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Diabetes is the missing link between cardiometabolic index and gallstones: a large cross-sectional study

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The cardiometabolic index (CMI), which integrates individual lipid and visceral fat parameters, represents a superior new predictive tool for cardiovascular and metabolic disorders, but its predictive value for gallstones (GS) is unclear. Therefore, the present study used this vacancy to explore the relationship between CMI levels and GS in US adults, assess the mediating role of diabetes mellitus in the pathogenesis of both, and provide new clinical ideas for early prevention and screening of GS in patients with diabetes mellitus. This survey extracted information from the National Health and Nutrition Examination Survey (NHANES) 2017–2020 vintage cycle. Cross-sectional analyses and a variety of statistical techniques were used to analyze the correlation between CMI and GS, including logistic regression, propensity score matching, subject work curves, and restricted cubic spline (RCS). Furthermore, mediation analysis was used to investigate whether and to what extent diabetes mediated the effect of CMI on GS. After analysis of 3,395 participants, a significant positive correlation was observed between elevated CMI levels and increased prevalence of GS In the fully corrected model (Model 4), the prevalence of GS exhibited a 23% increase for every incremental unit rise in logarithmically transformed CM. Mediation analysis showed that diabetes largely mediated the association between CMI and GS, with a mediation ratio of 15.1%. Higher CMI levels are closely linked to a greater occurrence of GS, and diabetes plays a key mediating role in the pathogenesis of both. Addressing dyslipidemia while not neglecting blood glucose levels, and co-management of the two may be a proven way to reduce GS risk.

Keywords Cardiometabolic index, Cross-sectional study, Gallstones

Abbreviations

GS	Gallstones
WHtR	Waist-to-height ratio
BMI	Body mass index
WC	Waist circumference
TG	Triglycerides
HDL-C	High-density lipoprotein cholesterol
CMI	Cardiovascular metabolic index
LAP	Lipid accumulation product
TyG	Triglyceride-glucos
NHANES	National Health and Nutrition Examination Survey
NCHS	National Center for Health Statistics
PIR	Ratio of household income to poverty

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RCS	Restricted cubic spline
CI	Confidence interval
OR	Odds ratio

Gallstones (GS) represent a prevalent gastrointestinal ailment globally, with a rising prevalence in recent times[1]. Approximately 10 to 15% of people in developed societies suffer from GS[2,3]. The United States witnesses over 800,000 cholecystectomies annually, incurring a substantial economic strain of nearly $6.5 billion yearly on households and the healthcare sector[4–6]. The intricate processes leading to GS formation encompass genetic predispositions, gallbladder contractile dynamics, microbiota, estrogen, and dietary factors[7–9]. Recent research indicates that the presence of GS can elevate the likelihood of developing additional health conditions, including cardiovascular diseases, pancreatitis, and malignant tumors, posing a serious threat to the individual's health and overall quality of life[10,11]. Consequently, identifying and utilizing simple and controllable clinical indicators are imperative for effectively preventing and managing GS.

Diabetes is a complex chronic metabolic disorder affecting a global population of 425 million individuals, with projections indicating a rise to 629 million by the year 2045[12,13]. Prior research has established that obesity is a significant contributor to the onset of various metabolic disorders, notably diabetes. Obesity can be assessed using a range of metrics, such as surrogate markers of general or central adiposity, like body mass index (BMI) or waist circumference (WC)[14,15]. It has been suggested that waist-to-height ratio (WHtR) serves as a more precise and responsive indicator of cardiovascular disease and diabetes compared to the conventional measure of obesity, given its capacity to discern between muscle mass and fat distribution. WHtR is a measure of visceral obesity that is calculated by dividing WC by height. It is a more effective indicator of cardiometabolic risk and various non-communicable diseases compared to traditional measures of obesity[16–19]. Additionally, several markers of lipid metabolism in humans, such as triglyceride (TG) to high-density lipoprotein cholesterol (HDL-C) ratio, lipid accumulation products (LAP), and triglyceride-glucose (TyG) index[20], have been recognized as reliable and practical indicators of insulin resistance and metabolic diseases[21].

Cardiovascular metabolic index (CMI) is defined by multiplying TG/HDL-C by WHtR, a novel metabolic index introduced by Ichiro Wakabayashi and colleagues[22,23]. CMI combines lipid and obesity parameters and is a reliable indicator for early identification of cardiovascular disease and diabetes. Numerous recent studies have confirmed a clear correlation between CMI and a variety of diseases such as coronary heart disease, stroke, atherosclerosis, hypertension, left ventricular dilatation, and kidney disease. In terms of predicting metabolic and cardiovascular diseases, CMI may be a promising clinical indicator[23–26]. Nevertheless, the relationship between CMI and GS and the prognostic utility of CMI in predicting GS remains unexplored in the literature. The major aim of this research was to examine the relationship between CMI levels and GS in the US adult population and to assess the possible mediating role of diabetes between the two, to provide new clinical ideas for early prevention and screening of GS in patients with diabetes.

Methods

Data collection and study subjects

The National Health and Nutrition Examination Survey (NHANES) constitutes a comprehensive and methodologically rigorous study of the U.S. population, utilizing advanced sampling techniques to gather extensive data on health indicators and diseases. This is achieved through personal interviews, standardized physical examinations, and laboratory tests. Administered and supervised by the National Center for Health Statistics (NCHS), NHANES provides a collection of nationally representative cross-sectional data. The database encompasses a broad spectrum of biological and medical domains, rendering it an invaluable resource for healthcare professionals and public health initiatives. The collection and distribution of NHANES data followed the Helsinki Principles and were approved by the NCHS Ethics Committee, with all participants signing informed consent forms.

Initially, individuals with missing GS data and those under the age of 20 ($n = 6{,}350$) were excluded. Additionally, pregnant women, individuals lacking information on education and marital status, and those with incomplete lipid data were also excluded. Furthermore, participants with missing disease history, dietary data, and incomplete information on covariates, including other physical examinations and laboratory tests, were not considered for inclusion. Following a rigorous assessment and screening process, a total of 3,395 adult participants were recruited for this study. Figure 1 illustrates the participant exclusion and inclusion process in detail and provides comprehensive information.

Diagnosis and definition of GS and diabetes

The assessment of GS was conducted using a questionnaire in which participants responded to the query, "Did your doctor diagnose you with GS?" A response of "yes" was taken as an indication of the presence of GS. This strategy is both uncomplicated and effective, having been extensively applied in past research of a similar nature[27,28]. A diagnosis of diabetes is established through the presence of a glycosylated hemoglobin level equal to or greater than 6.5%, confirmation by a medical practitioner or healthcare provider, self-reported acknowledgment of the condition, and/or use of medication or insulin to control your blood sugar[29].

