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Association between visceral lipid accumulation indicators and gallstones: a cross-sectional study based on NHANES 2017–2020

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Abstract

Background Obesity is a major contributing factor to the formation of gallstones. As early identification typically results in improved outcomes, we explored the relationship between visceral lipid accumulation indicators and the occurrence of gallstones.

Methods This cross-sectional study involved 3,224 adults. The researchers employed multivariable logistic regression, smoothed curve fitting (SCF), threshold effects analysis, and subgroup analysis to examine the relationship between metabolic scores for visceral fat (METS-VF), waist circumference (WC), lipid accumulation products (LAP), and visceral adiposity index (VAI) and gallstones. A Least Absolute Shrinkage and Selection Operator (LASSO) regression analysis was used to identify key factors which were then used in the construction of a nomogram model. The diagnostic efficacy of this model in detecting gallstones was then determined using receiver operating characteristic curves.

Results Visceral lipid accumulation indicators were strongly linked to the likelihood of having gallstones. Specific saturation effects for METS-VF, WC, LAP, and VAI and gallstones were determined using SCF. The inflection points for these effects were found to be 8.565, 108.400, 18.056, and 1.071, respectively. Subgroup analyses showed that associations remained consistent in most subgroups. The nomogram model, which was developed using critical features identified by LASSO regression, demonstrated excellent discriminatory ability, as indicated by an area under the curve value of 0.725.

Conclusions Studies have shown that increases in METS-VF, WC, LAP, and VAI are linked to increased prevalences of gallstones. The nomogram model, designed with critical parameters identified using LASSO regression, exhibits a strong association with the presence of gallstones.

Keywords Gallstones, Lipid accumulation, Cross-sectional study, NHANES, LASSO

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Introduction

Gallstones are a medical condition marked by the development of calculi in the gallbladder or bile ducts, primarily as a result of abnormally elevated amounts of cholesterol or bilirubin in the bile. Cholesterol stones are the predominant type, while bilirubin stones are most often associated with hemolytic disorders or abnormal liver function. Epidemiological studies indicate that approximately 10–20% of adults are diagnosed with gallstones [1]. The total annual cost of cholecystectomies and subsequent office visits in the USA is approximately $6.5 billion [2]. In 2015, 1.5 million people sought medical care for gallstone-related conditions, with a total national expenditure of $10.3 billion dedicated to gallstones [3], which places a considerable burden on individuals and society. Although gallstones are usually asymptomatic, over 20% of individuals may have issues like biliary colic or infection as adults, and 1–2% may experience serious complications [1, 4, 5]. Therefore, the search for novel and more precise biomarkers is crucial in achieving the timely identification of gallstones.

Multiple research investigations have demonstrated that obesity plays a substantial contributing factor in the induction of gallstones [1, 6]. One of the distinguishing features of obesity is the accumulation of visceral fat. Visceral fat has a more significant role on health compared to subcutaneous fat. It is a red flag for obesity and predisposes individuals to metabolic disorders which, in turn, may raise their susceptibility to cardiovascular disease, diabetes, gallstones, and fatty liver [7, 8]. However, traditional measurements, including body mass index (BMI), only provide a rough assessment of obesity and are unable to differentiate between subcutaneous and visceral fats. Although waist circumference (WC) can indicate the degree of visceral fat accumulation, its accuracy may be affected by body size, sex, age, and ethnicity in different individuals [9, 10]. Consequently, in order to overcome the constraints of WC, scholars have suggested the development of new metrics to precisely assess the buildup of visceral fat. The metabolic score for visceral fat (METS-VF), lipid accumulation product (LAP), and visceral adiposity index (VAI) serve as dependable markers of visceral fat accumulation. Many previous investigations have established strong associations between these metrics and various diseases [11–14].

However, the relationship between visceral lipid accumulation indicators and the likelihood of developing gallstones remains uninvestigated. Hence, the present research employed National Health and Nutrition Examination Survey (NHANES) data from 2017 to 2020 in an attempt to elucidate the potential association between these indicators and prevalence of gallstones.

Methods

Study population

The NHANES, conducted by the National Center for Health Statistics (NCHS) within the Centers for Disease Control and Prevention, constitutes a significant health and nutrition survey initiative, begun within the 1960s to collect the health and nutritional condition of the American population, including both adults and children. This study employs NHANES data from 2017 to 2020. Figure 1 illustrates the exclusion criteria applied as follows: (1) age < 20 years; (2) incomplete gallstones questionnaire; and (3) missing METS-VF, WC, VAI, and LAP information. Ultimately, a total of 3,224 samples were included.

Definition of gallstones

To determine whether individuals had gallstones, a survey question was phrased as: “Have you ever received a medical diagnosis of gallstones from a doctor?” Participants who acknowledged having gallstones were classified as gallstone patients, whereas those who denied having gallstones were placed in the nongallstone category.

Exposure factors measurement

Lipid accumulation indicators were determined to be the exposure variables investigated by the researchers. These variables were calculated using the formulas provided below [9]. Laboratory data provided information on triglycerides (TG), fasting blood glucose (FBG), and high-density lipoprotein cholesterol (HDL-C), whereas BMI, WC, and height data were obtained at the mobile screening center. In the METS-VF calculation, the value for sex was set to 1 for males and 0 for females [9, 15].

