BMC Gastroenterology

RESEARCH

Open Access

Association of cardiometabolic index with gallstone disease and insulin resistance based on NHANES data

Liu Yuan[1,2†], Shuqi Wang[2†], Dong Wang[2] and Enbo Wang[2*]

Abstract

Background Cardiometabolic index (CMI) is an index integrating visceral obesity and dyslipidemia. This study intends to scrutinize the connection between CMI and gallstone disease (GSD) and to elucidate the association between CMI and insulin resistance (IR) in patients with GSD.

Methods To explore the potential nonlinear association and determine the inflection point, a restricted cubic spline (RCS) analysis was performed. Following categorization of CMI based on the identified inflection point, multivariate logistic regression models, subgroup analyses, and interaction tests were utilized to assess the connection between CMI and GSD, as well as between CMI and IR in GSD patients. The homeostasis model assessment for IR (HOMA-IR) and triglyceride-glucose (TyG) index was applied to evaluate IR. Spearman analysis was implemented to investigate the connection between CMI and HOMA-IR. The predictive performance of each indicator was evaluated by the receiver operating characteristic (ROC) curve and the area under the curve (AUC).

Results The study included 2311 individuals, with a GSD prevalence of 10.90%. RCS analysis revealed a nonlinear positive correlation between CMI and GSD (nonlinear $P < 0.001$), as well as between CMI and IR (nonlinear $P < 0.001$). In the fully adjusted multivariable logistic regression analysis of covariates, compared with the low-category CMI group, the high-category CMI was significantly associated with the risk of GSD (OR = 1.547, 95% CI: 1.143–2.092, $P = 0.005$), IR (OR = 4.990, 95% CI: 2.517–9.892, $P < 0.001$). Subgroup analysis demonstrated that the correlation between CMI and GSD was stronger in females. Spearman correlation analysis showed a positive association between CMI and HOMA-IR in GSD patients ($r = 0.548$, $P < 0.001$). The ROC curve demonstrated the predictive performance of the CMI model for GSD (AUC = 0.743), which was superior to conventional indicators such as Body Mass Index and Waist Circumference; the predictive performance of CMI (AUC = 0.772) for IR was consistent with that of TyG (AUC = 0.772).

Conclusion Our research demonstrates that CMI exhibits a nonlinear positive correlation with the incidence of GSD and IR. This suggests that CMI may serve as a novel and valuable indicator for further investigating the intricate relationships among metabolic syndrome, obesity, and GSD.

Keywords Cardiometabolic index, Gallstone disease, Obesity, Insulin resistance, Cross-sectional study

†Liu Yuan and Shuqi Wang have contributed equally to this work.

*Correspondence:
Enbo Wang
wang891204@163.com

[1]China Medical University, Shenyang, China
[2]Central Hospital of Dalian University of Technology (Dalian Municipal Central Hospital), Dalian, China

Introduction

Gallstone disease (GSD) is a prevalent global health concern, affecting approximately 10–20% of the adult population worldwide [1]. Clinically significant complications related to GSD encompass cholecystitis, choledocholithiasis, pancreatitis, and ascending cholangitis [2]. Furthermore, GSD constitutes a considerable hazard element for the emergence of gallbladder carcinoma, a malignancy with an exceptionally poor prognosis [3, 4, 5]. Surgical intervention is often required for GSD, which has a postoperative recurrence rate ranging from 10 to 20% [6]. The pathogenesis of GSD is intricate, involving any factor that disrupts the cholesterol-bile acid-phospholipid balance or induces cholestasis [7], such as genetics, gallbladder motility disorders, intestinal factors, environmental factors, insulin resistance (IR) and abnormal lipid metabolism [1, 8]. Moreover, obesity has emerged as a critical risk factor for GSD, especially among the obese individuals who demonstrate an elevated likelihood of developing symptomatic GSD [9, 10].

The global prevalence of obesity has witnessed a marked increase in recent decades, posing a critical public health challenge [11]. Accumulating evidence indicates strong associations between obesity and numerous metabolic disorders [12]. Presently, body mass index (BMI) and waist circumference (WC) remain the most prevalently employed anthropometric measures for corpulence assessment. Nevertheless, BMI shows significant limitations as it is affected by age and sex variations, and more importantly, it is unable to distinguish between muscle mass and fat mass. Similarly, WC also fails to differentiate between visceral and subcutaneous fat [13].

In the past few decades, several novel anthropometric indices (AHIs) have been presented to distinguish the distribution of body fat and appraisal overweight, especially abdominal corpulence. AHIs are straightforward measurement indicators for assessing nutritional health and promptly ascertaining the risk of illness [14]. Among them, the Cardiometabolic index (CMI) is computed as Triglyceride (TG)/Highdensity lipid cholesterol (HDL-c) × waist-to-height ratio (WHtR) [15]. WHtR was regarded as a more accurate marker of specific health hazards compared with BMI, because it concentrated on the dispersion of body fat [16]. Furthermore, the TG/HDL-c ratio turned into a generally recognized indicator of lipid metabolism disorders [17]. By integrating these two parameters efficiently, CMI offers a comprehensive evaluation of abdominal adiposity and dyslipidemia, providing a more holistic approach to the assessment of metabolic health [18]. Several research demonstrated that CMI was a great potential indicator for metabolic syndrome, diabetes, renal dysfunction and cardiovascular disease [19, 20, 21, 22].

Despite these advancements, the connection between CMI and GSD remains ambiguous. Moreover, in GSD patients, the association between CMI and IR is also undetermined. This research utilized comprehensive data from the National Health and Nutrition Examination Survey (NHANES) database, to scrutinize the connection between CMI and GSD and to understand the association between CMI and IR in the GSD population.

Methods

Study population

The total number of 14,986 persons from the NHANES survey encompassing from 2017 to March 2020 were utilized in this study. Following the screening process (Fig. 1), we excluded those without GSD data (5,776), those lacking triglyceride and BMI data (5,351), and those deficient in other covariates (1548) participants. The final count of 2311 participants were incorporated in this study, among whom 252 cases reported gallstone cases. The data is derived from the publicly available official website of NHANES and was examined and sanctioned by The National Research Ethics Board of the United States.

Variables

The questionnaire survey method was employed to assess whether the patients were afflicted with GSD, and the existence of GSD was regarded as the outcome variable. The question in the GSD questionnaire survey is: "Has a doctor or other health professional ever told you that you had gallstone?"

CMI = [TG (mg/dL)/HDL-C (mg/dL)]×[WC (cm)/Height (cm)] [15].

IR is assessed indirectly by means of the HOMA-IR, which is the most prevalent approach because of its simplicity in practical implementation [23–24]. HOMA-IR = [fasting plasma glucose (FPG) (mmol/L) × fasting insulin (FSI) (μU/ml)]/22.5 [25]. The threshold for HOMA-IR is regarded as 2.5, and values exceeding this suggest the existence of IR [26]. Furthermore, a novel IR surrogate marker, namely the triglyceride-glucose index (TyG index), which has been robustly validated in large-scale population studies, was also employed in this study for the assessment of the IR status [27]. TyG = ln [fasting levels of TG (mg/dL) × FPG (mg/dl)/2].

Ascertainment of other covariates

The interview determined age, sex (male/female), race/ethnicity (Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, and Other Race), educational status (less than high school/high school/more than high school), marital status (cohabitation/solitude), poverty-income ratio (PIR), smoking history (characterized as having smoked no less than 100 cigarettes during