Calculation of the CMI, LAP and TyG

The determination of CMI, LAP, and TyG necessitates the acquisition of fasting blood samples from participants, along with physical measurements conducted within a laboratory environment[30]. To ensure the promptness and precision of biochemical marker assessments, blood samples are obtained either via a dedicated mobile screening unit or at a designated location, followed by processing and analysis in adherence to a standardized protocol. Certified medical personnel at the mobile screening centers are tasked with measuring participants'

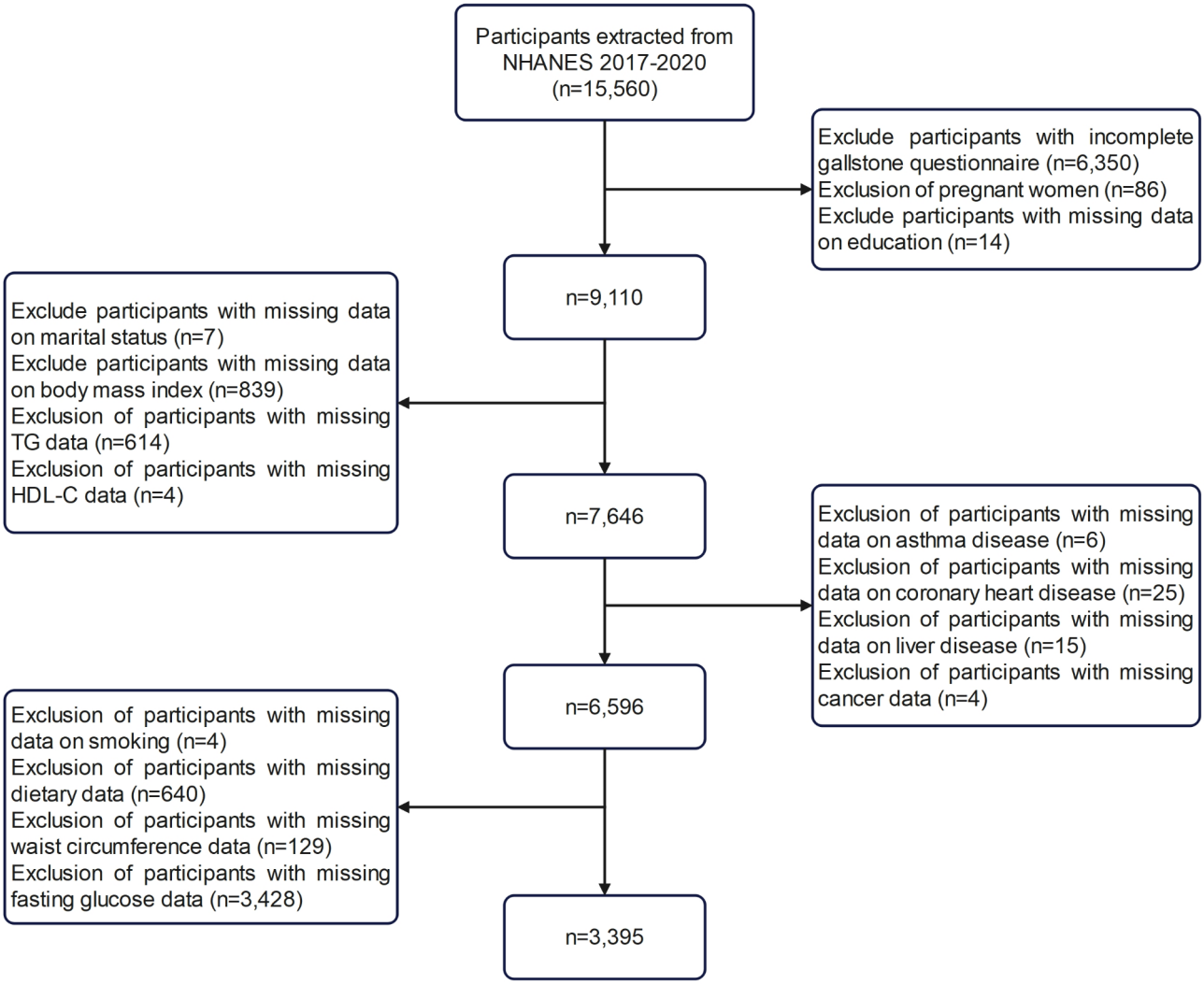

Fig. 1. NHANES 2017–2020 participant selection flowchart.

waist circumference and height. The WHtR is subsequently calculated by dividing waist circumference (in centimeters) by height (in centimeters). The ratio of total cholesterol to HDL cholesterol is utilized as an indicator of the relationship between these two cholesterol levels[31]. The formulae for the relevant indicators are set out below:

$$\mathrm{WHtR} = \mathrm{WC\ (cm)\,/Height\ (cm)}$$

$$\mathrm{CMI} = \mathrm{TG\ (mmol/L)\,/HDL-C\ (mmol/L)} \times \mathrm{WHtR}$$

$$\mathrm{Males:\ LAP} = (\mathrm{WC} - 65) * \mathrm{TG\ (mmol/L)}$$

$$\mathrm{Females:\ LAP} = (\mathrm{WC} - 58) * \mathrm{TG\ (mmol/L)}$$

$$\mathrm{TyG\ index} = \mathrm{Ln}\,[\mathrm{triglycerides\ (mg/dl)} \times \mathrm{fasting\ blood\ glucose\ (mg/dl)\,/2}]$$

Covariates included in the study

Considering the possible influence of other confounding variables on GS, this study incorporated a comprehensive set of covariates informed by expert clinical knowledge and previous literature. The primary variables in the demographic model include age, sex, race, marital status, and socioeconomic status. Socioeconomic status encompasses educational level and the ratio of household income to poverty (PIR). Lifestyle habits were predominantly characterized by smoking and alcohol consumption. Dietary intake factors comprised carbohydrate, protein, fat, and water intake. BMI and total plasma cholesterol were identified as significant confounding variables among the physical examination and laboratory test indices. The history of existing diseases incorporated covariates (hypertension, diabetes, asthma, coronary heart disease, liver disease, and cancer). Information regarding medication use was ascertained based on whether the subject's physician

had told the use of antihypertensive or lipid-lowering medications (statins and fibrates) as reported in the questionnaire[32].

Statistical analysis

Based on the statistical properties of the variables, the baseline characteristics of continuous variables were represented using either parametric tests (mean ± standard deviation) or nonparametric tests (median and interquartile range), while categorical variables were described using absolute values (n) and percentages (%). Stepwise regression analysis was employed to initially screen all covariates, construct a matrix of correlation coefficients, and assess the multicollinearity of the covariates using the condition number (κ) of the independent variable matrix. A condition number $\kappa < 100$ indicates a low degree of multicollinearity; κ between 100 and 1000 indicates some degree of multicollinearity; $\kappa > 1000$ indicates severe multiple multicollinearity. All covariates included in this study have κ values less than 100[33]. To thoroughly examine the relationship between CMI, LAP, the TyG index, and GS, four distinct models were developed utilizing one-way and multifactor logistic regression analyses. Model 1 served as the baseline single-factor model, excluding any covariates. Model 2 was adjusted for essential demographic variables, namely sex, age, and race. Building upon the foundation of Model 2, Model 3 incorporated additional variables such as socioeconomic status (education and PIR), marital status, BMI, total cholesterol, lifestyle behaviors (smoking and alcohol consumption), substance use, and medical history. Lastly, Model 4 further extended the analysis by including daily dietary intake as a covariate, resulting in a fully integrated model.