$$Males:\ LAP = (WC - 65) \times TG$$

$$Females:\ LAP = (WC - 58) \times TG$$

$$Males:\ VAI = \left(\frac{WC}{39.68 + 1.88 \times BMI}\right) \times \left(\frac{TG}{1.03}\right) \times \left(\frac{1.31}{HDL - C}\right)$$

$$Females:\ VAI = \left(\frac{WC}{36.58 + 1.89 \times BMI}\right) \times \left(\frac{TG}{0.81}\right) \times \left(\frac{1.52}{HDL - C}\right)$$

$$WHtR = \frac{WC}{Height}$$

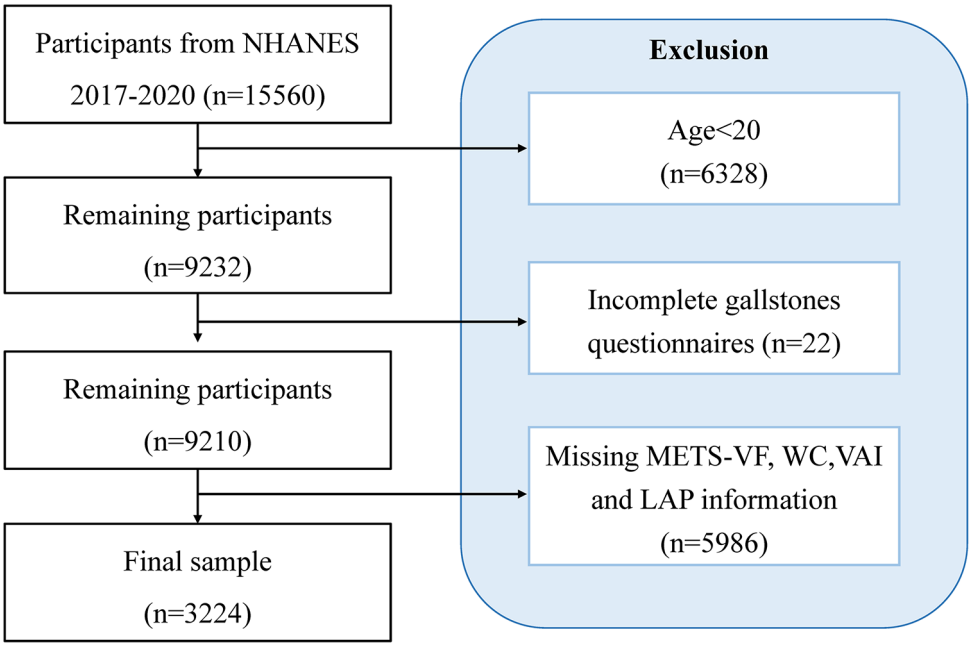

Fig. 1 A flowchart showing the selection of study participants

$$METS-IR=\frac{\ln\left(2\times\ FBG+TG\right)\times\ BMI}{\ln\left(HDL-C\right)}$$

$$\begin{aligned}METS-VF=&\ 4.466+0.01\times\left(\ln\left(METS-IR\right)\right)^3\\&+3.329\times\left(\ln\left(WHtR\right)\right)^3+0.319\\&\times gender+0.594\times\ln\left(age\right)\end{aligned}$$

Covariables

Sex, age, race, education, and the income-to-poverty ratio were considered to be the demographic covariables in the study. Variables derived from questionnaires included the following: smoking (individuals categorized as smokers had consumed at least one hundred cigarettes during their lifespan); alcohol use (individuals who have consumed alcohol were considered drinkers); and a history of medical disorders including diabetes and hypertension. These were accordingly documented on the basis of the participants' affirmative responses.

Statistical analysis

Visceral lipid accumulation indices were categorized by quartiles, and the lowest quartile was used as the reference group. Continuous variables were expressed as median and interquartile range (IQR) due to their non-normal distribution, which was determined by the Kolmogorov-Smirnov test (Table S1 and Figure S1), and categorical variables were expressed as proportions. Differences between groups for categorical variables were assessed by the chi-square test, while differences between groups for continuous variables were analyzed using the Mann-Whitney U test.

To explore the odds ratios (ORs) and 95% confidence intervals (CIs) between gallstones and these indicators, multivariable logistic regression was used. We constructed three regression models: model 1 (unadjusted), model 2 (adjusted only for sex, age, race, education, and marital status), and model 3 (fully adjusted for all covariables).

In addition, we assessed the potential nonlinear relationship between gallstones and visceral lipid accumulation metrics by smoothed curve fitting (SCF). The threshold effect of gallstones with these indicators was investigated by using a segmented linear regression model.

Subgroup analysis and interaction testing were used to delve deeper into potential differences across different populations. Sensitivity analysis was conducted to further assess the robustness of the outcomes. Total blood cholesterol was first adjusted to minimize its effect on gallstones. Second, participants with a history of smoking and diabetes were excluded, and then the association of these metrics with gallstones was reanalyzed in the remaining participants to check whether the results remained stable in the healthy population.

A Least Absolute Shrinkage and Selection Operator (LASSO) regression analysis was employed to evaluate all covariables as well as the indicators of visceral lipid accumulation. The penalty parameter lambda (λ) was determined using a process of 10-fold cross-validation, as shown in Fig. 3A. The algorithm was executed for 1,000

iterations in order to guarantee precision in this study. The model exhibiting the highest value within one standard error of the minimal binomial deviation, denoted as λ (λ=0.0171), was consistent with prior published findings (Fig. 3B). Six variables (sex, age, race, hypertension, WC, and LAP) were initially chosen to construct a preliminary nomogram model. However, after conducting a statistical analysis, only five factors, namely sex, age, race, hypertension, and WC, had a significant association with the model. The discriminative ability of the nomogram model to recognize gallstones was verified via the receiver operating characteristic (ROC) curve.

Missing values were filled in using multiple imputations. A p-value<0.05 was considered significant. R and EmpowerStats were implemented for the statistical analyses.

Results

Baseline characteristics

This research included 3,224 individuals who fulfilled specific inclusion and exclusion criteria. Among these participants, 54.68% were females. Participants had an average age of 50.97±17.38 years. Overall, 2,886 (89.52%) participants did not have gallstones and 338 (10.48%) had gallstones. The mean METS-VF, WC, LAP, and VAI were 8.28±1.67, 99.25±16.79, 43.93±34.93, and 1.39±1.02, respectively. Table 1 contains an elaborate account of the participants. In contrast to participants without gallstones, those with gallstones were more likely to be female; older in age (≥60 years); non-Hispanic white; married or living with a partner; diagnosed with diabetes; and exhibit higher levels of METS-VF, WC, LAP, and VAI (each $p<0.05$).

