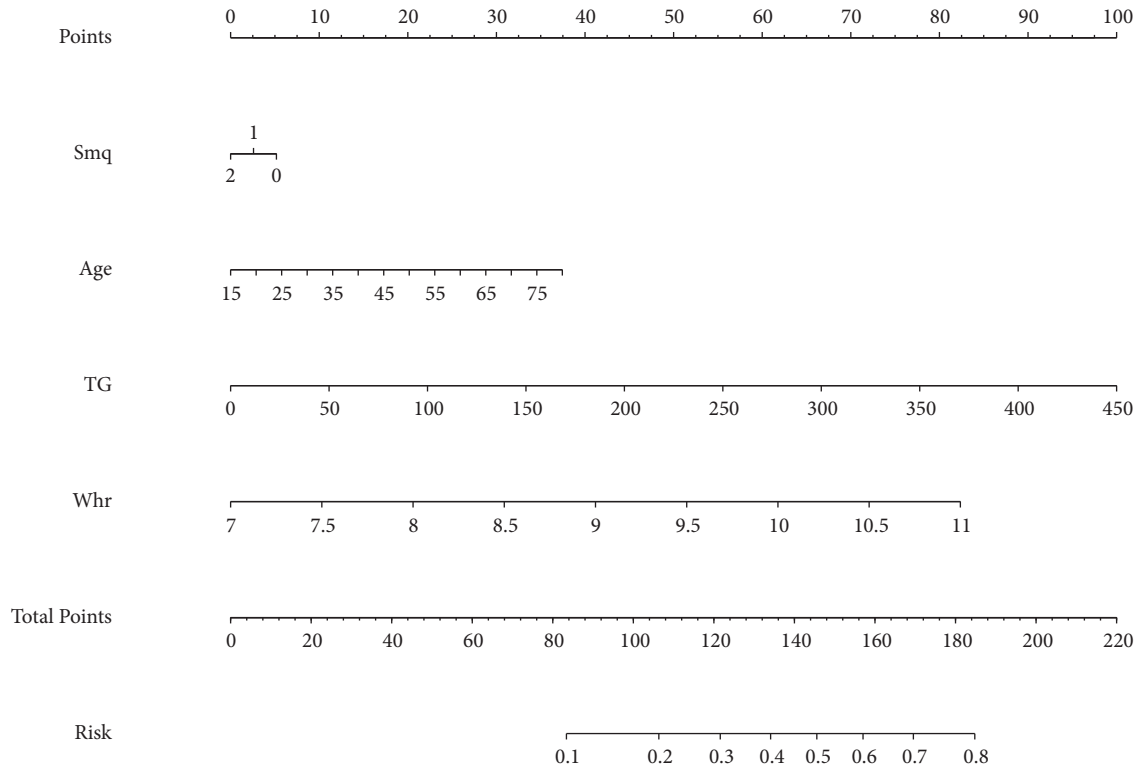


FIGURE 4: Bivariate exposure-response relationship between metabolism-related indicators and NAFLD in the nonobese population.

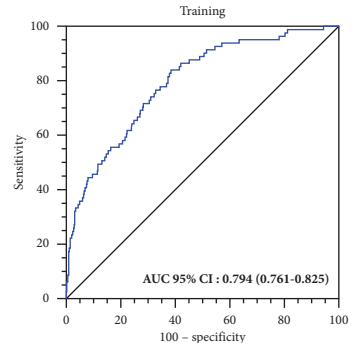
a cross-sectional survey (NHANES) with a weak ability to investigate causal relationships. Therefore, more prospective studies are needed to validate our findings. Logistic, WQS, and BKMR regression models were applied to evaluate the association between metabolic-related indicators and NAFLD in the nonobese population. Considering the results of the three models, we found that

WHR and TG were most significantly associated with NAFLD in the nonobese population. In the future, our study could help clinicians find the “hidden” problems associated with NAFLD in the nonobese population, formulate effective prevention strategies, and carry out early-stage medical interventions to reduce the social and medical burden of NAFLD.