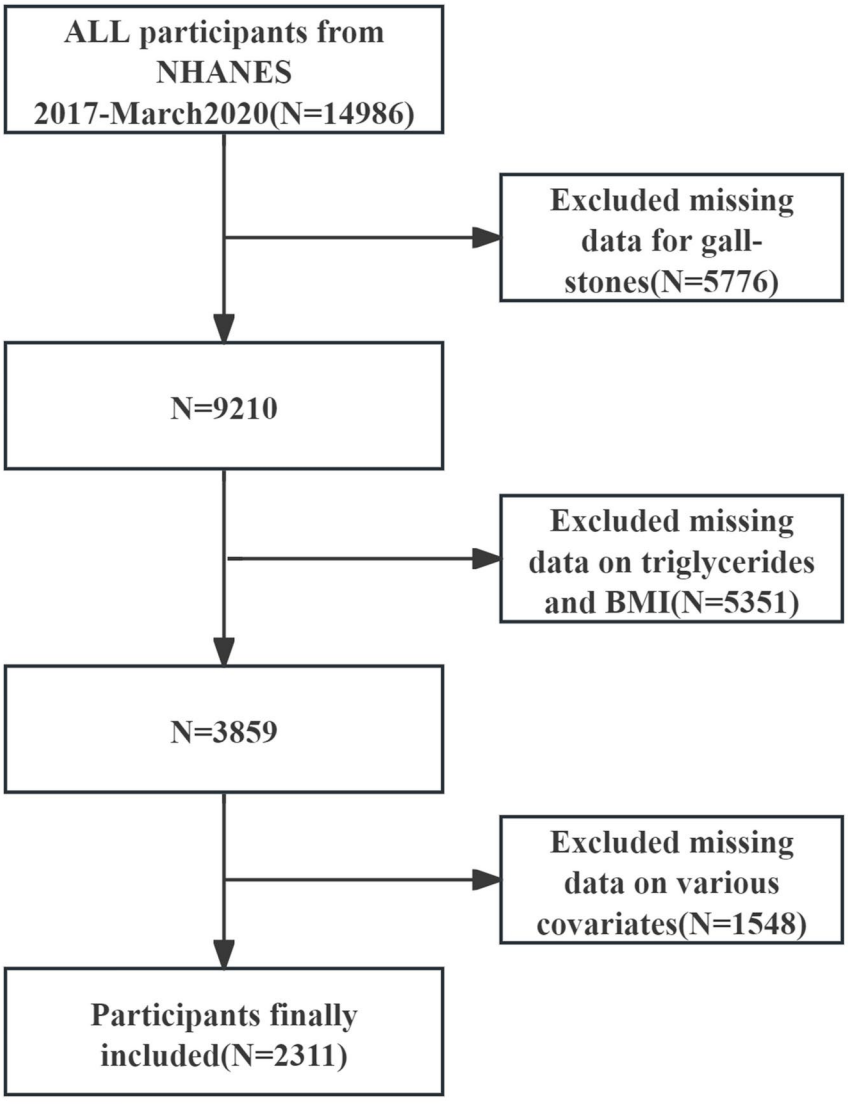

Fig. 1 Flow chart of participants selection. NHANES, National Health and Nutrition Examination Survey

one's lifetime) and alcohol consumption (assessed by the question: Have you ever consumed any type of alcoholic beverage?). Moreover, the researchers took into account the existence or non-existence of comorbidities like hypertension, diabetes, coronary heart disease (CHD), asthma, and cancer. These situations are generally closely related to healthy behaviors and are of vital importance in adjusting for potential confounding factors. Meanwhile, the study encompassed physical activity and dietary factors such as water, sugar, and fat intake. All participants were obligated to offer two 24-hour dietary recalls, and the average intake calculated from these two recalls was employed for our analysis.

Statistical analysis

The independent sample t-test was employed to analyze the differences in continuous variables that were normally distributed between the two groups, while the non-parametric Mann-Whitney U test was adopted for continuous variables with skewed distribution. Categorical variables of the two groups were presented as frequency and constituent ratio (n%) and in contrast through the chi-square test. To investigate the odds ratios (ORs) and 95% confidence intervals (CIs) between CMI, GSD and IR, multivariable logistic regression was employed. Three regression models were constructed: model 1 (unadjusted), model 2 (adjusted merely for age, sex, hypertension, diabetes, CHD, smoking, and alcohol

consumption), and model 3 (completely adjusted for all covariates). All the indicators are subjected to the independence test of Variance Inflation Factor (VIF). If the VIF values are all lower than 5, the collinearity issue can be disregarded. Restricted cubic spline (RCS) plot based on the Akaike Information Criterion (AIC) was applied to investigate the dose-response relationship between CMI and GSD, along with IR. The objective was to explore the potential nonlinear relationship, ascertain its inflection point and categorize CMI as a binary variable based on the cut-off point for subsequent multi-model logistic regression and trend analysis. Subsequently, subgroup analysis was carried out to assess whether potential variables modified the connection between CMI and GSD. Additionally, the receiver operating characteristic (ROC) curve and the area under the curve (AUC) were employed to assess and contrast the predictive performance of CMI, BMI, and WC for GSD, as well as that of CMI and TyG for IR. Spearman correlation analysis was utilized to explore the correlation between CMI and HOMA-IR. Statistical analyses were executed with R software. $P < 0.05$ is considered meaningful.

Results

Baseline characteristics

The meticulously comprehensive baseline characteristics of the GSD group and the control group are exhibited in Table 1. Among the 2,311 enrolled participants, 252 (10.90%) were assigned to the GSD group and 2,059 (89.10%) to the control group. The CMI was notably higher in the GSD group compared to the non-GSD group (0.60 vs. 0.44, $P < 0.001$). Furthermore, the GSD group presented higher values in terms of age, BMI, WC, WHtR, TG, HOMA-IR, TyG, FSI, and FPG. Moreover, the GSD group had a greater proportion of female and greater prevalence of hypertensive disease, diabetes, CHD, asthma and cancer.

The connection between CMI and GSD

As depicted in Table 2, the unadjusted model (Model 1) indicated that CMI was positively correlated with the increased prevalence of GSD (OR = 1.104, 95% CI: 1.005–1.213, $P = 0.039$). After adjusting for factors including age, sex, hypertension, diabetes, CHD, smoked, and alcohol use in Model 2, this positive correlation remained statistically significant (OR = 1.134, 95% CI: 1.027–1.253, $P = 0.013$). The dose-response relationship between CMI and GSD simulated by RCS further confirmed this correlation (nonlinear $P < 0.001$) (Fig. 2). The inflection point of CMI was 0.45, which was then used as the cutoff point to categorize CMI into binary variables for multifactorial logistic regression analysis. Even in the completely adjusted model (Model 3), the high category of CMI (CMI ≥ 0.45) was connected with an enhanced risk of GSD (OR = 1.547, 95% CI: 1.143–2.092, $P = 0.005$). All P-trends were statistically significant.

Subgroup analysis and interaction test were performed to further investigate the association between CMI and GSD. As depicted in Table 3, significant positive associations were observed in specific subgroups: females, individuals aged ≤ 60 years, individuals without CHD, individuals with hypertension, and smokers. Notably, the interaction test revealed significant sex-based effect modification (interaction $P < 0.001$).

To construct the ultimate predictive model, we integrated a wide range of covariates, including age, sex, hypertension, diabetes, CHD, smoking history, PIR, total sugar intake, total fat intake, total water intake, alcohol consumption, physical activity level, serum cholesterol, serum creatinine, FPG, FSI, HOMA-IR, asthma, and cancer. As shown in Fig. 3, this model presented outstanding forecasting performance. In contrast to conventional measures like BMI and WC, our model manifested significantly improved performance in predicting GSD. The AUC of the CMI model was 0.743 (95CI: 0.712–0.773), which was significantly higher than that of BMI at 0.639 (95CI: 0.604–0.674) and WC at 0.636 (95CI: 0.601–0.670).

The connection between CMI and IR in GSD patients

The median CMI in the IR group was notably higher compared to that in the non-IR group (0.74 vs. 0.32, $P < 0.001$). Furthermore, in contrast to the non-IR group, the IR group exhibited notably elevated levels of BMI, WC, WHtR, TG, FPG, FSI, TyG and HOMA-IR, while the level of HDL-c was lower (Table 4).