Association between METS-VF, WC, LAP, and VAI and gallstones

Table 2 presents the connection between visceral lipid accumulation indicators and the likelihood of having gallstones. We designed three distinct models for this analysis. Additionally, for enhanced clarity and analysis, we categorized these indicators into four levels. Model 1 showed that higher visceral lipid accumulation index scores were related to an increased prevalence of gallstones. After considering all covariables (model 3), we found that a notable connection between the four indicators and gallstones remained. More precisely, the occurrence of gallstones in the upper quartile of the METS-VF was demonstrated to be 238.8% more than that in the lower quartile of the METS-VF (OR=3.338, 95% CI: 2.158–5.164). The prevalence of gallstones in the upper quartile of the WC was found to be 215.4% more than that observed in the lower quartile of the WC (OR=3.154, 95% CI: 2.173–4.578). The frequency of gallstones in the top quartile of the LAP was 148.1% superior to in the bottom of the LAP (OR=2.481, 95% CI: 1.697–3.626). A significant increase of 88.5% in the occurrence of gallstones was seen in Q4 of VAI compared to Q1 (OR=1.885, 95% CI: 1.304–3.37).

To further visualize the link between visceral lipid accumulation indicators and gallstones, SCF was performed based on Model 3. Figure 2 shows a nonlinear association between the four indicators and prevalence of gallstones. Subsequently, a threshold effect analysis was conducted to elucidate the association (Table 3). The study identified the inflection point of METS-VF as 8.565, with a log-likelihood ratio of <0.001. This suggests that a reduction in METS-VF below 8.565 is linked to a 101.4% raised the probability of having gallstones for every additional one unit in METS-VF. When METS-VF levels exceeded 8.565, the relation between METS-VF and gallstone occurrence disappeared, indicating that subsequent elevations in METS-VF levels did not yield a statistically significant rise in gallstone prevalence. The findings on VAI exhibited a consistent pattern, showing an inflection point of 1.071 (log-likelihood ratio<0.001). This indicates that VAI had varying effects on the prevalence of gallstones below and beyond this threshold. Remarkably, we discovered that the association between WC and LAP, with gallstone occurrence, exhibited a consistent pattern on both sides of the critical threshold.

Subgroup analysis

The association between METS-VF, WC, LAP, and VAI and gallstones was consistent in most subgroups, with no significant interaction observed (Figure S2). Notably, an interaction with statistical significance was observed between METS-VF, WC, LAP, and VAI and sex (p for interaction<0.05). While a statistically significant positive association was found in females, this connection lost its significance among males. This indicates that elevated levels of visceral lipid accumulation indicators may increase the likelihood of gallstones in females.

LASSO regression and the nomogram model

We conducted LASSO regression and developed a nomogram model (Fig. 3A and B). The ROC curves demonstrated that the constructed nomogram model exhibited superior discriminatory ability when compared to METS-VF, WC, LAP, and VAI. The area under the curve (AUC) value was 0.725 (Fig. 3D). The results of the 10-fold cross-validation show that the average AUC value of the final model was 0.729 (Figure S3), which is close to the AUC value previously analyzed by the ROC curve (Fig. 3D), further demonstrating the robustness and strong association with gallstone occurrence.

Table 1 Baseline characteristics of participants from National Health and Nutrition Examination Survey (NHANES) 2017–2020

Variables	Overall	Gallstones		*P*-value
	(*n* = 3224)	NO (*n* = 2886)	YES (*n* = 338)	
Sex, n (%)				< 0.001
Male	1461 (45.32%)	1691 (50.86%)	110 (27.92%)	
Female	1763 (54.68%)	1634 (49.14%)	284 (72.08%)	
Age, Median (Q1-Q3)	52.00 (36.00–65.00)	51.00 (35.00–64.00)	60.00 (46.00–70.00)	
Age strata, n (%)				< 0.001
20–40	976 (30.27%)	926 (32.09%)	50 (14.79%)	
40–60	1064 (33.00%)	947 (32.81%)	117 (34.62%)	
≥ 60	1184 (36.72%)	1013 (35.10%)	171 (50.59%)	
Race, n (%)				< 0.001
Mexican American	400 (12.41%)	348 (12.06%)	52 (15.38%)	
Other Hispanic	319 (9.89%)	277 (9.60%)	42 (12.43%)	
Non-Hispanic White	1081 (33.53%)	951 (32.95%)	130 (38.46%)	
Non-Hispanic Black	850 (26.36%)	788 (27.30%)	62 (18.34%)	
Other Race	574 (17.80%)	522 (18.09%)	52 (15.38%)	
Education level, n (%)				0.161
Less than 9th grade	227 (7.04%)	204 (7.07%)	23 (6.80%)	
9-11th grade	343 (10.64%)	303 (10.50%)	40 (11.83%)	
High school graduate	759 (23.54%)	673 (23.32%)	86 (25.44%)	
Some college or associates degree	1056 (32.75%)	936 (32.43%)	120 (35.50%)	
College graduate or above	839 (26.02%)	770 (26.68%)	69 (20.41%)	
Marital status, n (%)				< 0.001
Married/Living with a partner	1912 (59.31%)	1706 (59.11%)	206 (60.95%)	
Divorced/Separated/Widowed	711 (22.05%)	618 (21.41%)	93 (27.51%)	
Never married	601 (18.64%)	562 (19.47%)	39 (11.54%)	
Income-to-poverty ratio, n (%)				0.407
< 1.3	721 (22.36%)	647 (22.42%)	74 (21.89%)	
1.3–1.85	415 (12.87%)	365 (12.65%)	50 (14.79%)	
1.85–3.5	1132 (35.11%)	1007 (34.89%)	125 (36.98%)	
≥ 3.5	956 (29.65%)	867 (30.04%)	89 (26.33%)	
Alcohol use, n (%)				0.469
Yes	2932 (90.94%)	2621 (90.82%)	311 (92.01%)	
No	292 (9.06%)	265 (9.18%)	27 (7.99%)	
Smoking, n (%)				0.590
Yes	1339 (41.53%)	1194 (41.37%)	145 (42.90%)	
No	1885 (58.47%)	1692 (58.63%)	193 (57.10%)	
Hypertension, n (%)				< 0.001
Yes	1203 (37.31%)	1021 (35.38%)	182 (53.85%)	
No	2021 (62.69%)	1865 (64.62%)	156 (46.15%)	
Diabetes, n (%)				< 0.001
Yes	493 (15.29%)	409 (14.17%)	84 (24.85%)	
No	2731 (84.71%)	2477 (85.83%)	254 (75.15%)	
METS-VF, Median (Q1-Q3)	8.10 (7.27–8.98)	8.02 (7.20–8.94)	8.41 (7.86–9.21)	< 0.001
WC, Median (Q1-Q3)	97.85 (87.10-109.80)	96.90 (86.60-108.50)	105.95 (95.43-116.68)	< 0.001
LAP, Median (Q1-Q3)	34.97 (18.78–58.54)	33.61 (17.98–55.83)	51.58 (30.29–75.36)	< 0.001
VAI, Median (Q1-Q3)	1.11 (0.68–1.78)	1.08 (0.66–1.74)	1.41 (0.96–2.17)	< 0.001

