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Cardiometabolic index as a predictor of gallstone risk: evidence from NHANES 2017–2020

Huachao Zheng[1†], Bo Wu[1†], Caixiang Zhuang[2], Jiesheng Mao[2], Min li[1], Yuncheng Luo[1], Lidong Huang[1], Sisi Lin[1], Feiyang Zhao[1] and Yiren Hu[1*]

Abstract

Background The Cardiometabolic Index (CMI), a composite marker integrating lipid profiles (triglycerides-to-HDL-C ratio) and abdominal obesity (waist-to-height ratio), we aimed to assess its association with gallstone prevalence.

Methods We analyzed data from 2,692 participants in the NHANES 2017–2020 dataset. Gallstones were identified through self-reported data, which may introduce bias in the diagnosis. This limitation should be considered when interpreting the results. Logistic regression modelling, smoothed curve fitting and threshold effect analysis assessed the association between CMI and gallstones.

Result Higher CMI was significantly associated with an increased risk of gallstones (OR = 1.90, 95% CI: 1.37–2.62, $P < 0.0001$). A threshold effect was observed at CMI = 0.85, below which risk increased significantly (OR = 2.62, 95% CI:1.34–5.12, $P = 0.0049$), but became non-significant above this value. The association was stronger in women.

Conclusion Our findings support the use of CMI as a potential predictive marker for gallstone risk, suggesting its integration into clinical assessments for early detection and prevention.

Keywords NHANES, Cross-sectional study, Gallstones, Cardiometabolic index, TyG index

Introduction

Gallstones are among the most common chronic digestive system diseases worldwide, with prevalence varying by region and ethnicity [1, 2]. In the US, gallstones affect approximately 10–20% of the population, imposing an economic burden of $6.2 billion annually in direct and indirect costs associated with gallbladder disease [3, 4]. Gallstones often cause symptoms such as abdominal discomfort, nausea, and vomiting, significantly impairing quality of life and potentially leading to life-threatening complications like cholangitis, pancreatitis, and gallbladder cancer [5, 6]. Research has also linked gallstones to coronary heart disease, diabetes mellitus, and autoimmune diseases, emphasizing the importance of predicting and preventing this condition in clinical settings [7–9].

Traditional markers of gallstone risk, such as body mass index (BMI) and waist circumference (WC), primarily reflect overall or central obesity but fail to capture the synergistic interplay between adiposity and metabolic dysfunction. For instance, BMI cannot distinguish between lean mass and visceral fat [10], while WC overlooks lipid

†Huachao Zheng and Bo Wu contributed equally to this work.

*Correspondence:
Yiren Hu
yirenhu@hotmail.com
[1]Department of General Surgery, The Third Clinical College of Wenzhou Medical University, Wenzhou People's Hospital, Wenzhou, Zhejiang, China
[2]Department of Neurology, Postgraduate Training Base Alliance of Wenzhou Medical University (WenzhouPeople's Hospital), Wenzhou, Zhejiang, China

abnormalities such as hypertriglyceridemia or low HDL-C levels—key drivers of biliary cholesterol supersaturation [11]. Moreover, these metrics lack sensitivity in identifying metabolically obese individuals with normal weight, a subgroup at elevated risk for gallstones [12]. The Cardiometabolic Index (CMI), which integrates waist-to-height ratio (WHtR) and the triglyceride-to-HDL-C ratio (TG/HDL-C), addresses these gaps by simultaneously quantifying abdominal adiposity and dyslipidemia. This dual assessment aligns with the multifactorial pathogenesis of gallstones, offering a more holistic risk evaluation than conventional indices [13, 14]. The Cardiometabolic Index (CMI), initially developed by Ichiro Wakabayashi and colleagues as a marker for diabetes, has gained attention as a significant metabolic health indicator [13]. This index has proven effective in depicting lipid metabolism in both obese adults and children, and is increasingly applied in studies addressing diabetes, nonalcoholic fatty liver disease, chronic kidney disease, asthma, and chronic obstructive pulmonary disease [15–19].

Recent advances in metabolic indices, such as the triglyceride-glucose (TyG) index, has been shown to have a strong correlation with atherosclerosis, cardiovascular disease, and cancer [20–22], and it has recently been suggested that higher TyG indices correlate with an increased likelihood of gallstones incidence [23].

Given the complex and multifactorial etiology of gallstones, including age, gender, obesity (especially abdominal obesity), lipid metabolism, and lifestyle, the relationship between CMI and gallstones warrants in-depth investigation [2, 24–26]. In this study, we hypothesized that CMI is also associated with gallstones, and compared its predictive ability with TyG index to provide new insights into early intervention and prevention strategies for gallstones.

Methods

This study utilized data from the National Health and Nutrition Examination Survey (NHANES), a nationally representative cross-sectional program conducted by the Centers for Disease Control and Prevention (CDC) to assess the health and nutritional status of the U.S. population. NHANES employs a complex, stratified, multistage sampling design, combining detailed interviews, physical examinations, and laboratory tests. The 2017–2020 cycles were selected for this analysis due to their inclusion of comprehensive gallstone-related questionnaires and metabolic biomarkers required for calculating the CMI and TyG index. The integration of demographic, clinical, and biochemical data in NHANES ensures robust generalizability to the U.S. population.