Due to their skewed distributions, CMI, TG/HDL and LAP were log-transformed before statistical analyses were performed and were treated as continuous variables (per 1-unit increment) in the aforementioned models[34]. The dose-response relationships among CMI, TG/HDL, LAP, TyG, and GS were examined through the application of restricted cubic spline (RCS) curve fitting to ascertain whether these relationships were linear or nonlinear. Hierarchical multiple regression was used in subgroup analyses to investigate possible differences in the relationship between CMI and GS among certain populations. To thoroughly assess heterogeneity among subgroups, particularly concerning gender and race, interaction terms were incorporated into the model and analyzed via the log-likelihood ratio test. Sensitivity analyses were performed to confirm the robustness of the findings. Furthermore, for trend analysis, CMI was converted from a continuous variable into quartiles. Additionally, CMI was categorized into dichotomous groups (high CMI and low CMI) for propensity score matching (PSM). Optimal pairwise matching ratios were employed, with matching variables including gender, age, and race. Finally, the four models were analyzed for causal mediation using the "mediation" software package, and 500 simulations were conducted using the Bootstrap method to assess the confidence intervals of the mediated effects to determine the proportion of the mediated effects attributable to diabetes. The model not only offers statistical evidence for rational analysis but also proves to be effective in uncovering pathways. Specifically, direct effects demonstrate the correlation between CMI and GS, while indirect effects ascertain whether this correlation is influenced by diabetes. Statistical analyses for this study were based on R and MSTATA software, with a predetermined level of significance set at a P value of less than 0.05.

Results

Clinical baseline characteristics of patients with GS

Table 1 compares the clinical characteristics of subjects with and without GS. Of the 3,395 subjects who participated in the study, 363 were diagnosed with GS, with an overall prevalence of 10.69%. The participants had a median age of 52 years, consisting of 49.10% men and 50.90% women. Regarding disease history, 45.18%, 4.27%, and 18.82% of the total were hypertensive, coronary artery disease, and diabetic patients respectively.

Table 2 presents the clinical baseline characteristics of the participants, stratified by gender. The data indicate a notably higher prevalence of GS in females compared to males, with prevalence rates of 15.05% and 6.18%, respectively. Conversely, the prevalence of diabetes mellitus and coronary heart disease is greater in males than in females. Additionally, the TG/HDL ratio, CMI, and TyG index are marginally elevated in males compared to females, with all associated P-values being less than 0.01. In contrast, the LAP values are equivalent between the two groups.

Association between CMI, TG/HDL, LAP, TyG index, and GS

Table 3 shows the results of univariate and multivariate logistic regression analyses between these indicators of CMI, TG/HDL, LAP and TyG and GS. A total of 4 Models were constructed and these results were based on the stepwise inclusion of different covariates. Univariate Model 1 and multivariate Model 2 (adjusted for adjustment for key demographic variables) showed statistically significant positive correlations between the four indices and GS (all P-values were less than 0.01). Model 3 further adjusted for additional factors including marital status, socioeconomic status (education level and PIR), BMI, medical history (hypertension, diabetes mellitus, coronary heart disease, asthma, cancer), total cholesterol, lifestyle habits, and medication use, based on Model 2. The positive correlations between three of the indices and GS remained significant, except for the TyG index (all P-values < 0.05). Upon incorporating all potential confounders in Model 4, only CMI and LAP retained statistically significant associations. Specifically, for each 1-unit increase in log-transformed CMI, the prevalence of GS increased by 23% (OR = 1.23; 95% CI 1.03–1.46), while LAP exhibited an even stronger association (OR = 1.37; 95% CI 1.11–1.69).

Subgroup analysis

To assess the heterogeneity between CMI and GS across subgroups, we performed subgroup analyses and interaction tests, the results of which are shown in Fig. 2. Notably, the positive correlation between CMI and GS was more pronounced in the subgroups of females, non-Hispanic other races, those with higher education

Characteristics	Overall, $N = 3,395$	Gallstones, $N = 363$	No gallstones, $N = 3,032$	P value
Age	52 (36, 64)	59 (46, 70)	51 (35, 63)	< 0.001
Sex, n (%)				< 0.001
Male	1,667 (49.10%)	103 (28.37%)	1,564 (51.58%)	
Female	1,728 (50.90%)	260 (71.63%)	1,468 (48.42%)	
Race, n (%)				0.001
Mexican American	434 (12.78%)	49 (13.50%)	385 (12.70%)	
Non-Hispanic White	1,191 (35.08%)	148 (40.77%)	1,043 (34.40%)	
Non-Hispanic Black	867 (25.54%)	62 (17.08%)	805 (26.55%)	
Other Races	903 (26.60%)	104 (28.65%)	799 (26.35%)	
Education level, n (%)				0.404
Grades 0–12	613 (18.06%)	71 (19.56%)	542 (17.88%)	
High school graduate/GED	809 (23.83%)	93 (25.62%)	716 (23.61%)	
Some college or above	1,973 (58.11%)	199 (54.82%)	1,774 (58.51%)	
Marital status, n (%)				0.001
Married/Living with Partner	2,010 (59.20%)	211 (58.13%)	1,799 (59.33%)	
Widowed/Divorced/Separated	738 (21.74%)	102 (28.10%)	636 (20.98%)	
Unmarried	647 (19.06%)	50 (13.77%)	597 (19.69%)	
PIR, n (%)				0.820
< 2	1,316 (38.76%)	143 (39.39%)	1,173 (38.69%)	
≥ 2	1,661 (48.92%)	179 (49.31%)	1,482 (48.88%)	
Unclear	418 (12.31%)	41 (11.29%)	377 (12.43%)	
BMI (kg/m^2)				< 0.001
< 25	870 (25.63%)	43 (11.85%)	827 (27.28%)	
25–30	1,071 (31.55%)	98 (27.00%)	973 (32.09%)	
≥ 30	1,454 (42.83%)	222 (61.16%)	1,232 (40.63%)	
Smoking, n (%)				0.004
Current smokers	638 (18.79%)	52 (14.33%)	586 (19.33%)	
Former smokers	844 (24.86%)	113 (31.13%)	731 (24.11%)	
Never smokers	1,913 (56.35%)	198 (54.55%)	1,715 (56.56%)	
Alcohol consumption, n (%)				< 0.001
Yes	1,891 (55.70%)	167 (46.01%)	1,724 (56.86%)	
No	1,504 (44.30%)	196 (53.99%)	1,308 (43.14%)	
Hypertension, n (%)				< 0.001
Yes	1,534 (45.18%)	217 (59.78%)	1,317 (43.44%)	
No	1,861 (54.82%)	146 (40.22%)	1,715 (56.56%)	
Diabetes, n (%)				< 0.001
Yes	639 (18.82%)	115 (31.68%)	524 (17.28%)	
No	2,756 (81.18%)	248 (68.32%)	2,508 (82.72%)	
Asthma, n (%)				< 0.001
Yes	545 (16.05%)	82 (22.59%)	463 (15.27%)	
No	2,850 (83.95%)	281 (77.41%)	2,569 (84.73%)	
Coronary heart disease, n (%)				< 0.001
Yes	145 (4.27%)	30 (8.26%)	115 (3.79%)	
No	3,250 (95.73%)	333 (91.74%)	2,917 (96.21%)	
Liver disease, n (%)				< 0.001
Yes	170 (5.01%)	37 (10.19%)	133 (4.39%)	
No	3,225 (94.99%)	326 (89.81%)	2,899 (95.61%)	
Cancer, n (%)				< 0.001
Yes	357 (10.52%)	64 (17.63%)	293 (9.66%)	
No	3,038 (89.48%)	299 (82.37%)	2,739 (90.34%)	
Use of antihypertensive drugs				< 0.001
Yes	1,002 (29.51%)	165 (45.45%)	837 (27.61%)	
No	2,393 (70.49%)	198 (54.55%)	2,195 (72.39%)	
Use of lipid-lowering drugs				< 0.001
Yes	746 (21.97%)	115 (31.68%)	631 (20.81%)	
No	2,649 (78.03%)	248 (68.32%)	2,401 (79.19%)	
Continued				