Sensitivity analysis

Results remained robust across multiple sensitivity analysis (Table S2). Specifically, after adjusting for total cholesterol, visceral lipid accumulation indicators consistently displayed a positive association with the likelihood of developing gallstones in all four models. Furthermore, the results remained consistent even after individuals with a pre-existing smoking or diabetes background were removed from the analysis.

Discussion

This study is the first to use the NHANES database to examine the association between multiple visceral lipid accumulation indicators and gallstones, including a total of 3,224 participants. The findings demonstrated a statistically substantial positive relationship between these indicators and the occurrence of gallstones. Importantly, a nonlinear association was observed between MEST-VF, WC, LAP, and VAI and gallstones, and the respective inflection points were identified. This suggests a strong connection between these indicators and gallstones within a certain range, implying that maintaining ideal levels of MEST-VF, WC, LAP, and VAI has potential clinical significance in reducing the prevalence of gallstones. In addition, these positive associations were largely consistent across population settings. Moreover, the nomogram model derived from the major parameters developed in this study has a good diagnostic ability in identifying gallstones.

Studies have indicated a close connection between obesity and the occurrence of gallstones, with visceral fat accumulation being a significant risk factor [16, 17]. A prospective cohort study demonstrated that obesity promotes gallstone formation independently, even in metabolically healthy individuals [18]. Furthermore, a prospective study spanning a duration of 2 years has established a noteworthy link between abdominal obesity and the onset of asymptomatic cholelithiasis [19]. Sekine et al. conducted an analysis on 717 participants who underwent both computed tomography (CT) and

Table 2 Association of METS-VF, WC, LAP, VAI and gallstones

	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
METS-VF			
Categories			
Q1	Reference	Reference	Reference
Q2	2.467 (1.630, 3.735)	1.950 (1.269, 2.995)	1.890 (1.227, 2.910)
Q3	3.933 (2.650, 5.836)	3.524 (2.329, 5.332)	3.264 (2.144, 4.969)
Q4	3.438 (2.306, 5.127)	3.731 (2.441, 5.703)	3.338 (2.158, 5.164)
P for trend	< 0.001	< 0.001	< 0.001
WC			
Categories			
Q1	Reference	Reference	Reference
Q2	1.742 (1.200, 2.530)	1.655 (1.125, 2.435)	1.604 (1.089, 2.362)
Q3	2.825 (1.990, 4.009)	2.803 (1.942, 4.048)	2.593 (1.790, 3.757)
Q4	3.484 (2.474, 4.905)	3.646 (2.539, 5.237)	3.154 (2.173, 4.578)
P for trend	< 0.001	< 0.001	< 0.001
LAP			
Categories			
Q1	Reference	Reference	Reference
Q2	2.024 (1.384, 2.960)	1.551 (1.048, 2.294)	1.511 (1.019, 2.241)
Q3	2.940 (2.046, 4.224)	2.216 (1.521, 3.230)	2.013 (1.374, 2.949)
Q4	4.030 (2.834, 5.730)	2.903 (2.010, 4.192)	2.481 (1.697, 3.626)
P for trend	< 0.001	< 0.001	< 0.001
VAI			
Categories			
Q1	Reference	Reference	Reference
Q2	2.044 (1.425, 2.933)	1.720 (1.189, 2.489)	1.677 (1.157, 2.431)
Q3	2.722 (1.922, 3.855)	2.143 (1.498, 3.065)	1.943 (1.353, 2.792)
Q4	3.066 (2.175, 4.324)	2.192 (1.531, 3.137)	1.885 (1.304, 2.724)
P for trend	< 0.001	< 0.001	0.013

Model 1: no covariates were adjusted

Model 2: Sex, age, race, education level, marital status were adjusted

Model 3: Sex, age, race, education level, marital status, PIR, alcohol use, smoking, diabetes, and hypertension were adjusted