The study initially included 15,560 participants. We excluded 11,173 due to incomplete data required to calculate cardiometabolic index (CMI) and TyG index. In addition, 692 participants were excluded due to missing data on gallstones and 1007 participants were excluded due to missing information on relevant covariates. After these exclusions, the study population was narrowed to 2719 individuals. Prior to analysis, we excluded extreme outliers in cardiometabolic index (CMI) to minimize their impact on the results. We identified and excluded CMI values above the 99th percentile of the distribution, and a total of 27 participants were excluded based on this criterion. The final analysis included 2692 participants. Figure 1 details the participant screening process, as well as the inclusion and exclusion criteria, and illustrates the participant screening flowchart.

Measurement of CMI and TyG

CMI was considered an exposure variable. The following metabolic profiles and body measurements of the subjects were used to calculate CMI: WHtR * [triglyceride (TG) /HDL-C].

The data of TyG index was designed as an exposure variable and was calculated as Ln [triglycerides (mg/dl) * fasting glucose (mg/dl)/2].

Definition of gallstones

Gallstones were the outcome variable. Gallstones were detected using data from the Medical Condition Questionnaire. Participants were considered to have gallstones when they were asked if they had ever been told by a doctor or professional that they had gallstones.

Relevant covariates

In this study, covariates included age, gender, race, marital status (cohabitation, solitary), educational level (below, high, and above high school), serum total cholesterol level, BMI (< 25, ≥ 25), serum total bilirubin, poverty-to-income ratio (PIR), Sedentary activities. Diabetes, alcohol consumption: individuals were categorized as drinkers if they consumed four or five drinks daily, smokers: if they smoked at least 100 cigarettes annually, hypertension, diabetes, coronary heart disease, thyroid disease, and cancer (those who replied 'yes' on the questionnaire were diagnosed with these conditions).

Statistical analysis

The survey respondents were divided into two groups by whether they had gallstones or not. Categorical variables were expressed as frequencies or percentages and continuous data were expressed as mean ± standard deviation. Shapiro-Wilk normality test was used to assess the distribution of continuous variables. For non-normally distributed variables, we used non-parametric tests such as the Mann-Whitney U test or the Kruskal-Wallis test. Normally distributed continuous and categorical variables were tested for between-group differences using chi-square tests and analysis of variance (ANOVA). The