Spearman correlation analysis revealed a significant positive correlation between CMI and HOMA-IR ($r = 0.584$, $P < 0.001$) in these GSD patients (Fig. 4). The relationship between CMI and IR is elaborated in Table 5. In the unadjusted model (Model 1), a statistically significant connection was noticed, suggesting that increased CMI levels are related to a higher occurrence of IR (OR = 8.199, 95% CI: 3.483–19.298, $P < 0.001$). After accounting for potential confounding factors like age, sex, hypertension, diabetes, CHD, smoked, and alcohol use in Model 2, this positive correlation stayed statistically significant (OR = 6.965, 95% CI: 2.902–16.717, $P < 0.001$). Additionally, as illustrated in Fig. 5, the positive association between CMI and IR in GSD patients was supported by RCS (nonlinear $P < 0.001$), where the inflection point value corresponding to CMI is 0.60. With this as the cut-off point, CMI was employed as a dichotomous variable for multivariate logistic regression analysis. In the adequately adjusted model (Model 3), the relationship between the high category of CMI (CMI ≥ 0.60) and IR still held statistical significance (OR = 4.990, 95% CI: 2.517–9.892, $P < 0.001$). Trend analysis affirmed

Table 1 Basic characteristics of participants

Characteristic	Without gallstone disease (*n* = 2059)	With gallstone disease (*n* = 252)	*P*
Age(years)	50.00 (34.00, 63.00)	59.00 (45.75, 69.00)	< 0.001
BMI(Kg/m^2)	28.50 (24.60, 33.60)	31.95 (27.58, 37.65)	< 0.001
WC (cm)	98.90 (88.00, 111.50)	106.85 (95.68, 119.62)	< 0.001
CMI	0.44 (0.25, 0.80)	0.60 (0.37, 0.97)	< 0.001
WHtR	0.59 (0.53, 0.66)	0.65 (0.59, 0.73)	< 0.001
HDL-c (mmol/L)	1.32 (1.09, 1.60)	1.31 (1.09, 1.56)	0.478
TG (mmol/L)	0.98 (0.68, 1.48)	1.19 (0.81, 1.62)	< 0.001
Total Cholesterol (mmol/L)	4.65 (3.98, 5.38)	4.55 (3.96, 5.39)	0.454
Fasting plasma glucose levels (mmol/L)	5.66 (5.27, 6.27)	5.91 (5.50, 6.84)	< 0.001
Fasting insulin (uU/mL)	9.76 (5.89, 15.98)	13.18 (8.54, 20.73)	< 0.001
HOMA-IR	2.50 (1.47, 4.58)	3.67 (2.05, 5.99)	< 0.001
TyG	8.44 (8.00, 8.92)	8.67 (8.21, 9.06)	< 0.001
Total Water (g)	960.00 (457.50, 1634.25)	836.25 (431.25, 1500.00)	0.177
Total Sugar (g)	87.58 (58.31, 127.33)	87.38 (59.24, 126.14)	0.895
Total Fat (g)	78.04 (56.12, 105.98)	73.55 (52.72, 99.26)	0.055
PIR	2.11 (1.15, 3.84)	1.94 (1.19, 3.47)	0.265
Serum Creatinine (μmol/L)	75.14 (62.76, 88.40)	71.16 (61.88, 85.08)	0.118
sex (%)			< 0.001
Male	1035 (50.27)	66 (26.19)	
Female	1024 (49.73)	186 (73.81)	
Hypertension (%)			< 0.001
Yes	727 (35.31)	142 (56.35)	
No	1332 (64.69)	110 (43.65)	
Diabetes (%)			< 0.001
Yes	296 (14.38)	64 (25.40)	
No	1763 (85.62)	188 (74.60)	
CHD (%)			< 0.001
Yes	83 (4.03)	23 (9.13)	
No	1976 (95.97)	229 (90.87)	
Smoked (%)			0.007
Yes	878 (42.64)	130 (51.59)	
No	1181 (57.36)	122 (48.41)	
Alcohol (%)			0.500
Yes	1904 (92.47)	236 (93.65)	
No	155 (7.53)	16 (6.35)	
Asthma (%)			
Yes	335 (16.27)	56 (22.22)	0.017
No	1724 (83.73)	196 (77.78)	
Cancer (%)			
Yes	201 (9.76)	45 (17.86)	< 0.001
No	1858 (90.24)	207 (82.14)	
Race (%)			0.005
Mexican American	245 (11.90)	32 (12.70)	
Other Hispanic	181 (8.79)	30 (11.90)	
Non-Hispanic White	783 (38.03)	116 (46.03)	
Non-Hispanic Black	557 (27.05)	44 (17.46)	
Other Race	293 (14.23)	30 (11.90)	
Marital status (%)			0.758
Cohabitation	1230 (59.74)	148 (58.73)	
Solitude	829 (40.26)	104 (41.27)	
Education level (%)			0.532
Less than high school	302 (14.67)	41 (16.27)	
High school	457 (22.20)	61 (24.21)	

Table 1 (continued)

Characteristic	Without gallstone disease ($n=2059$)	With gallstone disease ($n=252$)	*P*
More than high school	1300 (63.14)	150 (59.52)	
PA (%)			0.217
Vigorous	548 (26.61)	58 (23.02)	
Moderate	502 (24.38)	73 (28.97)	
Mild	1009 (49.00)	121 (48.02)	

For continuous variables, the median (Q25, Q75) was calculated. For categorical variables, percentages were used

BMI body mass index, WC Waist Circumference, CMI cardiometabolic index, WHtR waist-to-height ratio, HDL-c high-density lipoprotein cholesterol, TG triglycerides, HOMA-IR homeostasis model assessment for insulin resistance, CHD coronary heart disease, PA Physical Activity, TyG triglyceride-glucose, PIR poverty-income ratio

Table 2 Relationship between CMI and GSD

Variables	Model 1 OR (95%CI)	Model 2 OR (95%CI)	Model 3 OR (95%CI)
CMI	1.104 (1.005, 1.213) 0.039	1.134 (1.027, 1.253) 0.013	1.063 (0.946, 1.196) 0.305
CMI<0.45	1	1	1
CMI ≥ 0.45	1.929 (1.470, 2.531) < 0.001	1.800 (1.347, 2.405) < 0.001	1.547 (1.143, 2.092) 0.005
P for trend	< 0.001	< 0.001	0.005

Model 1: no covariates were adjusted

Model 2 was adjusted for age, sex, hypertension, diabetes, CHD, smoked, and alcohol use

Model 3 was adjusted for covariates in Model 2 + race, marital status, education level, physical activity, asthma, cancer, PIR, total water, total sugar, total fat, serum cholesterol, HOMA-IR

CMI cardiometabolic index, GSD gallstone disease, OR odds ratio, BMI body mass index, CHD coronary heart disease, CI confidence interval, PIR poverty-income ratio, HOMA-IR homeostasis model assessment for insulin resistance

a consistent positive correlation between the two categories (trend $P<0.001$).

To appraise the predictive performance of CMI for IR in GSD patients, the ROC curve was plotted. The results demonstrated that the AUC of CMI was 0.772 (95% CI: 0.706–0.838), which was consistent with the AUC of the TyG of 0.772 (95% CI: 0.708–0.835) (Fig. 6). Compared to TyG, the CMI model's exhibited slightly lower sensitivity (60.00% vs. 63.53%) but higher specificity (87.43% vs. 82.04%). This implies that CMI is a potential and effective marker for predicting IR in patients with GSD.

Discussion

Our research reveals that a significant and robust correlation still persists between elevated CMI levels and enhanced susceptibility to GSD and IR, even after comprehensive adjustment for relevant confounding factors.

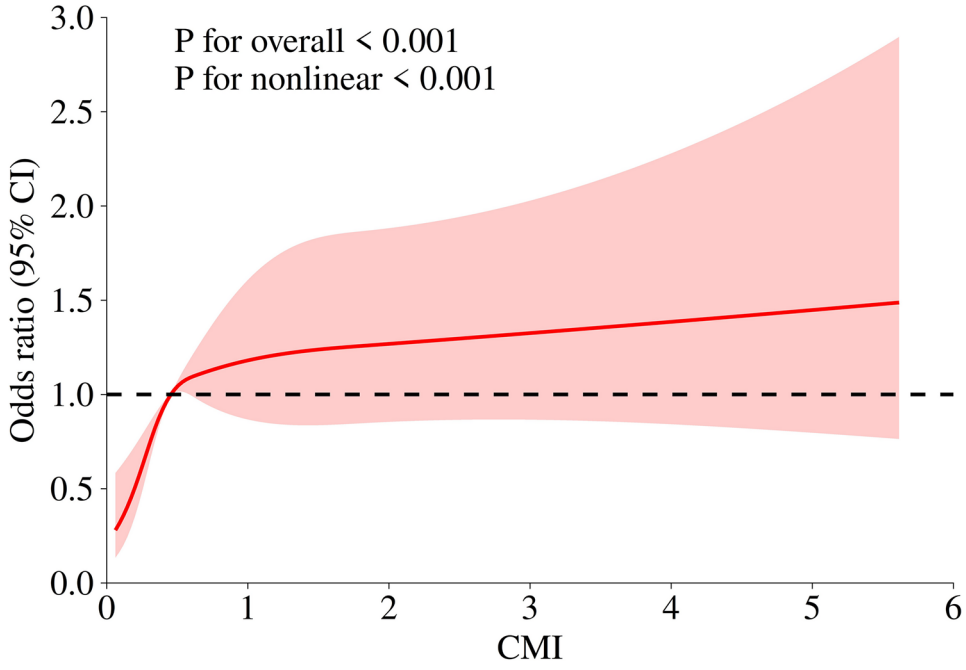

Fig. 2 The Dose–response relationship among CMI and GSD. The relationship between CMI and GSD was simulated by RCS based on the AIC. We adjusted the model fully for age, sex, hypertension, diabetes, CHD, PA, asthma, cancer, smoked, and alcohol use. The red solid line represents the curve fitting between variables, and the shaded area indicates the 95% CI of the fit. CMI, cardiometabolic index; GSD, gallstone disease; RCS, restricted cubic spline; AIC, Akaike Information Criterion; CHD, coronary heart disease; PA, Physical Activity; CI, confidence interval