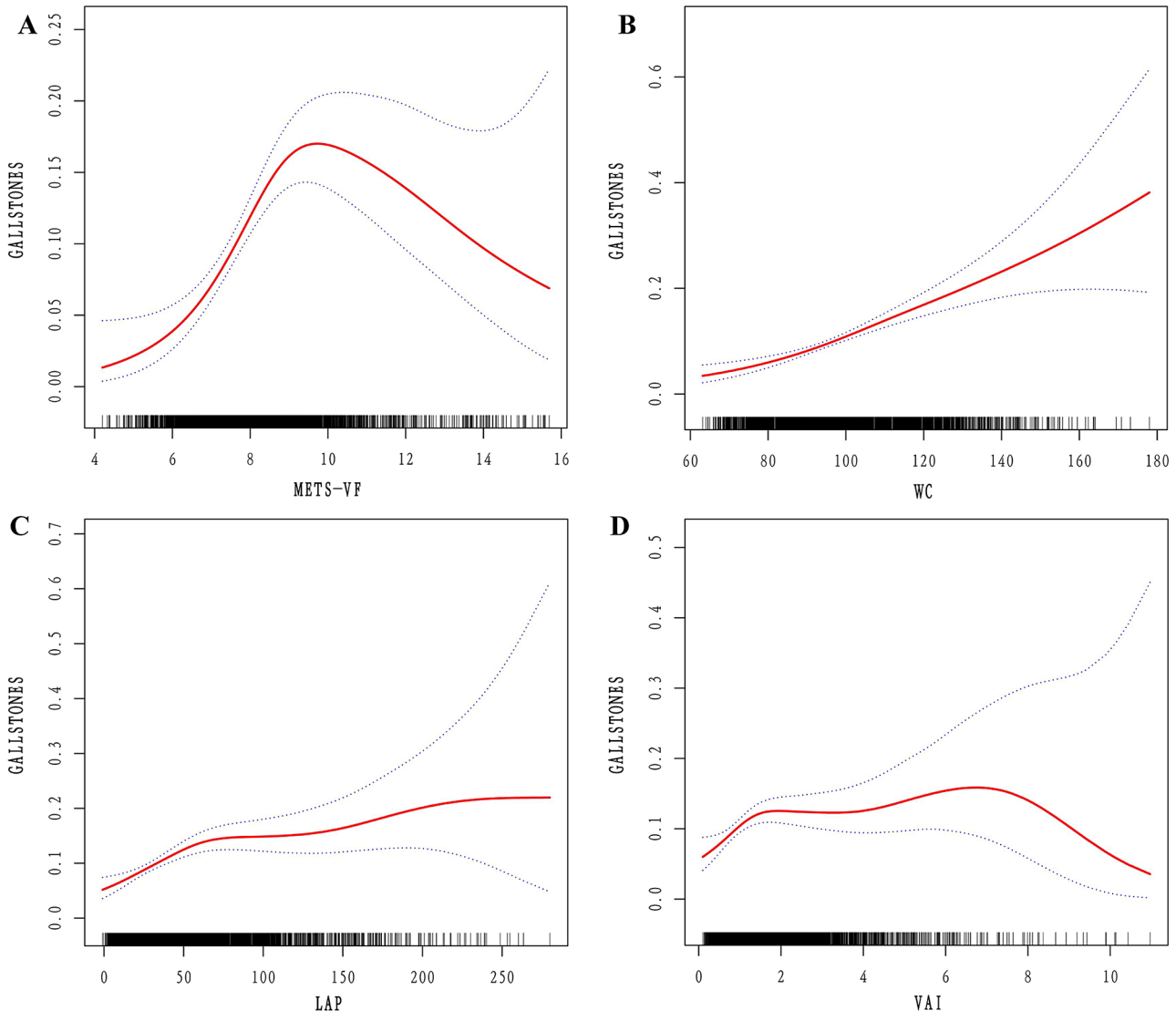

Fig. 2 The nonlinear relationship between indicators of visceral lipid accumulation and gallstones. The solid red line indicates a smooth curve fit between the variables. The blue band indicates the 95% confidence interval of the fit

ultrasound examinations. They examined the participants' BMI and subcutaneous fat and visceral fat areas, finding a relationship between the accumulation of abdominal visceral fat and an elevated risk of occurrence of gallstones [8]. Additionally, other research has indicated substantial associations between various obesity markers and gallstones [20–23]. For instance, Zhang et al., in a cross-sectional study involving 6,848 participants, found positive associations between multiple obesity markers and occurrence of gallstones [22]. Similarly, another cross-sectional study of 7,409 participants demonstrated a positive relationship between elevated VAI levels and a higher frequency of gallstones, as well as an earlier onset of gallbladder stone surgery [23].

Although substantial evidence confirms a robust association between obesity and gallstones, particularly the significant risk posed by abdominal visceral fat accumulation, the role of specific visceral lipid accumulation indicators in gallstone formation remains underexplored. While studies have examined the relationship between common obesity indicators, such as BMI, WC, and VAI and gallstones, fewer studies have specifically investigated the association of emerging visceral lipid accumulation indicators like METS-VF and LAP. The present study makes certain improvements and expands on the existing literature. First, unlike Sekine et al. who used CT and ultrasound for adiposity measurements, the present study focused on five key variables, namely sex, age, race, hypertension, and WC, which can be easily accessed through routine clinical data, possessing a higher degree of convenience and cost-effectiveness. Furthermore, these factors may provide a simple and actionable clinical

Table 3 Threshold effect analysis of METS-VF, WC, LAP, and VAI on gallstones using a two-piecewise logistic regression model in adults in the NHANES 2017–2020

Threshold effect analysis	Gallstones OR (95%CI) *P*-value
METS-VF	
Inflection point of METS-VF (K)	8.565
< K slope	2.014 (1.624, 2.498) < 0.0001
> K slope	0.903 (0.800, 1.020) 0.1012
Log-likelihood ratio test	< 0.001
WC	
Inflection point of WC (K)	108.400
< K slope	1.040 (1.026, 1.054) < 0.0001
> K slope	1.014 (1.002, 1.027) 0.0258
Log-likelihood ratio test	0.023
LAP	
Inflection point of LAP (K)	18.056
< K slope	1.116 (1.046, 1.191) 0.0009
> K slope	1.005 (1.002, 1.007) 0.0007
Log-likelihood ratio test	< 0.001
VAI	
Inflection point of VAI (K)	1.071
< K slope	3.060 (1.654, 5.662) 0.0004
> K slope	1.015 (0.928, 1.112) 0.7409
Log-likelihood ratio test	< 0.001

All covariates had been adjusted

tool in the assessment of cholelithiasis. Compared with methods relying on expensive imaging technology, the selection of variables in this study is simpler and more practical for large-scale clinical screening. Second, unlike Zhang et al. and other cross-sectional studies that used only a single obesity indicator, our model highlights more factors associated with gallstones and shows higher AUC values through ROC curve analysis, demonstrating its superiority in estimating the likelihood of gallstones. Compared with studies relying only on obesity indicators, this model was able to assess the probability of gallstone occurrence more precisely. This provides a practical tool for future mass screening and opens up new ideas for the study of the association between obesity and gallstones.