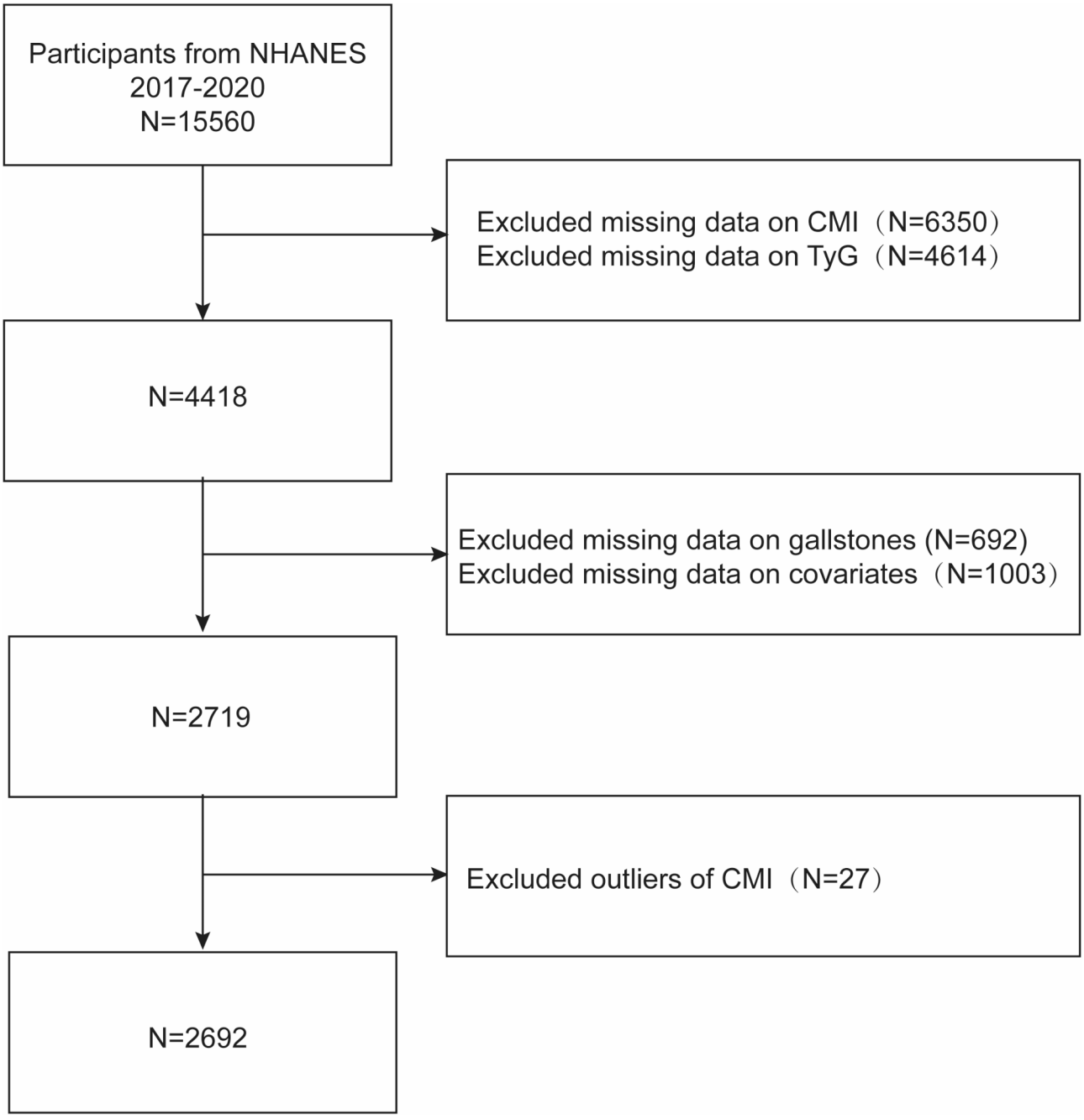

Fig. 1 Flow chart of participants selection

variance inflation factor (VIF) and tolerance were used to evaluate the variables in this study in order to remove multicollinearity. The results showed that the VIF for all covariates was less than 5, indicating that no severe multicollinearity existed. Multivariate logistic regression was used to evaluate the CMI in three models after it was split into quartiles, with the lowest quartile acting as the reference group. Model 1 remained unchanged. Model 2 adjusted for age, race, and gender. In model 3, all variables were changed and the non-linear relationship between CMI and gallstones was investigated using a smoothed curve-fitting method based on the generalised additive model (GAM), with threshold effect analysis using a segmented regression model, the Likelihood Ratio Test (LRT), and Bootstrap resampling. Through the use of subgroup analysis, the effects of heterogeneity were examined. *P*-values were considered statistically significant if they were less than 0.05. R software, version 4.2.3, and Empower(R) tools were used for all statistical analyses.

Results

Baseline characteristics of participants

Among the 2692 participants included in the analysis, 293 (10.9%) reported a history of gallstones. Compared to the non-gallstone group, participants with gallstones were more likely to be female (73.04% vs.26.96%, $P < 0.001$), older (mean age 57.74 vs. 49.12 years, $P < 0.001$), BMI ≥ 25 (89.08% vs.10.92%, $P < 0.001$), and had higher CMI values (0.82 vs. 0.68, $P < 0.001$). Additional significant differences were observed in hypertension prevalence (53.92% vs. (35.06%, $P < 0.001$) and diabetes (27.65% vs. 14.05%, $P < 0.001$). The baseline characteristics of participants with and without gallstones are detailed in Table 1: Baseline characteristics of participants with and without gallstones.

Association of CMI with gallstones

As shown in Table 2: Multivariable logistic regression analysis of the association between CMI and gallstone risk, the results indicate a significant association between CMI and gallstone risk. In the unadjusted model, each unit increase in CMI was associated with a 50% increase in the odds of developing gallstones (OR = 1.50; 95% CI: 1.24–1.82, $P < 0.0001$). This association remained significant after full adjustment for potential confounders (OR = 1.28, 95% CI: 1.00–1.65, $P = 0.0488$).

Further analysis using CMI as a categorical variable revealed that individuals in the highest CMI quartile faced a substantially higher risk compared to those in the lowest quartile. Specifically, the risk was up to 3.01 times higher in Model 2 and 2.02 times higher in Model 3, reinforcing the link between higher CMI and the development of gallstones.

Threshold effect analysis

To more intuitively describe the relationship between CMI and gallstone risk, we employed smoothed curve fitting and the generalized additive model (GAM), as shown in Fig. 2. We identified a nonlinear correlation and a potential saturation effect, and conducted a threshold effect analysis using a two-piecewise linear regression model, as shown in Table 3: Threshold effect analysis of CMI on gallstone risk using a two-piecewise linear regression model. The relationship between CMI and gallstones changed at the threshold of CMI = 0.85. Below this threshold, the odds of gallstones significantly increased (OR: 2.62, 95% CI: 1.34–5.12, $P = 0.0049$). Above this threshold, the association became non-significant (OR: 0.92, 95% CI: 0.63–1.33, $P = 0.6505$).