Table 3 Subgroup regression analysis of the association between CMI and GSD

Variables	*n* (%)	OR (95%CI)	*P*	*P* for interaction
All patients	2311 (100.00)	1.10 (1.01, 1.21)	0.039	
Age				0.663
≥ 60	791 (34.23)	1.07 (0.86, 1.32)	0.569	
<60	1520 (65.77)	1.12 (1.01, 1.25)	0.032	
BMI				0.807
≥ 30	1019 (44.09)	1.06 (0.94, 1.19)	0.324	
<30	1292 (55.91)	1.03 (0.81, 1.30)	0.828	
Sex				< 0.001
Female	1210 (52.36)	1.74 (1.37, 2.22)	< 0.001	
male	1101 (47.64)	1.07 (0.94, 1.21)	0.330	
Hypertension				0.194
Yes	869 (37.60)	1.17 (1.01, 1.35)	0.041	
No	1442 (62.40)	1.01 (0.85, 1.21)	0.890	
Diabetes				0.905
Yes	360 (15.58)	1.06 (0.93, 1.22)	0.396	
No	1951 (84.42)	1.07 (0.94, 1.23)	0.306	
CHD				0.403
Yes	106 (4.59)	0.80 (0.37, 1.75)	0.584	
No	2205 (95.41)	1.11 (1.01, 1.22)	0.035	
Stratified by smoke				0.348
Yes	1008 (43.62)	1.14 (1.01, 1.29)	0.038	
No	1303 (56.38)	1.04 (0.87, 1.23)	0.686	
Stratified by alcohol				0.270
Yes	2140 (92.60)	1.10 (1.00, 1.21)	0.058	
No	171 (7.40)	1.67 (0.83, 3.37)	0.152	

CMI cardiometabolic index, GSD gallstone disease, BMI body mass index, CHD coronary heart disease, OR odds ratio, CI confidence interval

The CMI represents an extensive evaluation of corpulence, integrating TG/HDL-c and WHtR, and provides a unified measurement method combining dyslipidemia with central adiposity. Our analysis disclosed significantly higher median CMI values in the GSD group compared to the non-GSD controls (0.60 vs. 0.44, $P < 0.001$). While the precise mechanisms linking elevated CMI with GSD pathogenesis require further elucidation through multicenter prospective cohort studies, the existing literature suggests several potential pathways. Previous research have presented that elevated TG levels was risk factors for GSD [28]. Cavallini et al. demonstrated that hypertriglyceridemia directly correlates with an increased cholesterol saturation index (CSI) [29] and accelerated cholesterol crystallization [30], which were essential antecedents for GSD establishment. Additionally, there is evidence indicating that excessive adiposity constitutes a considerable risk for the emergence of GSD [31]. Visceral adiposity is typically accompanied by hepatic fatty infiltration, which exacerbates the disturbances of cholesterol metabolism. The existence of hepatic fatty infiltration leads to a higher cholesterol concentratedness in the bile, thus enhancing the likelihood of GSD formation [32, 33, 34]. Apart from these metabolic disorders, visceral adiposity impairs gallbladder motility. Excessive abdominal adipose tissue reduces gallbladder contractility, leading to incomplete bile evacuation and creating a milieu conducive to cholesterol deposition in the gallbladder, which significantly increases the probability of GSD formation [35, 36]. Additionally, abdominal adiposity is correlated with intestinal microbiota imbalance, a circumstance marked by diminished diversity of microorganisms and an disproportion among particular bacterial groups. Such modifications in the intestinal microbiota can have a notable consequence on the metabolic process of bile acids, reinforcing the enterohepatic circulation of cholesterol and thereby further augmenting the risk of GSD [37, 38]. The endocrinal functionality of fatty tissue being dysregulated in the situation of corpulence also has a vital position [39]. The anomalous discharge of hormones and immunological mediators disturbs normal cholesterol homeostasis and modifies bile composition, thereby further promoting GSD predisposition [40, 41, 42].

For this research, we found a higher proportion of female in the GSD group, and subgroup analysis disclosed that the influence of CMI on GSD was more pronounced in female. The enhanced vulnerability among females might be associated with sex-dependent physiologic elements, especially those connected with hormonal disparities. The heightened estrogen levels in women, precisely during specific life phases like gestation or postmenopausal, can trigger alterations in metabolism of lipids. These hormonal variations regularly lead to an enhanced saturation of cholesterol within bile, a crucial predecessor for GSD formation. Hence, this biological procedure propelled by oestrogen could influence the greater incidence of GSD observed in females [43, 44]. In general, these mechanistic systems imply that females with raised quantities of visceral fatty indicators are more prone to GSD occurrence than male. This discovery emphasizes the significance of directed towards clinical interferences and preventive actions customized to the particular requirements of this extreme-risk group. By concentrating on the early identification and control of accumulation of visceral fatty, particularly in females, healthcare providers have the possibility to lower the occurrence of GSD and enhance the overall results for these people.

Previous studies have shown a considerable positive connection between GSD and the elevated morbidity related to chronic disorders, such as diabetes, hypertension, CHD, and cancer [13, 45, 46]. Consistent with these findings, our research detected a greater incidence of hypertensive disease, diabetes, CHD, asthma, and cancer in the GSD group. Furthermore, subgroup analysis also

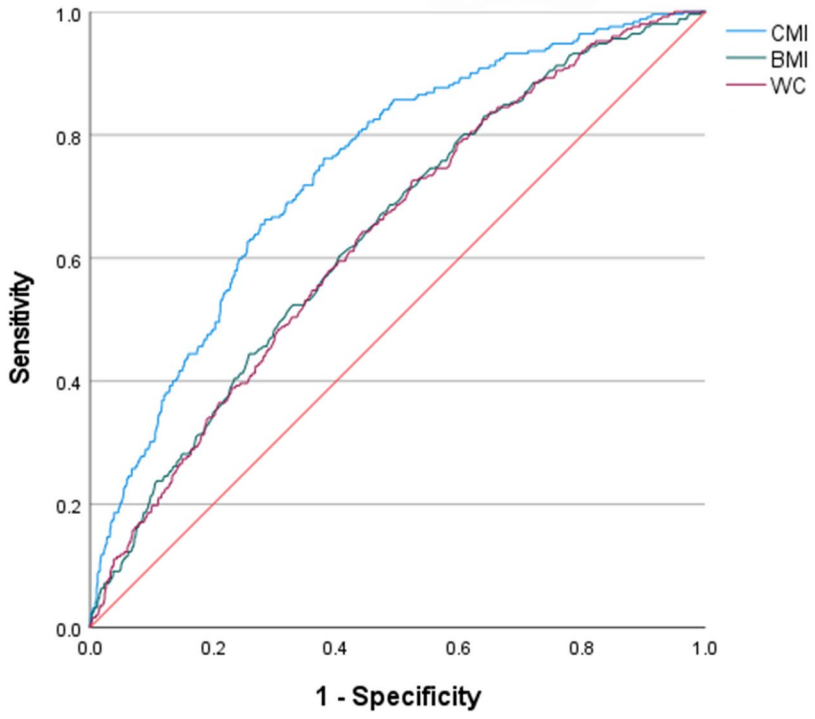

Fig. 3 ROC curves for CMI、BMI and WC prediction of GSD. CMI, Cardiometabolic Index; BMI, Body Mass Index; WC, Waist Circumference; GSD, gallstone disease

revealed that a statistically considerable positive correlation was present between CMI and GSD in individuals aged ≤ 60 years, individuals with hypertension, and smokers. These associations highlight the role of diverse lifestyles, dietary patterns, and metabolic states in GSD pathogenesis, emphasizing the significance of environmental factors in the progression of GSD.