Visceral obesity and gallstone formation are intricately connected through a variety of mechanisms (Fig. 4). The accumulation of visceral fat is a crucial element in the occurrence of gallstones as it leads to insulin resistance (IR), a significant contributor to the formation of these stones. IR promotes increased cholesterol synthesis while simultaneously reducing the production of bile salts. This dual effect disrupts the delicate balance between cholesterol and bile salts, leading to elevated cholesterol saturation in bile—a critical condition that predisposes individuals to gallstone formation [24, 25]. Moreover, visceral obesity is frequently associated with hepatic steatosis, or fatty liver, which further aggravates cholesterol metabolism disorders. The presence of hepatic steatosis results in an increased cholesterol concentration within the bile, thereby amplifying the susceptibility of gallstone occurrence [26–28].

In addition to these metabolic disturbances, visceral obesity can also impair gallbladder motility. The reduced contractility of the gallbladder due to excess visceral fat leads to incomplete bile emptying, creating an environment conducive to cholesterol deposition within the gallbladder, which significantly raises the likelihood of gallstone formation [29, 30]. Furthermore, visceral obesity is linked to gut microbiota dysbiosis, a condition characterized by decreased microbial diversity and an imbalance in specific bacterial populations. These alterations in the gut microbiota can significantly affect the metabolism of bile acids, enhancing the enterohepatic circulation of cholesterol and thus contributing further to the risk of gallstones [31, 32]. The dysregulated endocrine function of adipose tissue in the context of obesity also plays a crucial role [33]. Abnormal secretion of hormones and cytokines, including leptin, adiponectin, and resistin, disrupts normal cholesterol metabolism and alters bile composition, which further increases the susceptibility to gallstone formation [34–36]. Additionally, changes in sex hormone levels, particularly elevated estrogen levels often observed in obese individuals, especially women, can exacerbate the progress of cholesterol gallstones. Estrogen affects cholesterol metabolism and bile composition, thereby intensifying the risk of gallstone occurrence in those with visceral obesity [37, 38]. In summary, visceral obesity directly contributes to gallstone

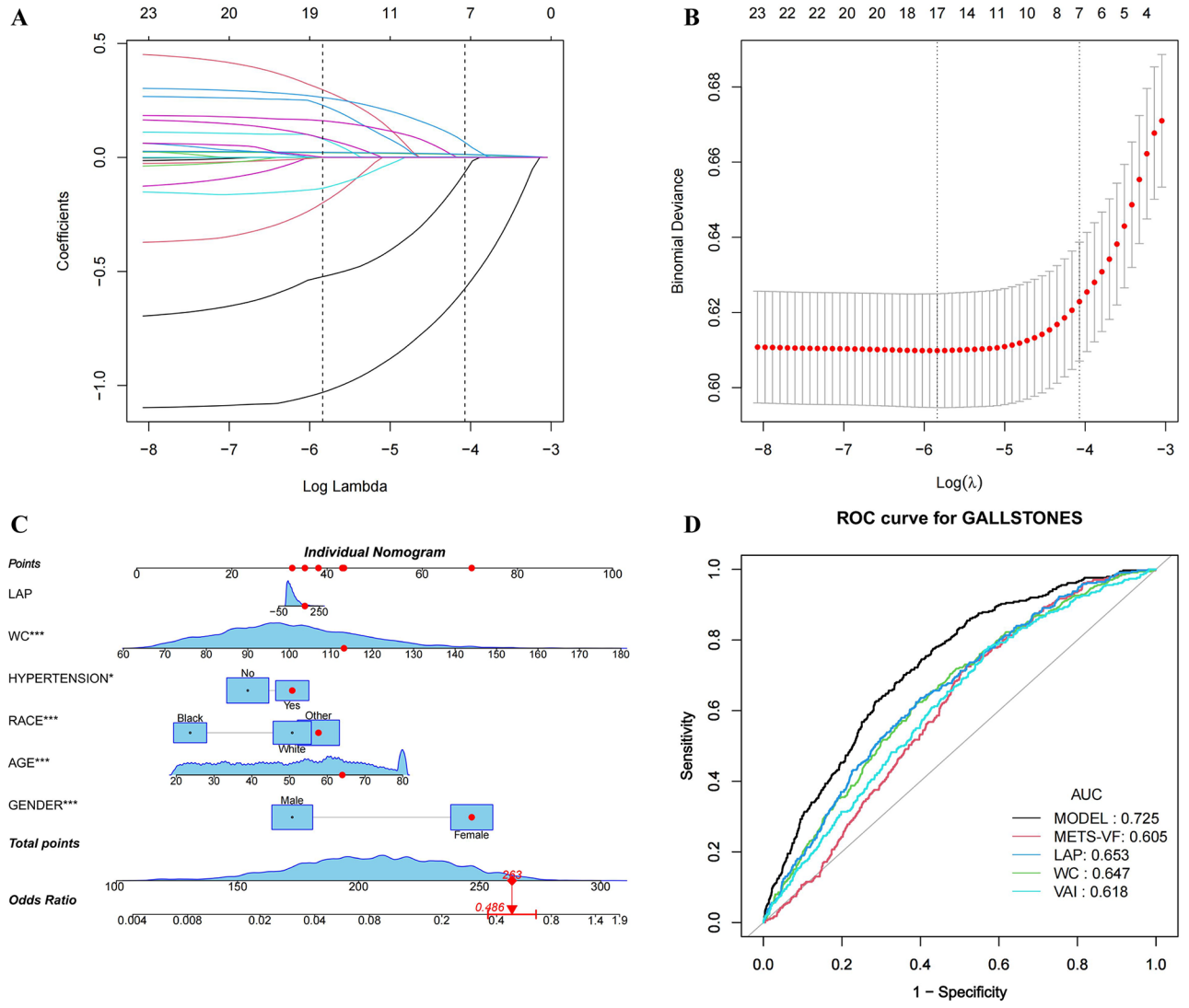

Fig. 3 LASSO regression analysis was used to screen the factors most associated with gallstones, and the results of the predictive modeling were based on this. (**A**) Plot for LASSO regression coefficients. (**B**) Crossvalidation plot. (**C**) Nomogram model based on the key dietary factors screened by LASSO regression, and the red points show an example. For the 64-year-old female participants with gallstones, the odds of having gallstones increased by 48.6%. (**D**) ROC curve for evaluating the diagnostic power of the nomogram model in this study