Subgroup analyses

As illustrated in Fig. 3, with the exception of the gender subgroup, which exhibited a significant interaction effect (P for interaction = 0.0086), no statistically significant interactions were observed across other subgroups (e.g., age, race, BMI, diabetes status; all interaction P-values > 0.05). This indicates that the direction and magnitude of the association between CMI and gallstone risk remained consistent in these subgroups, supporting the robustness of CMI as a predictive marker.

Predictive value of CMI for gallstones

The ROC curves in Fig. 4 show the diagnostic performance of CMI and TyG in identifying gallstones. CMI was slightly more accurate than TyG for gallstones, with an AUC value of 0.606 (95% CI: 0.574–0.638), compared to TyG of 0.599 (95% CI: 0.566–0.631).

Discussion

Ichiro Wakabayashi et al. proposed CMI as a novel measure for identifying diabetes in 2015 [13]. A large prospective study found that increased CMI was positively linked with all-cause mortality in older persons [27]. Several cross-sectional studies have demonstrated that a raised CMI is connected with an increased risk of depression, particularly in hypertensive populations, and Wang et al. found a 20% increase in risk of endometriosis for every unit rise in CMI when the CMI is greater than 0.67 [28]. A prospective study from China involving 117,326 subjects showed a positive correlation between CMI and the development of acute pancreatitis [29]. In addition to this, it has also been linked to diabetes, pulmonary function and stroke [15, 30, 31]. But CMI link with gallstones has not been seen yet, a study linking CMI with gallstones was carried out. The results showed that for every unit rise in the CMI index, the incidence of gallstones rose by 28% in the fully adjusted model (OR = 1.28, 95% CI: 1.00-1.65, $P = 0.0488$). Within a certain range, smoothed curve fitting also showed a positive correlation between gallstones and the CMI index. Based on the results of this investigation, CMI can be used to predict the risk of gallstones. We also compared the recent popular biomarker TyG, which has been shown to be significantly and positively associated with gallstone disease, we performed a ROC analysis and compared the ability of CMI to predict gallstones with TyG. We found that CMI had a statistically superior predictive ability for gallstones than TyG.

CMI Integrates abdominal obesity (via waist-to-height ratio) and dyslipidaemia (via TG/HDL-C ratio), directly addressing two key drivers of gallstone pathogenesis—visceral adiposity and cholesterol saturation [13]. TyG Focuses on the interplay between lipid and glucose metabolism, serving as a surrogate for insulin resistance, which may indirectly influence gallstone formation through hepatic cholesterol synthesis and gallbladder motility [32]. Recent evidence suggests that combining CMI and TyG could enhance risk stratification. For

Table 1 Baseline characteristics of participants with and without gallstones

Characteristic	Overall *n* = 2692	Non-stone formers *n* = 2399(89.1%)	Stone formers *n* = 293 (10.9%)	*P*-value
Waist (cm)	101.09 ± 17.45	100.14 ± 17.20	108.90 ± 17.56	< 0.001
Height(cm)	167.76 ± 9.73	168.20 ± 9.75	164.15 ± 8.82	< 0.001
Triglyceride (mmol/L)	1.35 ± 0.74	1.34 ± 0.74	1.49 ± 0.72	< 0.001
HDL-C(mmol/L)	1.40 ± 0.42	1.40 ± 0.42	1.37 ± 0.38	0.414
CMI	0.69 ± 0.55	0.68 ± 0.55	0.82 ± 0.56	< 0.001
Fasting triglycerides (mg/dL)	105.11 ± 63.59	103.75 ± 63.68	116.25 ± 61.84	< 0.001
Fasting Glucose (mg/dL)	112.40 ± 36.42	111.53 ± 36.17	119.51 ± 37.80	< 0.001
TyG	8.49 ± 0.67	8.47 ± 0.67	8.68 ± 0.62	< 0.001
Age(years)	50.06 ± 17.19	49.12 ± 17.21	57.74 ± 14.94	< 0.001
PIR	2.69 ± 1.63	2.70 ± 1.64	2.59 ± 1.54	0.408
Triglyceride (mmol/L)	1.35 ± 0.74	1.34 ± 0.74	1.49 ± 0.72	< 0.001
HDL-C(mmol/L)	1.40 ± 0.42	1.40 ± 0.42	1.37 ± 0.38	0.414
Total cholesterol (mg/dL)	183.41 ± 41.53	183.53 ± 40.91	182.45 ± 46.32	0.289
Total bilirubin(mg/dL)	8.42 ± 5.04	8.41 ± 5.01	8.56 ± 5.23	0.574
Sedentary activity(min)	339.56 ± 202.56	337.55 ± 201.65	356.01 ± 209.53	0.218
Gender(%)				< 0.001
Male	1358 (50.45%)	1279 (53.31%)	79 (26.96%)	
Female	1334 (49.55%)	1120 (46.69%)	214 (73.04%)	
Race(%)				< 0.001
Mexican American	341 (12.67%)	294 (12.26%)	47 (16.04%)	
Other Hispanic	252 (9.36%)	215 (8.96%)	37 (12.63%)	
Non-Hispanic White	1024 (38.04%)	900 (37.52%)	124 (42.32%)	
Non-Hispanic Black	663 (24.63%)	617 (25.72%)	46 (15.70%)	
Other Race	412 (15.30%)	373 (15.55%)	39 (13.31%)	
Educational level(%)				0.116
Below high school	412 (15.30%)	369 (15.38%)	57 (19.45%)	
High school	635 (23.59%)	562 (23.43%)	73 (24.91%)	
Above high school	1631 (60.59%)	1468 (61.19%)	163 (55.63%)	
Marital status(%)				0.856
Cohabitation	1613 (59.92%)	1436 (59.86%)	177 (60.41%)	
Solitude	1079 (40.08%)	963 (40.14%)	116 (39.59%)	
BMI (%)				< 0.001
<25	687 (25.52%)	655 (27.30%)	32 (10.92%)	
≥ 25	2005 (74.48%)	1744 (72.70%)	261 (89.08%)	
Diabetes(%)				< 0.001
Yes	418 (15.53%)	337 (14.05%)	81 (27.65%)	
No	2274 (84.47%)	2062 (85.95%)	212 (72.35%)	
Alcohol(%)				0.831
Yes	425 (15.79%)	380 (15.84%)	45 (15.36%)	
No	2267 (84.21%)	2019 (84.16%)	248 (84.64%)	
Smoke status(%)				0.127
Yes	1256 (46.66%)	1107 (46.14%)	149 (50.85%)	
No	1436 (53.34%)	1292 (53.86%)	144 (49.15%)	
Hypertension(%)				< 0.001
Yes	999 (37.11%)	841 (35.06%)	158 (53.92%)	
No	1693 (62.89%)	1558 (64.94%)	135 (46.08%)	
Coronary heart disease(%)				< 0.001
Yes	123 (4.57%)	96 (4.00%)	27 (9.22%)	
No	2569 (95.43%)	2303 (96.00%)	266 (90.78%)	
Thyroid disease(%)				< 0.001
Yes	306 (11.37%)	239 (9.96%)	67 (22.87%)	
No	2386 (88.63%)	2160 (90.04%)	226 (77.13%)	