The median CMI in the IR group was remarkably higher than that in the non-IR group (0.74 vs. 0.32, $P < 0.001$). Subsequent multivariate analysis indicated a statistically considerable association between heightened CMI levels and enhanced susceptibility to IR. Furthermore, in contrast to the non-IR group, the IR group exhibited notably elevated levels of BMI, WC, WHtR, TG, FPG, FSI, TyG and HOMA-IR, while the level of HDL-c was lower (Table 4). Previous studies have demonstrated that TG/HDL-c is closely related to IR [47]. Elevated TG concentrations may impair insulin receptor density on adipocytes and interfere with insulin-receptor binding. Concurrently, diminished HDL-c levels contribute to both impaired insulin secretion and reduced insulin sensitivity [48]. Obesity-related metabolic disturbances, particularly excessive free fatty acids and elevated WHtR, may cause IR by inhibiting the activity of glucose transporters and disrupting insulin-mediated glucose metabolism [49]. IR serves as a remarkable contributing element for the formation of GSD. Specifically, IR promotes cholesterol synthesis while reducing bile salt synthesis, disrupting the delicate balance between cholesterol and bile salts. This dual effect increases cholesterol saturation in bile, a key condition predisposing individuals to GSD formation [50, 51]. Our findings revealed that complex interactions exist among metabolic syndrome, obesity and GSD, and IR might be the central mechanism connecting these diseases.

Spearman correlation analysis in GSD patients revealed a significant positive correlation between CMI and HOMA-IR ($r = 0.584$, $P < 0.001$). The AUC for CMI was 0.772 (95% CI: 0.706–0.838), which was consistent with that of TyG, 0.772 (95% CI: 0.708–0.835). This implies that CMI is a potential and effective marker for predicting IR in GSD patients, thereby providing novel insights into the interrelationships among metabolic syndrome, obesity, and GSD.

This research possesses several crucial advantages. NHANES and its representative American sample strictly comply with the elaborately formulated research protocol, encompassing strict quality control and guarantee approaches, thereby reinforcing the dependability of our research results. Secondly, NHANES offers a substantial amount of larithmic and metabolic information, enabling comprehensive modifications for the main confusing factors in our multivariate model. Subgroup analysis further affirmed the signification of CMI in particular patient

Table 4 Basic characteristics of GSD with IR and without IR

Characteristic	gallstone disease Without IR (*n* = 85)	gallstone disease With IR (*n* = 167)	*P*
Age(years)	55.00 (43.00, 68.00)	61.00 (47.50, 69.00)	0.083
BMI(Kg/m2)	29.20 (25.40, 33.50)	33.90 (29.05, 39.55)	< 0.001
WC (cm)	98.20 (90.10, 107.00)	112.70 (102.20, 123.50)	< 0.001
CMI	0.32 (0.24, 0.58)	0.73 (0.48, 1.07)	< 0.001
WHtR	0.60 (0.54, 0.66)	0.68 (0.61, 0.75)	< 0.001
HDL-c (mmol/L)	1.53 (1.22, 1.73)	1.24 (1.06, 1.46)	< 0.001
TG (mmol/L)	0.81 (0.69, 1.29)	1.31 (0.96, 1.77)	< 0.001
Total Cholesterol (mmol/L)	4.55 (3.83, 5.33)	4.55 (3.98, 5.48)	0.597
Fasting plasma glucose levels (mmol/L)	5.55 (5.16, 5.88)	6.16 (5.72, 7.44)	< 0.001
Fasting insulin (uU/mL)	6.77 (5.42, 8.54)	16.77 (13.28, 25.52)	< 0.001
HOMA-IR	1.75 (1.33, 2.06)	4.89 (3.69, 8.22)	< 0.001
TyG	8.20 (7.99, 8.64)	8.87 (8.51, 9.16)	< 0.001
Total Water (g)	892.80 (493.50, 1500.00)	806.88 (363.75, 1488.75)	0.730
Total Sugar (g)	81.29 (56.11, 109.43)	90.39 (64.34, 132.72)	0.072
Total Fat (g)	69.42 (45.66, 91.44)	76.50 (54.69, 99.56)	0.111
PIR	2.08 (1.28, 3.28)	1.90 (1.16, 3.54)	0.524
Serum Creatinine (μmol/L)	69.84 (64.53, 82.21)	71.60 (60.11, 87.52)	0.937
sex (%)			0.598
Male	24 (28.24)	42 (25.15)	
Female	61 (71.76)	125 (74.85)	
Hypertension (%)			0.008
Yes	38 (44.71)	104 (62.28)	
No	47 (55.29)	63 (37.72)	
Diabetes (%)			< 0.001
Yes	9 (10.59)	55 (32.93)	
No	76 (89.41)	112 (67.07)	
CHD (%)			0.050
Yes	12 (14.12)	11 (6.59)	
No	73 (85.88)	156 (93.41)	
Smoking status (%)			0.447
Yes	41 (48.24)	89 (53.29)	
No	44 (51.76)	78 (46.71)	
Alcohol (%)			0.155
Yes	77 (90.59)	159 (95.21)	
No	8 (9.41)	8 (4.79)	
Asthma (%)			0.059
Yes	13 (15.29)	43 (25.75)	
No	72 (84.71)	124 (74.25)	
Cancer (%)			0.146
Yes	11 (12.94)	34 (20.36)	
No	74 (87.06)	133 (79.64)	
Race (%)			0.929
Mexican American	9 (10.59)	23 (13.77)	
Other Hispanic	11 (12.94)	19 (11.38)	
Non-Hispanic White	38 (44.71)	78 (46.71)	
Non-Hispanic Black	16 (18.82)	28 (16.77)	
Other Race	11 (12.94)	19 (11.38)	
Marital status (%)			0.770
Cohabitation	51 (60.00)	97 (58.08)	
Solitude	34 (40.00)	70 (41.92)	
Education level (%)			0.885
Less than high school	14 (16.47)	27 (16.17)	
High school	19 (22.35)	42 (25.15)	

Table 4 (continued)

Characteristic	gallstone disease Without IR (*n* = 85)	gallstone disease With IR (*n* = 167)	*P*
More than high school	52 (61.18)	98 (58.68)	
PA (%)			0.518
Vigorous	22 (25.88)	36 (21.56)	
Moderate	21 (24.71)	52 (31.14)	
Mild	42 (49.41)	79 (47.31)	

For continuous variables, the median (Q25, Q75) was calculated. For categorical variables, percentages were used

BMI body mass index, WC Waist Circumference, CMI cardiometabolic index, WHtR waist-to-height ratio, HDL-c high-density lipoprotein cholesterol, TG triglycerides, HOMA-IR homeostasis model assessment for insulin resistance, CHD coronary heart disease, PA Physical Activity, PIR poverty-income ratio, TyG, triglyceride-glucose

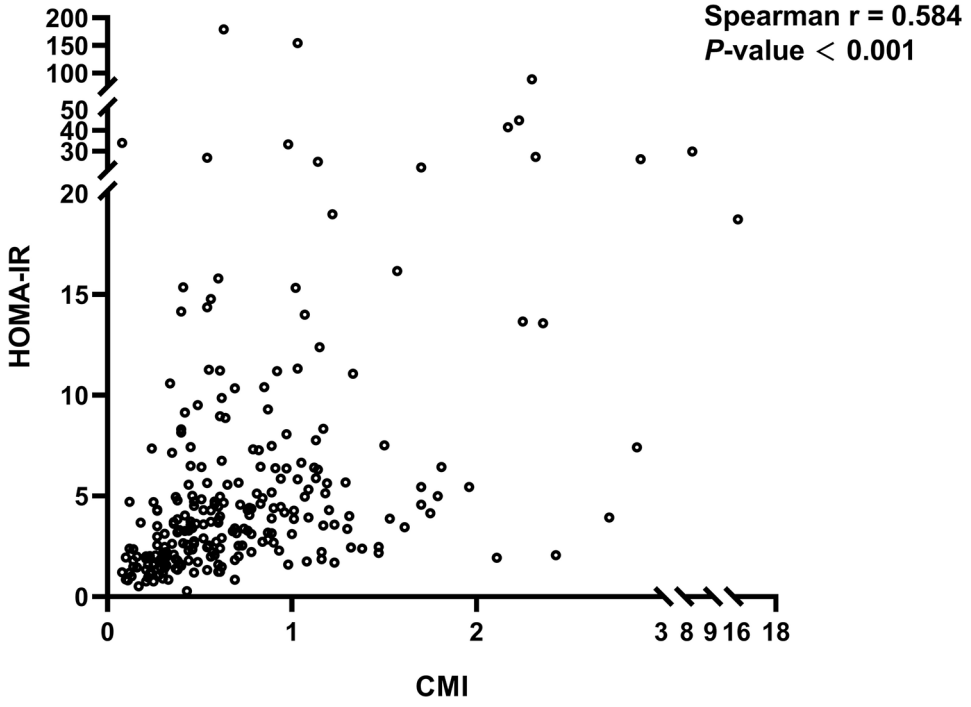

Fig. 4 Spearman correlation analysis between CMI and HOMA-IR. CMI, cardiometabolic index; HOMA-IR, homeostasis model assessment for insulin resistance