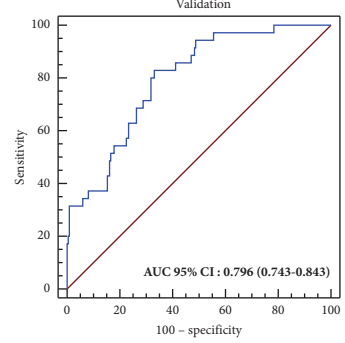




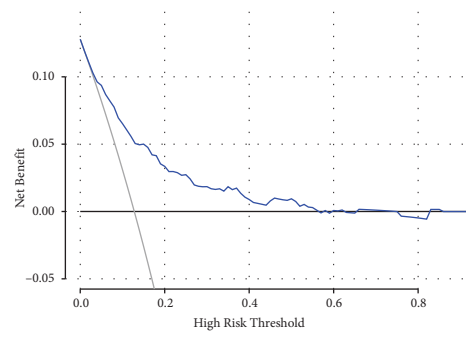
(a)



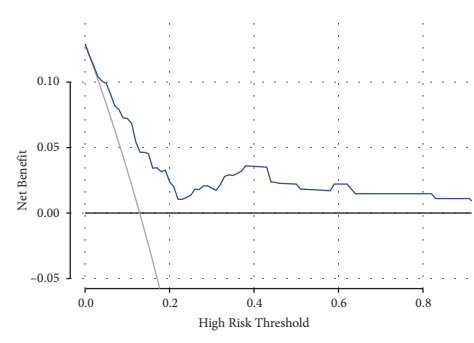
(b)



(c)



(d)



(e)

FIGURE 5: Continued.

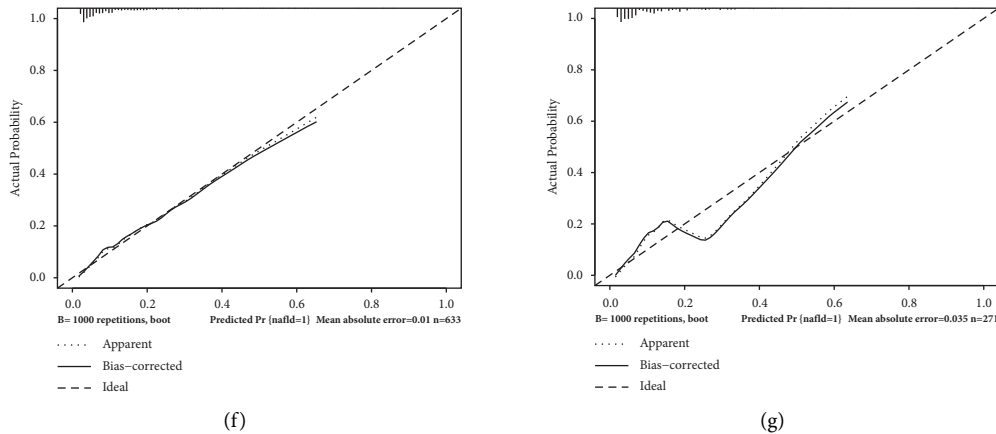


FIGURE 5: The nomogram for predicting the risk of NAFLD in the nonobese population (a). By summing the scores of each point and locating it on the total score scale, the estimated probability of NAFLD was determined. The AUROC validates the discrimination power of the model in the training cohort (b) and the validation cohort (c). Decision curve analysis in the training cohort (d) and the validation cohort (e). Calibration curves in the training cohort (f) and the validation cohort (g).

## Data Availability

Publicly available datasets were analyzed in this study. The raw data used in the article are available from NHANES.

## Ethical Approval

The studies involving human participants were reviewed and approved by National Center for Health Statistics Ethics Review Board.

## Consent

NHANES obtained the written informed consent from all participants, which was approved by the National Center for Health Statistics Institutional Review Board.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

## Authors' Contributions

All authors made substantial contributions to the conception, design, analysis, and interpretation of data. XZ collected the data and drafted the article. HW and GN conducted the formal statistical analysis and data management. XL and JY revised the manuscript critically for important intellectual content. All authors have read and approved the final manuscript.

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## Supplementary Materials

Supplementary Table 1: characteristics of the study population by nonobese NAFLD status. Supplementary Table 2: univariate and multivariate analyses for the prediction of nonobese NAFLD. (*Supplementary Materials*)

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