Table 1 (continued)

Characteristic	Overall *n* = 2692	Non-stone formers *n* = 2399(89.1%)	Stone formers *n* = 293 (10.9%)	*P*-value
Cancer(%)				< 0.001
Yes	283 (10.51%)	229 (9.55%)	54 (18.43%)	
No	2409 (89.49%)	2170 (90.45%)	239 (81.57%)	

Abbreviation: CMI: Cardiometabolic index; TyG: triglyceride glucose; PIR: income to poverty ratio; HDL-C: high-density lipoprotein cholesterol BMI: body mass index

Table 2 Multivariable logistic regression analysis of the association between CMI and gallstone risk

CMI	OR (95% CI), *P*-value		
	Model 1	Model 2	Model 3
Continuous	1.50 (1.24, 1.82) < 0.0001	1.59 (1.29, 1.97) < 0.0001	1.28 (1.00, 1.65) 0.0488
Quartile 1[0.06, 0.31]	1.00 (reference)	1.00 (reference)	1.00 (reference)
Quartile 2[0.31, 0.53]	1.76 (1.15, 2.70) 0.0091	1.66 (1.07, 2.58) 0.0232	1.33 (0.84, 2.09) 0.2232
Quartile 3[0.53, 0.89]	2.98 (2.00, 4.44) < 0.0001	2.70 (1.79, 4.08) < 0.0001	1.97 (1.26, 3.07) 0.0029
Quartile 4[0.89, 3.30]	3.05 (2.05, 4.54) < 0.0001	3.01 (1.98, 4.56) < 0.0001	2.02 (1.27, 3.22) 0.0031
P for trend	< 0.0001	< 0.0001	0.0040

Notes:

Model 1: crude model

Model 2: adjusted for age, gender and race

Model 3: adjusted for age, gender, race, educational level, PIR, marital status, total cholesterol, BMI, total bilirubin, sedentary activity, diabetes, alcohol, smoke status, hypertension, coronary heart disease, thyroid disease, cancer

CMI: Cardiometabolic index; OR: odds ratio; CI: confidence interval; PIR: income to poverty ratio;