Table 5 Relationship between CMI and IR in GSD

Variables	Model 1 OR (95%CI)	Model 2 OR (95%CI)	Model 3 OR (95%CI)
CMI	8.199 (3.483, 19.298) < 0.001	6.965 (2.902, 16.717) < 0.001	6.964 (2.701, 17.954) < 0.001
CMI<0.60	1	1	1
CMI ≥ 0.60	5.161 (2.877, 9.259) < 0.001	4.710 (2.501, 8.869) < 0.001	4.990 (2.517, 9.892) < 0.001
P for trend	< 0.001	< 0.001	< 0.001

Model 1: no covariates were adjusted

Model 2 was adjusted for age, sex, hypertension, diabetes, CHD, smoked, and alcohol use

Model 3 was adjusted for covariates in Model 2 + race, marital status, education level, physical activity, asthma, cancer, PIR, total water, total sugar, total fat, serum cholesterol

CMI cardiometabolic index, GSD gallstone disease, IR insulin resistance, OR odds ratio, BMI body mass index, CHD coronary heart disease, CI confidence interval, PIR poverty-income ratio

groups, providing novel approaches and perspectives for the progress of personalized therapeutics. Additionally, our discoveries unveiled a nonlinear positive correlation between CMI and GSD as well as IR. In contrast to conventional indicators like BMI and WC, the CMI model demonstrated outstanding predictive capability in forecasting GSD, with an AUC of 0.743. Spearman correlation analysis indicated that CMI was positively correlated with HOMA-IR ($r = 0.584$, $P < 0.001$). Regarding the prediction of IR, the predictive performance of CMI was consistent with that of TyG, with both AUCs being 0.722. This implies that CMI is a potential indicator for investigating obesity, GSD, and IR, providing a fresh perspective for exploring the relationship among metabolic syndrome, obesity, and GSD.

Nevertheless, this investigation possesses certain restrictions. As this constituted a cross-sectional investigation lacking time series data, there are constraints

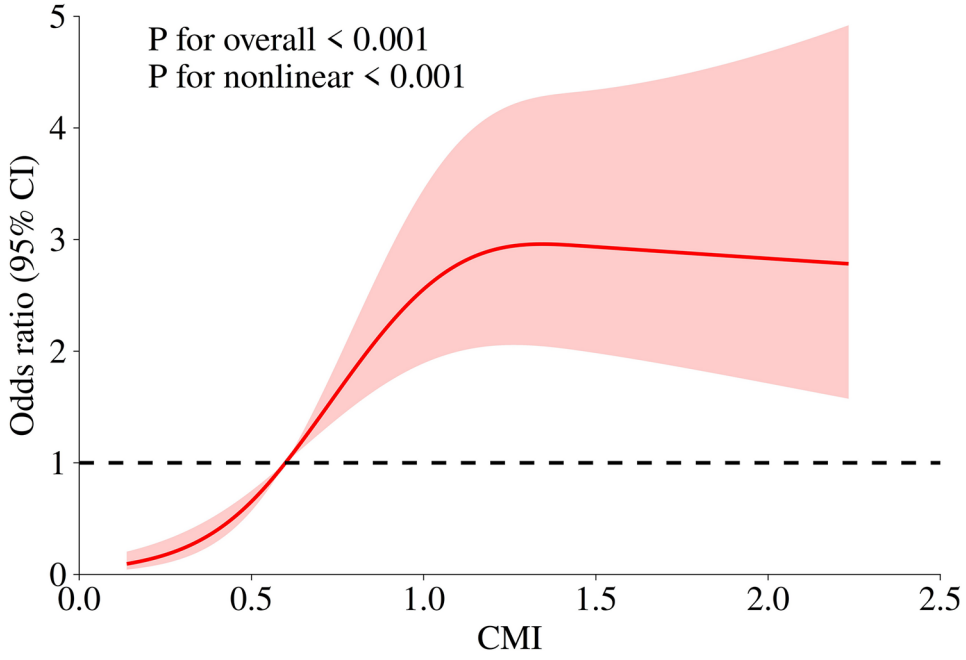

Fig. 5 The Dose–response relationship among CMI and IR in GSD. The relationship between CMI and IR was simulated by RCS based on the AIC. We adjusted the model fully for age, sex, hypertension, diabetes, CHD, PA, asthma, cancer, smoked, and alcohol use. The red solid line represents the curve fitting between variables, and the shaded area indicates the 95% CI of the fit. CMI, cardiometabolic index; IR, insulin resistance; GSD, gallstone disease; RCS, restricted cubic spline; AIC, Akaike Information Criterion; CHD, coronary heart disease; PA, Physical Activity; CI, confidence interval

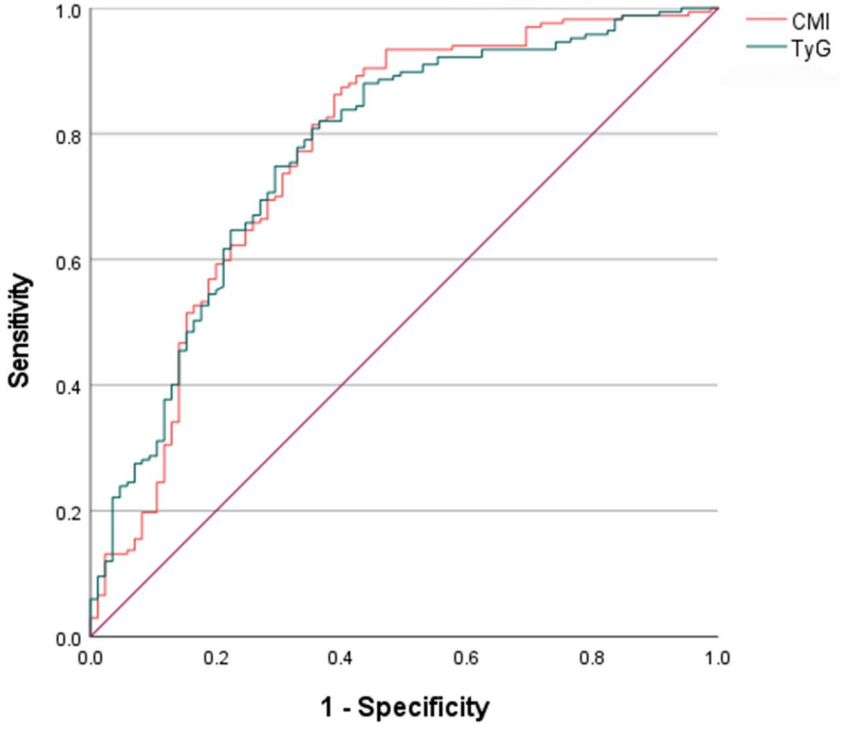

Fig. 6 ROC curves for CMI、TyG prediction of IR. CMI, cardiometabolic index; TyG, triglyceride-glucose; IR, insulin resistance

in demonstrating causal relationships between variables. This research employed self-reported outcome variables and was devoid of imaging diagnosis. Given that the majority of GSD are asymptomatic clinically, the study results were affected by whether the participants had received medical care. Participants might have been misdiagnosed as having or not having GSD, thereby potentially introducing research biases in this report. Additionally, this report lacked information regarding the type of GSD, and we were precluded from conducting further subgroup analyses stratified by the composition of gallstones. Future studies could clarify the diagnosis of GSD via imaging examinations such as ultrasound, computed tomography, and magnetic resonance cholangiopancreatographg, and carry out quantitative analysis of stone components in patients undergoing surgical lithotomy to further explore the association between CMI and different types of GSD. Through constructing a verification system integrating "imaging - biochemistry - clinical" aspects, this issue can be effectively addressed. When it comes to analyzing IR in GSD patients, the small sample size might have an impact on the reliability of the results. The research results are derived from the US population sample. It is proposed that this relationship be explored more comprehensively in other populations in the future. Finally, despite the inclusion of numerous concomitant variables in the multivariate regression analysis, there could still be some remanent confounder. Notwithstanding these restrictions, our study still constitutes the initial exploration of the correlation between CMI and GSD as well as IR in patients with GSD. In this regard, subsequent multicenter prospective longitudinal studies are requisite to further investigate the capacity of CMI as a risk predictor and explore the specific mechanisms of the causal pathways among CMI, GSD, and IR.