Characteristics	Overall, *N* = 3,395	Gallstones, *N* = 363	No gallstones, *N* = 3,032	*P* value
Protein intake (g)	72 (54, 96)	65 (49, 87)	73 (55, 97)	< 0.001
Carbohydrate intake (g)	221 (163, 292)	212 (149, 279)	223 (164, 294)	0.018
Total fat intake (g)	76 (54, 105)	74 (52, 99)	77 (54, 106)	0.047
Water intake (g)	2,541 (1,897, 3,357)	2,419 (1,818, 3,138)	2,561 (1,902, 3,374)	0.031
Total cholesterol (mg/dl)	180 (155, 208)	177 (153, 210)	180 (156, 208)	0.310
Fasting glucose (mg/dl)	103 (96, 115)	108 (99, 125)	103 (96, 114)	< 0.001
Height (cm)	167 (160, 174)	164 (158, 170)	167 (160, 175)	< 0.001
Waist circumference (cm)	99 (89, 112)	107 (97, 119)	99 (88, 111)	< 0.001
TG/HDL ratio	0.76 (0.46, 1.28)	0.87 (0.59, 1.45)	0.75 (0.44, 1.25)	< 0.001
CMI	0.46 (0.25, 0.82)	0.60 (0.37, 0.97)	0.44 (0.24, 0.79)	< 0.001
LAP	39 (21, 67)	57 (34, 84)	38 (20, 64)	< 0.001
TyG index	8.47 (8.03, 8.94)	8.69 (8.22, 9.08)	8.45 (8.00, 8.91)	< 0.001

Table 1. Demographic and baseline characteristics of the gallstones group versus the no gallstones group. Median for continuous variables; N (%) for categorical variables. GED, General equivalency diploma; PIR, Ratio of household income to poverty; BMI, Body mass index; TG, Triglyceride; HDL, High density lipoprotein cholesterol; CMI, Cardiometabolic index; LAP, Lipid accumulation products; TyG index, Triglyceride-glucose index.

or higher education, and those who drank alcohol (all *P*-values were below 0.05). Interestingly, interaction tests revealed a significant interaction effect for gender (*P* for interaction = 0.046). In contrast, no statistically significant associations were found in the subgroups regardless of whether alcohol was consumed or not, or whether diabetes was present.

Sensitivity analyses

To confirm the stability of the findings, sensitivity analyses were performed and the results are shown in Table 4. CMI was further converted from a continuous variable to quartiles and tested for trend. The results showed that in Model 4, which fully adjusted for all covariates, the prevalence of GS increased by 91% (OR = 1.91; 95% CI 1.25–2.98) in participants with the highest quartile of CMI, using the lowest quartile of CMI as the reference group, with a statistically significant effect of the test for trend (*P* for trend = 0.013). Furthermore, we performed supplementary analyses employing propensity score matching with a 1:1 matching ratio, utilizing gender, age, and ethnicity as matching variables. As demonstrated in Supplementary Table 1, there was an observed 88% increase in the prevalence of GS among individuals with high CMI compared to those with low CMI following matching (OR = 1.88; *P* < 0.001).

RCS curve fitting analysis

The RCS smoothing curve fitting is quite intuitive and can be visualized through adaptable modeling, as depicted in Fig. 3. Subfigures 3 A through 3D show the dose-response relationship between CMI, TG/HDL, LAP, TyG changes, and GS, respectively. The results showed a statistically significant nonlinear positive correlation between CMI, LAP, and GS (*P*-overall < 0.05), with the nonlinear component not dominating (*P*-nonlinear > 0.05). In contrast, the linear positive correlation between TG/HDL, TyG index, and GS was higher (*P*- overall > 0.05).

The mediating role of diabetes

Mediation analyses investigated whether and to what extent diabetes mediated the effect of CMI on GS. Figure 4 visually illustrates the pathways and patterns of mediation analyses. In terms of the overall population, all three effects (including total, direct, and indirect effects) were significant (*P* < 0.01), suggesting that diabetes mediated the relationship to some extent and that the mediating proportion was as high as 15.1%. Interestingly, the mediating effect was not significant in the male group, whereas it remained significant in the female group. The results of the mediation analyses are summarized in Table 5.

Discussion

This study provides a new perspective on the mediating role of diabetes between CMI and GS, and, at the same time, cross-sectionally compares the predictive ability of several similar metrics (LAP, TG/HDL, TyG) for GS. Through cross-sectional analyses of 3,395 adult participants, a significant association was observed between high levels of CMI and the GS population, with diabetes playing a substantial role in mediating this relationship. Furthermore, regression analyses from Model 2 to Model 4 revealed that CMI remained independently associated with GS even after controlling for various potential confounding factors. As part of the sensitivity analyses, subgroup stratification analyses and propensity score matching visually verified the stability of the positive correlation between the two, particularly in the subgroups of females, non-Hispanics of other races, those with high levels of education or attainment, and drinkers. In addition, mediation analyses suggested that diabetes may be a mediator and bridge to the development of GS in people with higher CMI. Overall, increased CMI raised the risk of GS to some extent, and this positive association was mediated in part by diabetes. This