BMI: body mass index

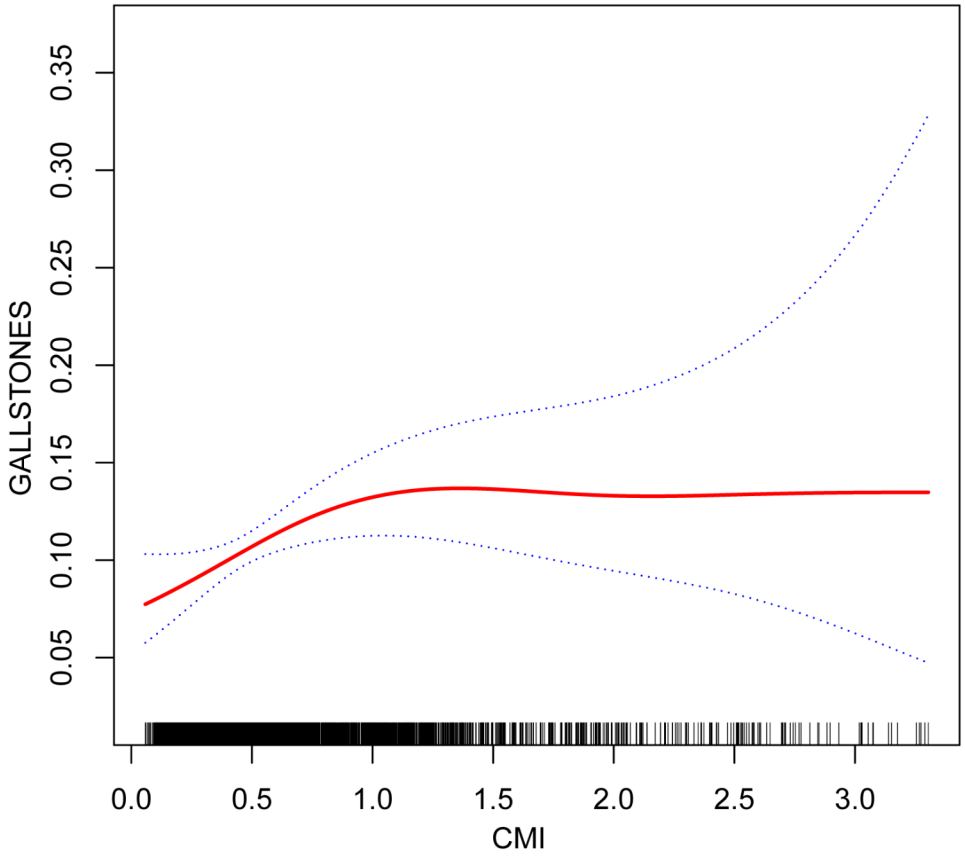

Fig. 2 The association between CMI and gallstones

Table 3 Threshold effect analysis of cardiometabolic index on gallstone risk using a two-piecewise linear regression model

Threshold effect analysis	Gallstones OR (95%CI)
CMI	
The inflection point (K)	0.85
< K slope	2.62 (1.34, 5.12) 0.0049
> K slope	0.92 (0.63, 1.33) 0.6505
Log-likelihood ratio test	0.019

Notes: The analysis was based on Model 3; CMI: Cardiometabolic index; OR: odds ratio

Subgroup	participants	OR(95%CI)	*P*–value	*P* for interaction
Gender				**0.0086**
male	1358	0.81 (0.53, 1.25)	0.3448	
female	1334	1.58 (1.16, 2.14)	0.0036	
Age(years)				0.8761
<40	853	1.44 (0.79, 2.65)	0.2353	
≥40,<60	926	1.24 (0.83, 1.86)	0.2868	
≥60	913	1.20 (0.81, 1.76)	0.3643	
Race				0.7016
Mexican American	341	0.97 (0.46, 2.06)	0.9401	
Other Hispanic	252	0.89 (0.39, 2.01)	0.7744	
Non−Hispanic White	1024	1.27 (0.87, 1.87)	0.2206	
Non−Hispanic Black	663	1.15 (0.51, 2.58)	0.7348	
Other Race	412	1.73 (0.93, 3.23)	0.0836	
BMI				0.6611
<25	687	1.51 (0.60, 3.80)	0.3822	
≥25	2005	1.22 (0.94, 1.57)	0.1378	
Diabetes				0.9249
Yes	418	1.21 (0.76, 1.93)	0.4223	
No	2274	1.24 (0.93, 1.67)	0.1487	
Hypertension				0.5518
Yes	999	1.34 (0.95, 1.88)	0.0905	
No	1693	1.16 (0.81, 1.65)	0.4100	
Smoke status				0.3401
Yes	1256	1.14 (0.82, 1.58)	0.4483	
No	1436	1.45 (0.99, 2.11)	0.0547	
Alcohol				0.5071
Yes	425	1.03 (0.55, 1.95)	0.9235	
No	2267	1.30 (0.99, 1.71)	0.0574	
Coronary heart disease				0.2540
Yes	123	0.77 (0.31, 1.90)	0.5647	
No	2569	1.30 (1.01, 1.68)	0.0429	
Thyroid disease				0.3719
Yes	306	1.57 (0.89, 2.77)	0.1160	
No	2386	1.19 (0.90, 1.56)	0.2215	
Cancer				0.8868
Yes	283	1.30 (0.75, 2.25)	0.3470	
No	2409	1.25 (0.94, 1.64)	0.1209	