formation through mechanisms such as IR and hepatic steatosis and indirectly increases the risk through multiple interconnected pathways. These include impaired gallbladder function, gut microbiota dysbiosis, endocrine disturbances in adipose tissue, and alterations in hormone levels. Together, these factors create a complex network of interactions that significantly elevate the likelihood of gallstone formation in individuals with visceral obesity.

In this study, subgroup analysis revealed that females with higher levels of visceral fat accumulation were significantly more prone to developing gallstones compared to their males. This increased susceptibility in women may be linked to sex-specific physiological factors, particularly those related to hormonal differences. Elevated levels of estrogen in females, especially during certain life stages such as pregnancy or post menopause, can induce changes in lipid metabolism. These hormonal fluctuations often result in an increased saturation of cholesterol in bile, a key precursor to gallstone formation. This physiological process, driven by estrogen, may therefore affect the elevated prevalence of gallstones identified in women [39]. Furthermore, the accumulation of visceral fat is strongly connected with IR and metabolic syndrome (MetS), both of which are significant contributors to the occurrence of gallstones. The presence of IR leads to alterations in glucose and lipid metabolism, which exacerbates cholesterol saturation in bile and impairs gallbladder motility, creating an environment conducive to gallstone formation [40–42]. Postmenopausal women

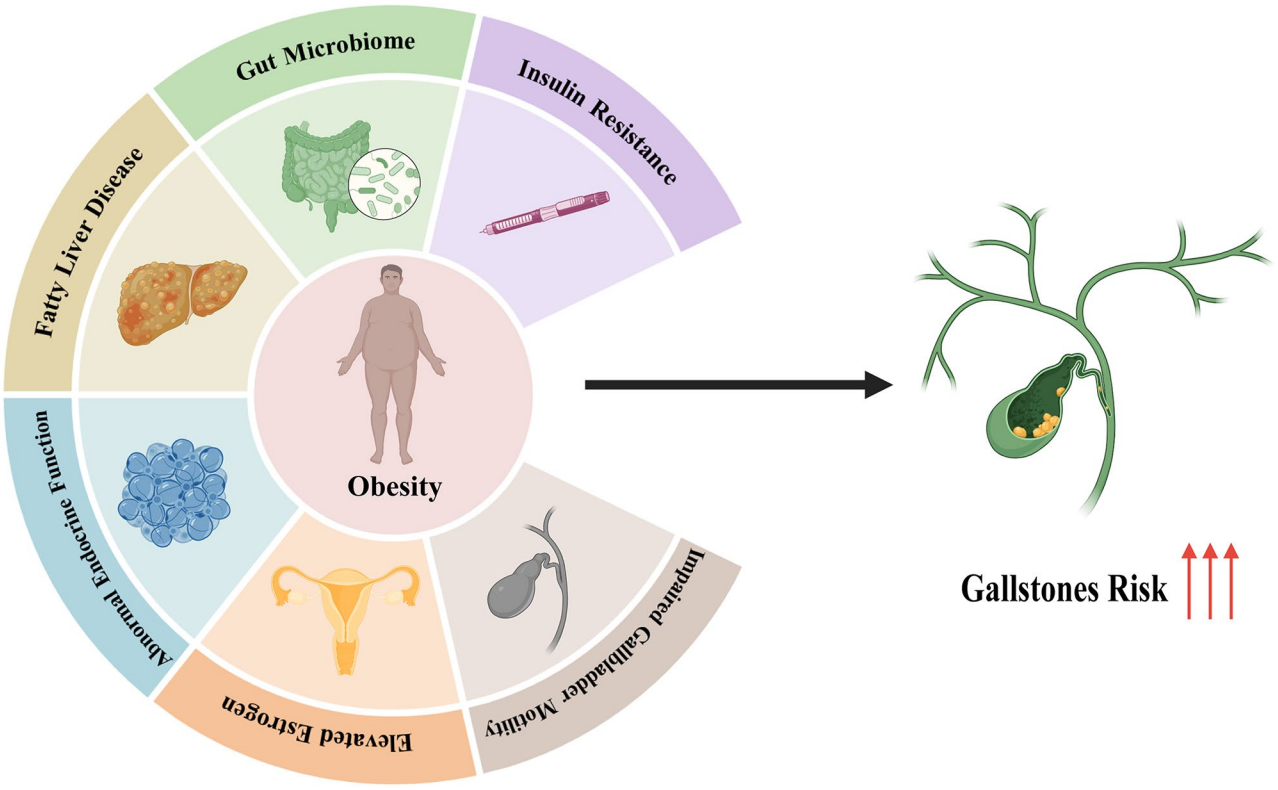

Fig. 4 Visceral obesity significantly elevates the risk of gallstone formation through various interconnected mechanisms. Created with BioRender.com

are particularly vulnerable to an increase in visceral fat, a change that is often accompanied by a worsening of IR. This combination of factors may further heighten the risk of gallstones in this demographic, making them a particularly high-risk group [43]. Overall, these mechanisms suggest that women with elevated levels of visceral fat indicators have a greater propensity for gallstone occurrence compared to males. This finding underscores the importance of targeted clinical interventions and preventive measures aimed at addressing the specific needs of this high-risk population. By focusing on early detection and the management of visceral fat accumulation, especially in women, healthcare providers can potentially reduce the frequency of gallstones and improve overall outcomes for these individuals.