Characteristic	Sex		*P* value
	Male, *N* = 1,667	Female, *N* = 1,728	
Age	52 (36, 65)	51 (35, 63)	0.079
Race, n (%)			0.117
Mexican American	221 (13.26%)	213 (12.33%)	
Non-Hispanic White	612 (36.71%)	579 (33.51%)	
Non-Hispanic Black	411 (24.66%)	456 (26.39%)	
Other Races	423 (25.37%)	480 (27.78%)	
Education level, n (%)			0.010
Grades 0–12	333 (19.98%)	280 (16.20%)	
High school graduate/GED	400 (24.00%)	409 (23.67%)	
Some college or above	934 (56.03%)	1,039 (60.13%)	
Marital status, n (%)			< 0.001
Married/Living with Partner	1,072 (64.31%)	938 (54.28%)	
Widowed/Divorced/Separated	287 (17.22%)	451 (26.10%)	
Unmarried	308 (18.48%)	339 (19.62%)	
PIR, n (%)			0.012
< 2	605 (36.29%)	711 (41.15%)	
≥ 2	855 (51.29%)	806 (46.64%)	
Unclear	207 (12.42%)	211 (12.21%)	
BMI (kg/m^2)			< 0.001
< 25	412 (24.72%)	458 (26.50%)	
25–30	609 (36.53%)	462 (26.74%)	
≥ 30	646 (38.75%)	808 (46.76%)	
Smoking, n (%)			< 0.001
Current smokers	372 (22.32%)	266 (15.39%)	
Former smokers	510 (30.59%)	334 (19.33%)	
Never smokers	785 (47.09%)	1,128 (65.28%)	
Alcohol consumption, n (%)			< 0.001
Yes	1,127 (67.61%)	764 (44.21%)	
No	540 (32.39%)	964 (55.79%)	
Hypertension, n (%)			0.172
Yes	773 (46.37%)	761 (44.04%)	
No	894 (53.63%)	967 (55.96%)	
Diabetes, n (%)			0.033
Yes	338 (20.28%)	301 (17.42%)	
No	1,329 (79.72%)	1,427 (82.58%)	
Asthma, n (%)			< 0.001
Yes	217 (13.02%)	328 (18.98%)	
No	1,450 (86.98%)	1,400 (81.02%)	
Coronary heart disease, n (%)			< 0.001
Yes	103 (6.18%)	42 (2.43%)	
No	1,564 (93.82%)	1,686 (97.57%)	
Liver disease, n (%)			0.304
Yes	90 (5.40%)	80 (4.63%)	
No	1,577 (94.60%)	1,648 (95.37%)	
Cancer, n (%)			0.206
Yes	164 (9.84%)	193 (11.17%)	
No	1,503 (90.16%)	1,535 (88.83%)	
Gallstones			< 0.001
Yes	103 (6.18%)	260 (15.05%)	
No	1,564 (93.82%)	1,468 (84.95%)	
Use of antihypertensive drugs			0.083
Yes	469 (28.13%)	533 (30.84%)	
No	1,198 (71.87%)	1,195 (69.16%)	
Use of lipid-lowering drugs			0.003
Yes	402 (24.12%)	344 (19.91%)	
Continued			

Characteristic	Sex		*P* value
	Male, *N* = 1,667	Female, *N* = 1,728	
No	1,265 (75.88%)	1,384 (80.09%)	
Protein intake (g)	84 (63, 110)	63 (49, 82)	< 0.001
Carbohydrate intake (g)	251 (183, 332)	198 (146, 257)	< 0.001
Total fat intake (g)	87 (63, 120)	67 (49, 91)	< 0.001
Water intake (g)	2,749 (2,065, 3,661)	2,340 (1,748, 3,013)	< 0.001
Total cholesterol (mg/dl)	177 (152, 206)	183 (159, 211)	< 0.001
Fasting glucose (mg/dl)	105 (98, 117)	101 (94, 112)	< 0.001
Height (cm)	174 (169, 179)	160 (156, 165)	< 0.001
Waist circumference (cm)	101 (91, 112)	98 (87, 111)	< 0.001
TG/HDL ratio	0.87 (0.51, 1.46)	0.67 (0.40, 1.10)	< 0.001
CMI	0.51 (0.28, 0.92)	0.42 (0.23, 0.73)	< 0.001
LAP	39 (21, 67)	39 (21, 67)	0.902
TyG index	8.53 (8.11, 9.01)	8.39 (7.97, 8.86)	< 0.001

Table 2. Baseline characteristics of participants grouped according to sex. Median for continuous variables; N (%) for categorical variables. GED, General equivalency diploma; PIR, Ratio of household income to poverty; BMI, Body mass index; TG, Triglyceride; HDL, High density lipoprotein cholesterol; CMI, Cardiometabolic index; LAP, Lipid accumulation products; TyG index, Triglyceride-glucose index.

Exposure	OR (95%CI); *P* value			
	Model 1	Model 2	Model 3	Model 4
Log (TG/HDL)	1.38 (1.20, 1.58); <0.001	1.48 (1.26, 1.73); <0.001	1.20 (1.00, 1.44); 0.044	1.20 (1.00, 1.44); 0.052
Log (CMI)	1.52 (1.33, 1.73); <0.001	1.58 (1.37, 1.82); <0.001	1.23 (1.03, 1.46); 0.020	1.23 (1.03, 1.46); 0.024
Log (LAP)	1.88 (1.64, 2.16); <0.001	1.79 (1.54, 2.08); <0.001	1.38 (1.12, 1.70); 0.003	1.37 (1.11, 1.69); 0.003
TyG index	1.53 (1.32, 1.78); <0.001	1.47 (1.24, 1.73); <0.001	1.16 (0.94, 1.44); 0.156	1.16 (0.94, 1.44); 0.166

Table 3. Association between CMI, TG/HDL ratio, LAP, TyG index and gallstones. OR: odds ratio; 95% Cl: 95% confidence interval. Model 1: no adjustment for covariates. Model 2: adjusted for sex, age, and race. Model 3: adjusted for sex, age, race, education level, marital status, PIR, BMI, hypertension, diabetes mellitus, asthma, coronary heart disease, liver disease, cancer, smoking, alcohol use, total cholesterol, use of antihypertensive medications, and use of lipid-lowering medications. Model 4: adjusted for sex, age, race, education level, marital status, PIR, BMI, hypertension, diabetes mellitus, asthma, coronary heart disease, liver disease, cancer, smoking, alcohol use, total cholesterol, use of antihypertensive medications, use of lipid-lowering medications, protein intake, carbohydrate intake, total fat intake, and water intake.

finding provides new information on the metabolic risk factors for GS and deepens our understanding of the intricate interactions between diabetes and dyslipidaemic diseases.