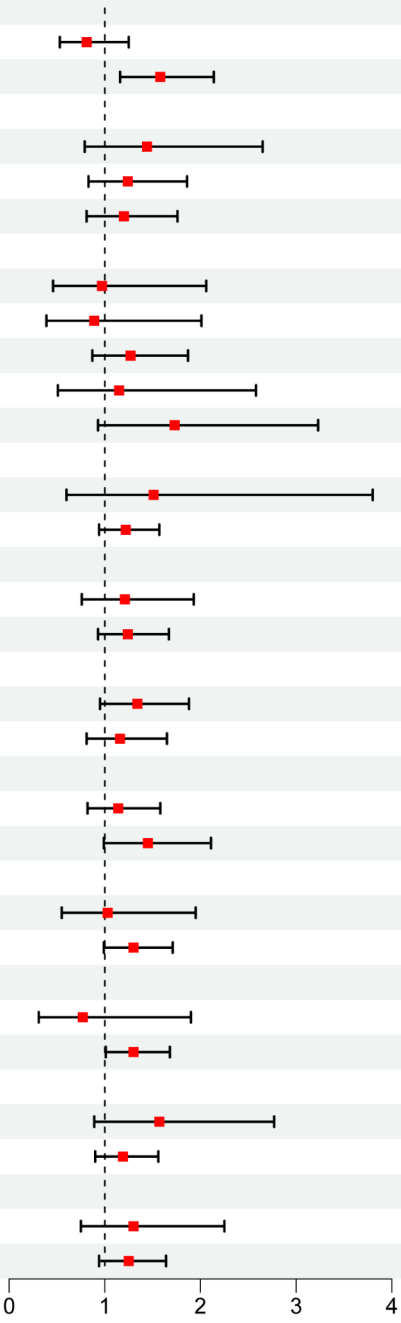

Fig. 3 Subgroup analysis of the association between CMI and gallstones. Adjusted for all covariates except effect modifier

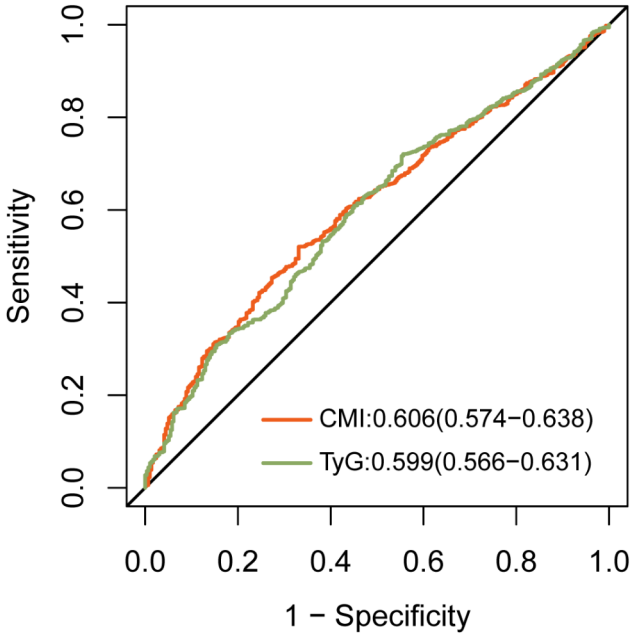

Fig. 4 Predictive value of CMI and TyG for gallstones

example, Feng et al. proposed that dual assessment of adiposity (via CMI) and insulin resistance (via TyG) improves the prediction of metabolic disorders [33]. In the context of gallstones, CMI's emphasis on visceral fat distribution may identify individuals with obesity-driven biliary cholesterol supersaturation, while TyG could flag those with glucose-lipid dysregulation exacerbating hepatic cholesterol secretion.ero.

In subgroup analyses, the positive correlation between CMI and gallstones was more significant for women, because low estrogen levels in men reduce the expression of the 3-hydroxy-3-methyl glutaryl coenzyme A reductase(HMG-CoA-r)gene and its transcription factor sterol regulatory element-binding protein(SREBP) −2 in the liver, which affects the formation of gallstones through the reduction of cholesterol synthesis [34].

The study observed a threshold effect between CMI and gallstone risk (the risk sharply increases when CMI < 0.85, and becomes saturated when CMI > 0.85), which may be attributed to the following mechanisms: Dysregulated Lipid Metabolism: When CMI is low, mild metabolic disturbances (such as elevated blood lipids and abdominal fat accumulation) can lead to bile cholesterol supersaturation, significantly increasing the risk of gallstones. When CMI exceeds 0.85, metabolic disturbances (such as insulin resistance and chronic inflammation) reach a critical point, and bile cholesterol saturation stabilizes, thus diminishing the increase in risk [32]. Inflammation and Oxidative Stress: Abdominal obesity and dyslipidemia activate chronic inflammation (e.g., elevated IL-6 and TNF-α). At low CMI, the pro-stone effects of inflammatory mediators intensify as CMI increases, with decreasing HDL-C and increasing TG levels disrupting the oxidative-antioxidative balance, promoting cholesterol crystal nucleation. At high CMI, inflammatory signaling pathways (e.g., NF-κB) become saturated, and the risk increase slows. The depletion of the antioxidant system further limits its contribution to gallstone formation [35, 36].