Conclusions

Our research demonstrates that CMI exhibits a nonlinear positive correlation with the incidence of GSD and IR. This suggests that CMI may serve as a novel and valuable indicator for further investigating the intricate relationships among metabolic syndrome, obesity, and GSD.

Abbreviations

CMI	cardiometabolic index
GSD	gallstone disease
RCS	restricted cubic spline
AHIs	anthropometric indices
TG	triglycerides
HDL-c	high-density lipoprotein cholesterol
BMI	body mass index
WC	Waist Circumference
HC	Hip Circumference
WHpR	waist-to-hip ratio
WHtR	waist-to-height ratio
CHD	coronary heart disease
CSI	cholesterol saturation index
ROC	Receiver operating characteristic
AUC	Area under the curve
CI	Confidence interval
OR	Odds ratio
AIC	Akaike Information Criterion

Acknowledgements

We would like to thank all participants in this study.

Author contributions

LY methodology, investigation, writing original draft, data curation, formal analysis, validation, visualization. SW methodology, investigation, conceptualization, formal analysis. DW and EW conceptualization, supervision, review and editing. All authors reviewed the manuscript.

Funding

This work did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

Data availability

The publicly accessible data sets were analyzed in this research. These data are available at https://www.cdc.gov/nchs/nhanes/index.htm.

Declarations

Ethics approval and consent to participate

The protocol of NHANES was approved by the Ethical Review Board of the National Center for Health Statistics, and the participants provided written informed consent prior to their participation.

Consent for publication

Not Applicable.

Competing interests

The authors declare no competing interests.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Received: 15 January 2025 / Accepted: 28 April 2025
Published online: 09 May 2025

References

1. Sun H, Warren J, Yip J, Ji Y, Hao S, Han W, Ding Y. Factors influencing gallstone formation: A review of the literature. Biomolecules. 2022;12(4):550. https://doi.org/10.3390/biom12040550.
2. Patel H, Jepsen J. Gallstone disease: common questions and answers. Am Fam Physician. 2024;109(6):518–24.
3. Ishiguro S, Inoue M, Kurahashi N, Iwasaki M, Sasazuki S, Tsugane S. Risk factors of biliary tract cancer in a large-scale population-based cohort study in Japan (JPHC study); with special focus on cholelithiasis, body mass index, and their effect modification. Cancer Causes Control. 2008;19(1):33–41. https://doi.org/10.1007/s10552-007-9067-8.
4. Randi G, Franceschi S, La Vecchia C. Gallbladder cancer worldwide: geographical distribution and risk factors. Int J Cancer. 2006;118(7):1591–602. https://doi.org/10.1002/ijc.21683.
5. Bertran E, Heise K, Andia ME, Ferreccio C. Gallbladder cancer: incidence and survival in a high-risk area of Chile. Int J Cancer. 2010;127(10):2446–54. https://doi.org/10.1002/ijc.25421.
6. European Association for the Study of the Liver (EASL). Electronic address: Easloffice@easloffice.eu. EASL clinical practice guidelines on the prevention, diagnosis and treatment of gallstones. J Hepatol. 2016;65(1):146–81. https://doi.org/10.1016/j.jhep.2016.03.005.
7. Portincasa P, Moschetta A, Palasciano G. Cholesterol gallstone disease. Lancet. 2006;368(9531):230–9. https://doi.org/10.1016/S0140-6736(06)69044-2.