The ROC curves revealed that the indicators of visceral lipid accumulation exhibited limited diagnostic accuracy in relationship to gallstone occurrence. Given this limitation, we proceeded to employ LASSO regression analysis to identify variables that were more strongly linked to gallstone formation. Through this analysis, we discovered that sex, age, race, hypertension, WC, and LAP were all highly correlated with the presence of gallstones. Among these variables, sex, age, race, hypertension, and WC were identified as having a statistically significant association with gallstone formation. Consequently, these factors were selected for inclusion in the model due to their strong association with the outcome. The choice to incorporate these specific variables was based on their robust association with gallstones, as determined by statistical analysis. Notably, the association between the primary parameters investigated in the present research and gallstones has already been documented in the literature [1, 18, 22]. This consistency with existing research underscores the validity of our results and the significance of variables in forecasting the potential probability of gallstones.

Although this study model only includes sex, age, race, hypertension, and WC, these variables can indirectly reflect multiple high-risk factors for gallstones. Sex and age are important factors in gallbladder function changes. Women, due to higher estrogen levels, especially during pregnancy and menopause, face an increased risk of cholesterol supersaturation, which leads to stone formation [39]. Advancing age may diminish gallbladder contraction, hence elevating the risk of bile stasis and the production of gallstones [1, 44]. Racial differences reflect variations in metabolism, dietary habits, and genetic backgrounds among different populations [1]. The higher prevalence of gallstones in Mexican Americans and Native Americans suggests the role of genetic factors and lifestyle [1]. Hypertension, as a manifestation of MetS, is associated with systemic inflammation and biliary inflammation. MetS is also considered a substantial risk

factor for gallstones [1, 45]. As an indicator of abdominal obesity, WC can reflect abnormal cholesterol metabolism and lifestyle factors, such as a high-fat diet and insufficient exercise, as well as the potential risk of gallstones [46, 47]. Therefore, although the model cannot directly incorporate high-risk factors such as gallbladder dysfunction, biliary inflammation, and lifestyle, the existing variables can indirectly reflect their effects on gallstone formation. However, given the lack of relevant direct variables in the NHANES database, our model still has certain limitations in explaining the multifactorial pathophysiology of gallstone formation.

Study strengths and limitations

The present analysis has some notable research strengths. Adjustments were made to account for distracting variables that could potentially interfere with the outcomes and which established a connection between visceral lipid accumulation indicators and gallstones. Furthermore, the nonlinear associations of these indicators with gallstones were explored by SCF and threshold effect analysis. Ultimately, a LASSO regression analysis was used to figure out the prominent characteristics related to gallstones and construct a nomogram model with enhanced discriminatory capability.

However, the implementation of a cross-sectional design in the present investigation presents constraints in terms of the ability to demonstrate causal links among the variables. In addition, completely eliminating the effects of all potential variables could distort the results. Finally, the NHANES database used in this study did not contain direct measurements of visceral fat such as CT or MRI, so we chose current widely recognized indirect indicators, such as METS-VF, WC, LAP, and VAI. These indicators have high operability in large-scale population studies and are reliable assessment tools for visceral fat accumulation that reflect individual metabolic risk [11–14, 48, 49]. In the absence of direct measurement data, these indirect indicators can reasonably reflect the association between visceral fat accumulation and gallstone occurrence. However, compared with direct measurements such as CT or magnetic resonance imaging (MRI), these indirect indicators do not provide precise quantification or distribution information of visceral fat, which may lead to underestimation or overestimation of the extent of visceral fat accumulation, thus affecting the accuracy of the association between gallstones and visceral fat accumulation.

To enhance the validation of this study's findings, future studies should collect more clinical data based on direct measurements of visceral fat by CT or MRI through a retrospective or prospective design. In addition, integrating clinical data from other databases and combining direct measurements with indirect measurements would help reveal the potential association between visceral fat accumulation and gallstone occurrence more comprehensively, thereby deepening the understanding of this relationship and further validating the findings of this study.

Conclusions

The findings demonstrate a noteworthy relationship between visceral lipid accumulation indicators and the probability of developing gallstones. The model we constructed demonstrates the potential to identify individuals with a predisposition to gallstone formation before the onset of clinical symptoms: and supports earlier and more targeted interventions, particularly in addressing modifiable risk factors such as visceral fat accumulation. Managing visceral fat may be crucial in reducing the likelihood of gallstone formation and potentially decreasing the need for surgical treatments such as cholecystectomy. Compared to ultrasound, the model offers significant advantages in optimizing gallstone screening and resource allocation, enhancing early risk management. However, while the model shows promise, additional research is required to validate its efficacy in routine clinical practice and to explore how best to integrate it with existing diagnostic protocols to strengthen preventive care strategies.

Abbreviations

AUC	Area Under the Curve
BMI	Body Mass Index
CIs	Confidence Intervals
FBG	Fasting Blood Glucose
HDL-C	High-Density Lipoprotein Cholesterol
IR	Insulin Resistance
LAP	Lipid Accumulation Products
LASSO	Least Absolute Shrinkage and Selection Operator
MetS	Metabolic Syndrome
METS-VF	Metabolic Score for Visceral Fat
NCHS	National Center for Health Statistics
NHANES	Nutrition Examination Survey
ORs	Odds Ratios
ROC	Receiver Operating Characteristic
SCF	Smoothed Curve Fitting
TG	Triglycerides
VAI	Visceral Adiposity Index
WC	Waist Circumference

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Not applicable.

Author contributions

WGW wrote the main manuscript text. YCP, JLW and QZL gathered and examined the data. YCP and JLW analyzed the data. WC meticulously

scrutinized, revised, and approved the manuscript. The work has undergone a comprehensive review and has received approval from all authors.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The survey protocol was approved by the NCHS Ethics Review Board. The approved protocol can be found at this link: https://www.cdc.gov/nchs/nhanes/irba98.htm. Additionally, every participant in the survey supplied written informed permission.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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