CMI is a composite indicator that integrates abdominal obesity and dyslipidemia, which are key drivers of metabolic disorders. While body mass index(BMI)estimates of body fat in obese people have limitations in distinguishing between the contributions of muscle mass and adipose tissue to obesity, the WHtR, due to its greater emphasis on body fat distribution, has been proposed as a more accurate indicator of certain health risks [37, 38]. In addition, the TG/HDL-C ratio has been found to be highly correlated with coronary heart disease, diabetes mellitus, chronic kidney disease, and metabolic syndrome, and it often represents an indicator of lipid metabolism disorders [39–41]. Gallstone risk factors include lipid metabolism disorders and abdominal obesity. By effectively combining these two indicators, CMI is regarded as a more thorough evaluation of dyslipidemia and abdominal obesity, offering a more comprehensive approach to triglyceride evaluating metabolic health. The exact mechanism by which elevated CMI is linked to an increased risk of gallstones is unclear, but based on prior research, we propose that the causes are multifactorial: First of all, high serum triglyceride levels are linked to fast cholesterol crystal nucleation and increased biliary cholesterol saturation, both of which are significant risk factors for gallstones. Increased biliary cholesterol saturation and insufficient bile acid secretion are linked to lower serum HDL-C, which decreases cholesterol solubility in the bile and causes gallstones [14, 42, 43]. Secondly, chronic systemic inflammation and oxidative stress exists in obese and dyslipidaemic populations, and as inflammatory mediators continue to increase, such as interleukin (IL) -6 and IL-12, they can stimulate the production of tumour necrosis factor-α (TNF-α) by T-cells and natural killer cells, which directly affects the uptake, secretion, and function of the gallbladder epithelial cells, and impairs the gallbladder's normal contractile ability, thereby increasing the risk of gallstone formation [35, 44]. Then higher HDL-C inhibits the production of various chemokines, hinders oxidative stress, suppresses inflammatory responses, and contributes to cholesterol efflux [36]. In addition, insulin resistance (IR) frequently coexists with obesity and metabolic disorders. By activating the 3-hydroxy-3-methylglutaryl coenzyme, it might accelerate hepatic cholesterol release and cholesterol supersaturation and deteriorate gallbladder dynamics, which may result in the production of gallstones [32, 45, 46]. IR is an important marker for type 2 diabetes, which

explains the increased risk of developing stones among diabetics with high CMI levels in the study as well. Lastly, a high waist-to-height ratio usually implies obesity, which is an important risk factor for metabolic diseases. Obese individuals usually suffer from comorbidities such as diabetes mellitus and non-alcoholic fatty liver disease. Both of them have been shown to be associated with an increased risk of gallstones [15, 16]. The high fat content of obese patients increases leptin secretion, which regulates bile acid metabolism through the leptin receptor/AMP activated protein kinase/bile salt efflux pump (OB-Rb/AMPK/BSEP) axis resulting in the formation of gallstones [47, 48]. The positive correlation between blood pressure and leptin levels may account for the increased risk of gallstones in hypertensive people with elevated CMI levels [49]. Lastly, a high waist-to-height ratio is often indicative of obesity, a key risk factor for metabolic diseases. Obese individuals usually suffer from comorbidities such as diabetes mellitus, non-alcoholic fatty liver disease, cardiovascular disease and metabolic syndrome than non-obese individuals. These have been shown to be associated with an increased risk of gallstones.

To the best of our knowledge, this is the first study to look into the connection between gallstones and CMI. To clarify the relationship and validate the validity and reliability of the results, we used subgroup analyses, multivariate logistic regression analysis. These findings have significant implications for future gallstone prevention and early intervention methods. Although a correlation could be seen, causality could not be concluded because this study was observational and included the impact of temporal connection ambiguity. Because asymptomatic gallstones may exist, this study relied on self-reported health information on gallstones, which is prone to reporting bias and affects the accuracy of the findings. Although we took into account as many covariates as feasible when conducting the logistic regression analyses, there may still be potential confounders that were not included in the analyses and affect the interpretation of the findings. Due to constraints in the included population, the statistical usefulness of subgroup analyses and interaction tests may be limited by the relatively small sample sizes of certain subgroups.

Conclusions

This study found that cardiometabolic index (CMI) was significantly and positively associated with the risk of developing gallstones, particularly in the female population. These findings provide new scientific rationale for utilising CMI as a component of early screening and prevention strategies for asymptomatic gallstones. However, longitudinal studies are needed to confirm our findings, and future studies should also explore advanced predictive tools, such as machine learning algorithms combining CMI, TyG and other biomarkers, to develop personalised risk stratification models. Such models could guide targeted ultrasound screening of at-risk populations to optimise early diagnosis and prevention.

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Author contributions
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Data availability
This study examines data that is available to the public. You may get the complete set of data at https://www.cdc.gov/nchs/nhanes/index.htm.

Declarations

Ethics approval
The datasets were obtained from the NHANES database, and all data were under ethics approval before recorded in the database.

Consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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