In recent years, the interaction of cardiovascular and metabolic diseases with GS has received extensive attention from scholars. In an 8-year prospective cohort study conducted by Wirth et al. in Europe, involving 46,486 participants, it was demonstrated that the risk of cardiovascular disease was 24% higher in individuals with GS compared to those without GS[11]. Following and meta-analyzing 270,000 participants from the United States, Zheng and colleagues found that subjects with GS have an increased risk of coronary atherosclerotic heart disease by 17%. Interestingly, this correlation was stronger in healthy groups without obesity, diabetes, and hypertension. Furthermore, a meta-analysis incorporating data from seven cohorts demonstrated that the random-effects model pooled risk ratio for individuals with GS was 1.23, irrespective of traditional risk factors, in comparison to individuals without GS[35]. Ratheesh et al. conducted a comprehensive national population-based cohort study to investigate the association between GS and diabetic individuals both before and following the initiation of insulin therapy. According to the study, insulin-treated diabetic patients experienced a 46% increase in GS incidence compared to those without insulin treatment[36]. The aforementioned findings underscore the multiple common pathological and physiological underpinnings between GS and cardiovascular diseases, and it has been challenging to separate these common risk factors from potential causally linked pathogenesis. However, a potential association between CMI and GS has not been reported in the literature, and it remains uncertain whether diabetes is involved in and regulates the link between CMI and GS pathogenesis.

CMI represents a novel metabolic indicator that is developed through the amalgamation of obesity parameters and lipid levels, which is simple and cost-effective. CMI has a high potential clinical value in the prediction of cardiovascular and metabolic-related diseases. Previous epidemiological studies with different target populations have reported an association between CMI and various systemic diseases. Tang et al.[37] conducted a retrospective analysis of 2,243 patients with type 2 diabetes mellitus and found a significant positive correlation between CMI

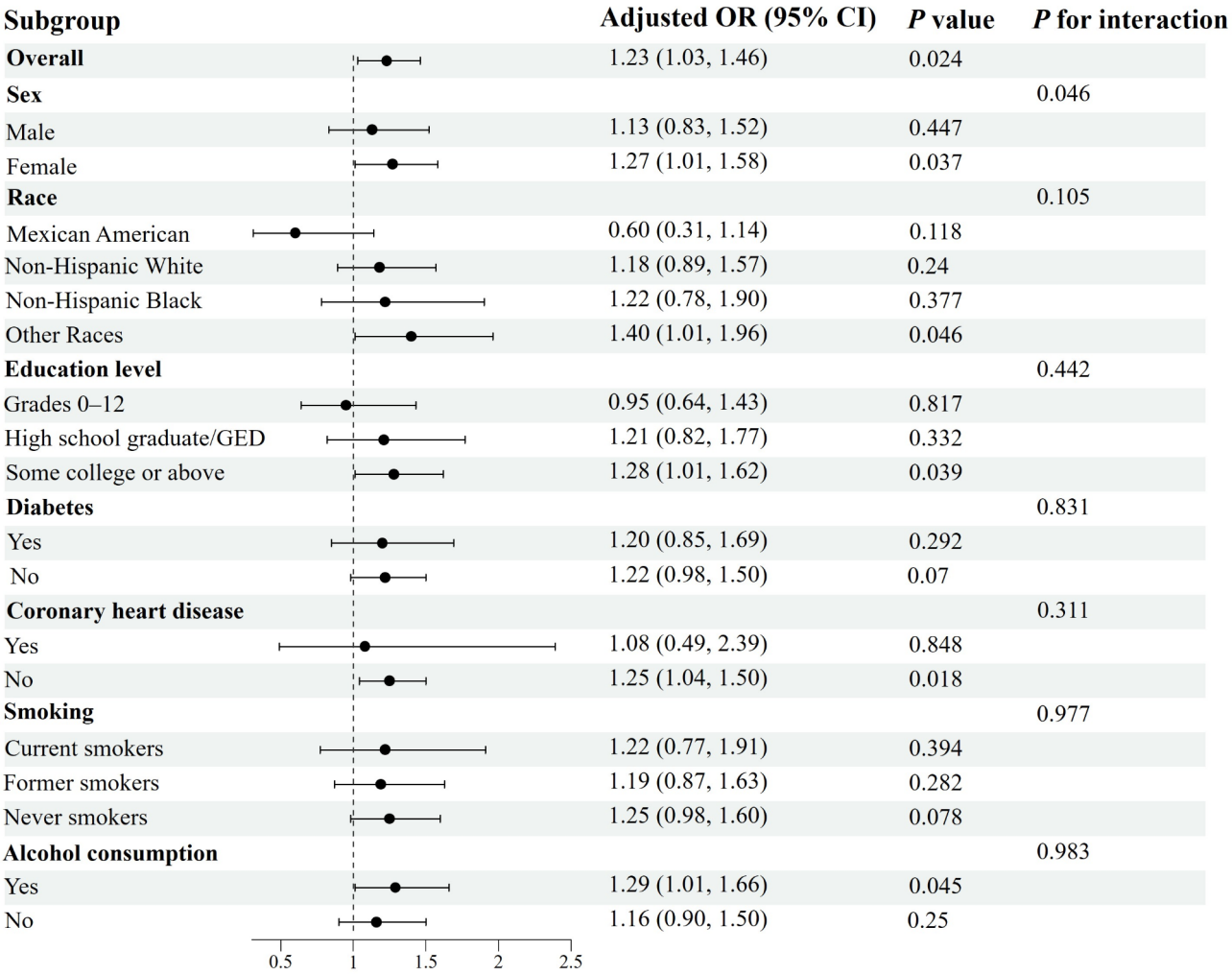

Fig. 2. Subgroup analyses and interaction tests of the relationship between CMI and GS. Notes: Adjusted for all covariates except effect modifier.

CMI	OR (95%CI); *P* value			
	Model 1	Model 2	Model 3	Model 4
Q1 [0.0273,0.254)	Reference	Reference	Reference	Reference
Q2 [0.254,0.461)	2.34 (1.61, 3.46); <0.001	2.27 (1.55, 3.39); <0.001	1.68 (1.12, 2.54); 0.012	1.68 (1.13, 2.55); 0.012
Q3 [0.461,0.818)	2.78 (1.93, 4.08); <0.001	2.60 (1.78, 3.85); <0.001	1.70 (1.13, 2.59); 0.012	1.69 (1.12, 2.59); 0.013
Q4 [0.818,24.5]	3.47 (2.43, 5.05); <0.001	3.43 (2.36, 5.07); <0.001	1.91 (1.25, 2.96); 0.003	1.91 (1.25, 2.98); 0.003
P for trend	<0.001	<0.001	0.012	0.013

Table 4. Logistic regression analysis of GS prevalence based on CMI quartiles. OR: odds ratio; 95% Cl: 95% confidence interval. Model 1: no adjustment for covariates. Model 2: adjusted for sex, age, and race. Model 3: adjusted for sex, age, race, education level, marital status, PIR, BMI, hypertension, diabetes mellitus, asthma, coronary heart disease, liver disease, cancer, smoking, alcohol use, total cholesterol, use of antihypertensive medications, and use of lipid-lowering medications. Model 4: adjusted for sex, age, race, education level, marital status, PIR, BMI, hypertension, diabetes mellitus, asthma, coronary heart disease, liver disease, cancer, smoking, alcohol use, total cholesterol, use of antihypertensive medications, use of lipid-lowering medications, protein intake, carbohydrate intake, total fat intake, and water intake.