8. Chen L, Qiu W, Sun X, Gao M, Zhao Y, Li M, Fan Z, Lv G. Novel insights into causal effects of serum lipids and lipid-modifying targets on cholelithiasis. Gut. 2024;73(3):521–32. https://doi.org/10.1136/gutjnl-2023-330784.
9. Tsai CJ, Leitzmann MF, Willett WC, Giovannucci EL. Prospective study of abdominal adiposity and gallstone disease in US men. Am J Clin Nutr. 2004;80(1):38–44. https://doi.org/10.1093/ajcn/80.1.38.
10. Lammert F, Miquel JF. Gallstone disease: from genes to evidence-based therapy. J Hepatol. 2008;48(Suppl 1):S124–35. https://doi.org/10.1016/j.jhep.2008.01.012.
11. Gaskin CJ, Cooper K, Stephens LD, Peeters A, Salmon J, Porter J. Clinical practice guidelines for the management of overweight and obesity published internationally: A scoping review. Obes Rev. 2024;25(5):e13700. https://doi.org/10.1111/obr.13700.
12. Rhee EJ. The influence of obesity and metabolic health on vascular health. Endocrinol Metab (Seoul). 2022;37(1):1–8. https://doi.org/10.3803/EnM.2022.101.
13. Wang H, Feng X, Huang Q, Zheng X. Association between lipid accumulation products and gallstones: an analysis of the National health and nutrition examination survey 2017–2020. BMC Gastroenterol. 2024;24(1):311. https://doi.org/10.1186/s12876-024-03410-9.
14. Zwierzchowska A, Kantyka J, Rosołek B, Nawrat-Szołtysik A, Małecki A. Sensitivity and specificity of anthropometric indices in identifying obesity in women over 40 years of age and their variability in subsequent decades of life. Biology (Basel). 2022;11(12):1804. https://doi.org/10.3390/biology11121804.
15. Wakabayashi I, Sotoda Y, Hirooka S, Orita H. Association between cardiometabolic index and atherosclerotic progression in patients with peripheral arterial disease. Clin Chim Acta. 2015;446:231–6. https://doi.org/10.1016/j.cca.2015.04.020.
16. Orsi E, Solini A, Penno G, et al. Body mass index versus surrogate measures of central adiposity as independent predictors of mortality in type 2 diabetes. Cardiovasc Diabetol. 2022;21(1):266. https://doi.org/10.1186/s12933-022-01706-2. Published 2022 Dec 2.
17. Hajian-Tilaki K, Heidari B. Variations in the pattern and distribution of non-obese components of metabolic syndrome across different obesity phenotypes among Iranian adults' population. Diabetes Metab Syndr. 2019;13(4):2419–24. https://doi.org/10.1016/j.dsx.2019.06.003.
18. Li FE, Luo Y, Zhang FL, et al. Association between cardiometabolic index and stroke: A Population- based Cross-sectional study. Curr Neurovasc Res. 2021;18(3):324–32. https://doi.org/10.2174/1567202618666211013123557.
19. Duan S, Yang D, Xia H, Ren Z, Chen J, Yao S. Cardiometabolic index: A new predictor for metabolic associated fatty liver disease in Chinese adults. Front Endocrinol (Lausanne). 2022;13:1004855. https://doi.org/10.3389/fendo.2022.1004855. Published 2022 Sep 16.
20. Merkin SS, Karlamangla A, Elashoff D, Grogan T, Seeman T. Change in cardiometabolic score and incidence of cardiovascular disease: the multi-ethnic study of atherosclerosis. Ann Epidemiol. 2015;25(12):912–e71. https://doi.org/10.1016/j.annepidem.2015.09.006.
21. Zha F, Cao C, Hong M, et al. The nonlinear correlation between the cardiometabolic index and the risk of diabetes: A retrospective Japanese cohort study. Front Endocrinol (Lausanne). 2023;14:1120277. https://doi.org/10.3389/fendo.2023.1120277. Published 2023 Feb 16.
22. Miao M, Deng X, Wang Z, et al. Cardiometabolic index is associated with urinary albumin excretion and renal function in aged person over 60: data from NHANES 2011–2018. Int J Cardiol. 2023;384:76–81. https://doi.org/10.1016/j.ijcard.2023.04.017.
23. Yamada C, Mitsuhashi T, Hiratsuka N, Inabe F, Araida N, Takahashi E. Optimal reference interval for homeostasis model assessment of insulin resistance in a Japanese population. J Diabetes Investig. 2011;2(5):373–6. https://doi.org/10.1111/j.2040-1124.2011.00113.x.
24. Park HM, Lee HS, Lee YJ, Lee JH. The triglyceride-glucose index is a more powerful surrogate marker for predicting the prevalence and incidence of type 2 diabetes mellitus than the homeostatic model assessment of insulin resistance. Diabetes Res Clin Pract. 2021;180:109042. https://doi.org/10.1016/j.diabres.2021.109042.
25. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28(7):412–9. https://doi.org/10.1007/BF00280883.
26. Ozturk D, Sivaslioglu A, Bulus H, Ozturk B. TyG index is positively associated with HOMA-IR in cholelithiasis patients with insulin resistance: based on a retrospective observational study. Asian J Surg. 2024;47(6):2579–83. https://doi.org/10.1016/j.asjsur.2024.03.004.
27. Nayak SS, Kuriyakose D, Polisetty LD, Patil AA, Ameen D, Bonu R, Shetty SP, Biswas P, Ulrich MT, Letafatkar N, Habibi A, Keivanlou MH, Nobakht S, Alotaibi A, Hassanipour S, Amini-Salehi E. Diagnostic and prognostic value of triglyceride glucose index: a comprehensive evaluation of meta-analysis. Cardiovasc Diabetol. 2024;23(1):310. https://doi.org/10.1186/s12933-024-02392-y.
28. Zhang M, Mao M, Zhang C, Hu F, Cui P, Li G, Shi J, Wang X, Shan X. Blood lipid metabolism and the risk of gallstone disease: a multi-center study and meta-analysis. Lipids Health Dis. 2022 Mar 2;21(1):26. https://doi.org/10.1186/s12944-022-01635-9
29. Cavallini A, Messa C, Mangini V, Argese V, Misciagna G, Giorgio I. Serum and bile lipids in young women with radiolucent gallstones. Am J Gastroenterol. 1987;82(12):1279–82.
30. Janowitz P, Wechsler JG, Kuhn K, Kratzer W, Tudyka J, Swobodnik W, et al. The relationship between serum lipids, nucleation time, and biliary lipids in patients with gallstones. Clin Investig. 1992;70(5):430–6. https://doi.org/10.1007/BF00235527
31. Man S, Gao Y, Lv J, Tong M, Yin J, Wang B, Ning Y, Li L. Metabolically healthy obesity was significantly associated with increased risk of gallstones. Eur J Endocrinol. 2022;186(2):275–83. https://doi.org/10.1530/EJE-21-0802.
32. Liu F, Chen S, Li X, Li S, Xiao Y, Han J, Tu Y, Bao Y, Bai W, Yu H. Obesity-Induced hepatic steatosis is partly mediated by visceral fat accumulation in subjects with overweight/obesity: A Cross-Sectional study. Obes Facts. 2023;16(2):164–72. https://doi.org/10.1159/000527595.
33. Zhang C, Dai W, Yang S, Wu S, Kong J. Resistance to cholesterol gallstone disease: hepatic cholesterol metabolism. J Clin Endocrinol Metab. 2024;109(4):912–23. https://doi.org/10.1210/clinem/dgad528.
34. Acalovschi M. Gallstones in patients with liver cirrhosis: incidence, etiology, clinical and therapeutical aspects. World J Gastroenterol. 2014;20(23):7277–85. https://doi.org/10.3748/wjg.v20.i23.7277.
35. Bonfrate L, Wang DQ, Garruti G, Portincasa P. Obesity and the risk and prognosis of gallstone disease and pancreatitis. Best Pract Res Clin Gastroenterol. 2014;28(4):623–35. https://doi.org/10.1016/j.bpg.2014.07.013.
36. Petroni ML. Review Article: gall-bladder motor function in obesity. Aliment Pharmacol Ther. 2000;14(Suppl 2):48–50. https://doi.org/10.1046/j.1365-2036.2000.014s2048.x.
37. Wang Q, Hao C, Yao W, Zhu D, Lu H, Li L, Ma B, Sun B, Xue D, Zhang W. Intestinal flora imbalance affects bile acid metabolism and is associated with gallstone formation. BMC Gastroenterol. 2020;20(1):59. https://doi.org/10.1186/s12876-020-01195-1.
38. Grüner N, Mattner J. Bile acids and microbiota: multifaceted and versatile regulators of the Liver-Gut Axis. Int J Mol Sci. 2021;22(3):1397. https://doi.org/10.3390/ijms22031397.
39. Ricci R, Bevilacqua F. The potential role of leptin and adiponectin in obesity: a comparative review. Vet J. 2012;191(3):292–8. https://doi.org/10.1016/j.tvjl.2011.04.009.
40. Méndez-Sánchez N, Bermejo-Martínez LB, Viñals Y, Chavez-Tapia NC, Vander Graff I, Ponciano-Rodríguez G, Ramos MH, Uribe M. Serum leptin levels and insulin resistance are associated with gallstone disease in overweight subjects. World J Gastroenterol. 2005;11(39):6182–7. https://doi.org/10.3748/wjg.v11.i39.6182.
41. Koshiol J, Castro F, Kemp TJ, Gao YT, Roa JC, Wang B, Nogueira L, Araya JC, Shen MC, Rashid A, Hsing AW, Hildesheim A, Ferreccio C, Pfeiffer RM, Pinto LA. Association of inflammatory and other immune markers with gallbladder cancer: results from two independent case-control studies. Cytokine. 2016;83:217–25. https://doi.org/10.1016/j.cyto.2016.05.003.
42. Jin CG, Jiang FR, Zhang J, Ma JR, Ling XF. Role of osteopontin in diet-induced brown gallstone formation in rats. Chin Med J (Engl). 2021;134(9):1093–100. https://doi.org/10.1097/CM9.0000000000001519.
43. Wang HH, de Bari O, Arnatt CK, Liu M, Portincasa P, Wang DQ. Activation of Estrogen receptor G Protein-Coupled receptor 30 enhances cholesterol cholelithogenesis in female mice. Hepatology. 2020;72(6):2077–89. https://doi.org/10.1002/hep.31212.
44. Everson GT, McKinley C, Kern F Jr. Mechanisms of gallstone formation in women. Effects of exogenous Estrogen (Premarin) and dietary cholesterol on hepatic lipid metabolism. J Clin Invest. 1991;87(1):237–46. https://doi.org/10.1172/JCI114977.
45. Fu C, Li X, Wang Y, Chen J, Yang Y, Liu K. Association between triglyceride glucose index-related indices with gallstone disease among US adults. Lipids Health Dis. 2024;23(1):203. https://doi.org/10.1186/s12944-024-02194-x.

46. Zhang J, Liang D, Xu L, Liu Y, Jiang S, Han X, Wu H, Jiang Y. Associations between novel anthropometric indices and the prevalence of gallstones among 6,848 adults: a cross-sectional study. Front Nutr. 2024;11:1428488. https://doi.org/10.3389/fnut.2024.1428488.
47. Yang Y, Wang B, Yuan H, Li X. Triglycerides to High-Density lipoprotein cholesterol ratio is the best surrogate marker for insulin resistance in Nonobese Middle-Aged and elderly population: A Cross-Sectional study. Int J Endocrinol. 2021;2021:6676569. https://doi.org/10.1155/2021/6676569. Published 2021 Apr 30.
48. Quispe R, Martin SS, Jones SR. Triglycerides to high-density lipoprotein-cholesterol ratio, glycemic control and cardiovascular risk in obese patients with type 2 diabetes. Curr Opin Endocrinol Diabetes Obes. 2016;23(2):150–6. https://doi.org/10.1097/MED.0000000000000241.
49. Oh YS, Bae GD, Baek DJ, Park EY, Jun HS. Fatty Acid-Induced Lipotoxicity in Pancreatic Beta-Cells During Development of Type 2 Diabetes. Front Endocrinol (Lausanne). 2018;9:384. Published 2018 Jul 16. https://doi.org/10.3389/fendo.2018.00384
50. Tsai CJ, Leitzmann MF, Willett WC, Giovannucci EL. Macronutrients and insulin resistance in cholesterol gallstone disease. Am J Gastroenterol. 2008;103(11):2932–9. https://doi.org/10.1111/j.1572-0241.2008.02189.x.
51. Wang HH, Portincasa P, Liu M, Wang DQ. Effects of biliary phospholipids on cholesterol crystallization and growth in gallstone formation. Adv Ther. 2023;40(3):743–68. https://doi.org/10.1007/s12325-022-02407-8.

Publisher's note