and atherosclerosis and concluded that CMI is an independent risk factor for atherosclerosis in patients with type 2 diabetes mellitus and is a key marker for predicting atherosclerosis risk. Zhou and colleagues surveyed 3,794 participants and found that elevated CMI levels increased the risk of depression[38]. Zha et al.[39] conducted a retrospective cohort study involving over fifteen thousand Japanese adults to investigate the correlation

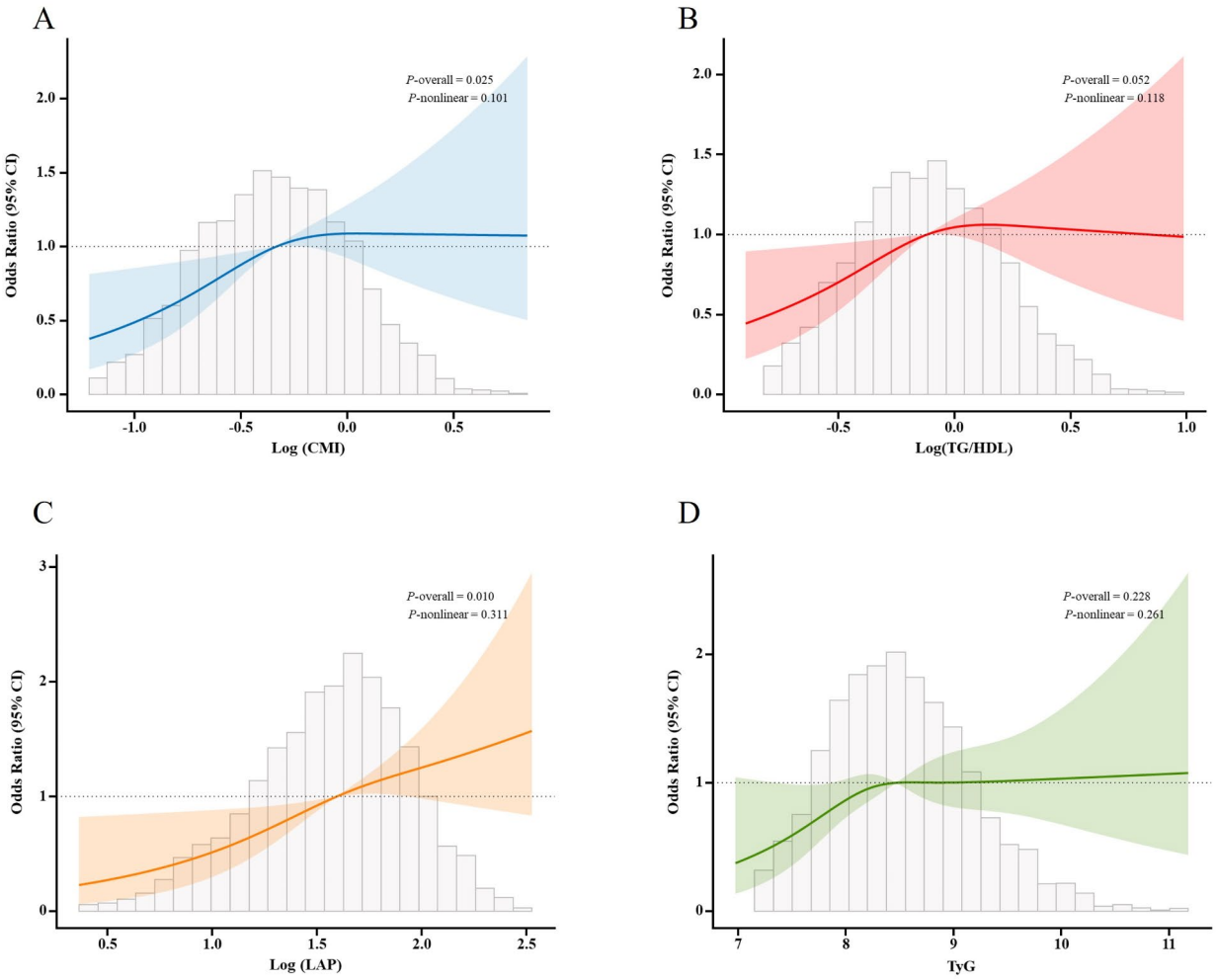

Fig. 3. RCS curve fitting between CMI and GS. Solid lines represent smooth curve fits between variables. Shaded bands represent 95% confidence intervals from the fit. Subfigure 3 (**A**): dose-response relationship between CMI and GS; Subfigure 3(**B**): dose-response relationship between TG/HDL and GS; Subfigure 3(**C**): dose-response relationship between LAP and GS; Subfigure 3(**D**): dose-response relationship between TyG and GS.

between CMI and incident diabetes. Their findings indicated a positive association between elevated levels of CMI at baseline and the risk of developing diabetes. A growing number of emerging clinical epidemiological investigations have demonstrated the unique benefits of CMI in the assessment of cardiovascular disease and other metabolic disorders.

In contemporary medical practice, CMI is garnering heightened attention from healthcare professionals as a novel evaluative tool. Clinical practices stand to benefit from the integration of CMI monitoring alongside the co-management of GS risk factors. For instance, conducting comprehensive metabolic assessments—including evaluations of blood glucose, insulin levels, and lipid profiles—on patients exhibiting abnormal CMI values can facilitate the early detection of prediabetes or metabolic syndrome[40]. Moreover, by considering the patient's lifestyle and familial medical history, clinicians can devise personalized management plans aimed at mitigating the risk of GS development. Specific guidelines should encompass regular CMI assessments, the identification of outliers, and the implementation of suitable interventions. Prioritizing the management of metabolic dysfunctions, particularly dyslipidemia and insulin resistance, is essential as both a preventive and therapeutic strategy. Dietary modifications are advised for patients with elevated CMI, such as increasing the consumption of foods rich in dietary fiber (e.g., whole grains, vegetables, and fruits) to lower cholesterol levels and diminish the risk of GS formation, while reducing the intake of high-sugar and high-fat foods to alleviate insulin resistance[41]. Secondly, increased physical activity with moderate-intensity aerobic exercise can improve insulin sensitivity, lower blood lipid levels, and improve gallbladder function. Finally, clinicians should also regularly follow up with patients with abnormal metabolic function. This will not only reduce the incidence of GS but also improve the overall cardiometabolic health of the at-risk population.

The present research is pioneering in examining the connection between CMI and GS with authoritative published data from a substantial sample size, analyzing diabetes as a potential mediator and link. The specific mechanism of how elevated CMI influences the pathogenesis and advancement of GS through diabetes mellitus

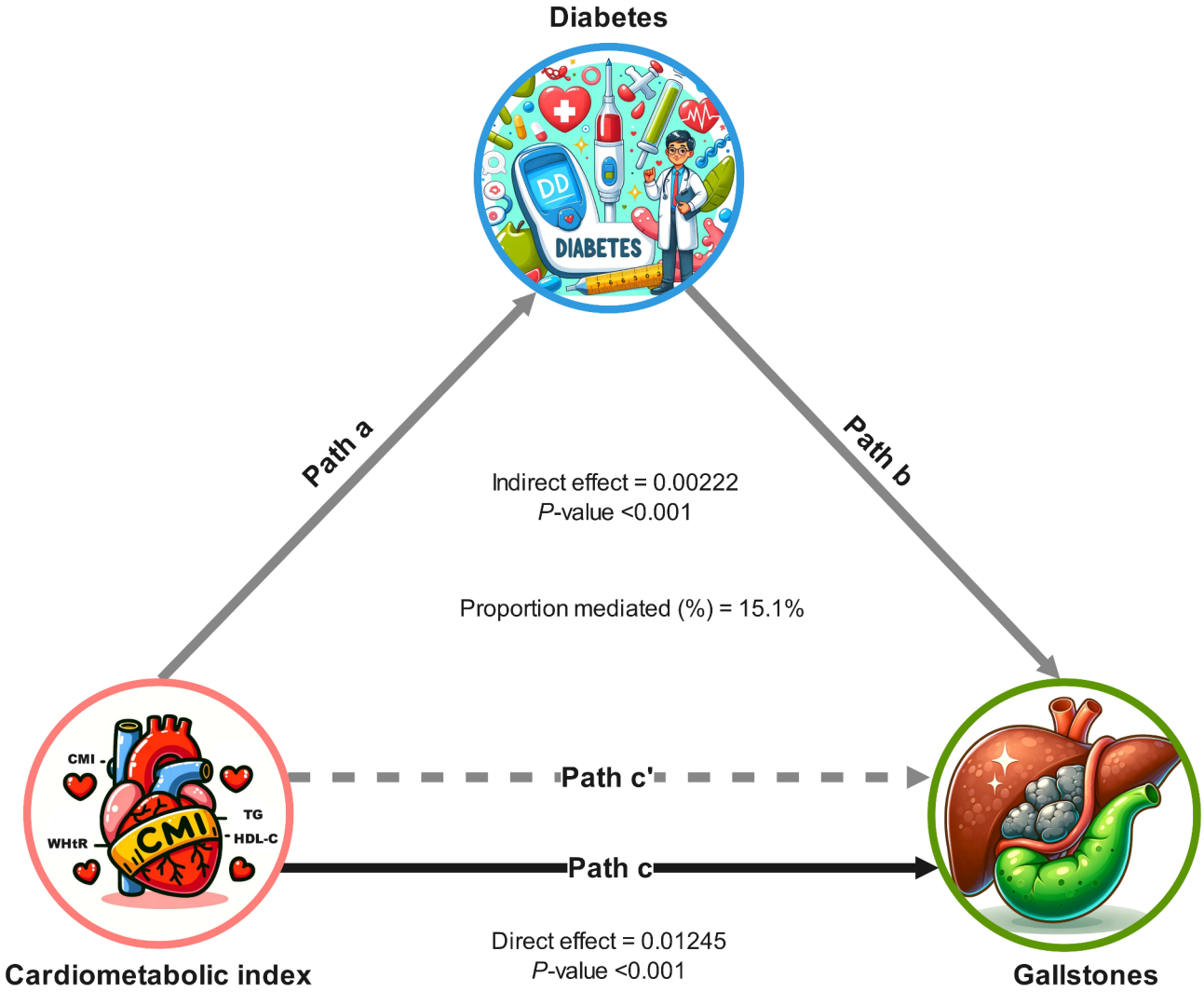

Fig. 4. Modal pathways for mediated analyses. CMI is defined as the independent variable; GS is the outcome variable; and diabetes is the mediating variable. Path a represents the regression coefficient for the relationship between CMI and diabetes. Path b represents the regression coefficient of the relationship between diabetes and GS. Path c represents the simple total effect of CMI on GS. Path c' represents the direct effect of CMI on GS after controlling for diabetes.

Independent variable	Mediator	Group	Coefficient (95% CI); *P* value			Proportion mediated
			Total effect	Indirect effect	Direct effect	
CMI	Diabetes	Overall	0.01466 (0.00620, 0.02756); < 0.001	0.00222 (0.00069, 0.00558); < 0.001	0.01245 (0.00454, 0.02356); < 0.001	15.1%
		Male	0.00434 (-0.00902, 0.01114); 0.540	0.00094 (-0.00072, 0.00338); 0.280	0.00340 (-0.00943, 0.01073); 0.580	21.7%
		Female	0.06396 (0.03220, 0.09252); < 0.001	0.00706 (0.00089, 0.01341); 0.020	0.05691 (0.02491, 0.08766); < 0.001	11.0%

Table 5. Mediation effect of diabetes for the association between CMI and GS. In causal mediation analyses, CMI is treated as the independent variable, diabetes is treated as the mediator variable, and GS is treated as the outcome variable.

is unknown. Visceral obesity, insulin resistance, and dysregulated levels of lipid metabolism may be responsible for assessing the vulnerability of diabetic patients to GS. Elevated free fatty acids due to disorders of lipid metabolism may stimulate fatty acid oxidation and peroxidation, resulting in the production of oxidative free radicals, which may exacerbate pancreatic islet cell dysfunction. Secondly, hyperesterolaemia in diabetic patients is usually accompanied by low HDL-C levels, which play an important role in reverse cholesterol transport, and

this can lead to a reduced ability of the liver to remove cholesterol, which further exacerbates the accumulation of cholesterol in the bile[42,43]. Additionally, reduced levels of HDL-C may impair β-cell function, thereby impacting insulin secretion. In individuals with high WHtR, there is a reduction in the number and binding efficiency of insulin receptors on target tissues, resulting in impaired glucose processing[44,45]. Furthermore, adipocytes in hyperlipidemic states disrupt insulin signaling through various pathways, including activating pro-inflammatory cytokines, elevated levels of free fatty acids, and increased lipotoxicity. These alterations contribute to the onset of insulin resistance, which ultimately affects diabetes development[46–48].

The association between diabetes mellitus and GS is biologically plausible, given that diabetes mellitus influences several critical processes involved in GS formation, including altered cystic motility, changes in bile composition, and insulin resistance. Autonomic neuropathy is frequently observed in diabetic patients, particularly those with chronic poor glycemic control. This neuropathy impairs the innervation of the gallbladder, leading to a reduced response to stimuli. The contraction of the gallbladder is primarily regulated by the vagus nerve, and diabetes-induced vagal dysfunction results in diminished gallbladder contractility and prolonged bile retention, thereby facilitating the formation of cholesterol crystals. Furthermore, a hyperglycemic state may directly impair the function of gallbladder smooth muscle cells. Chronic hyperglycemia induces increased oxidative stress and an enhanced inflammatory response, which subsequently compromise the structure and function of gallbladder smooth muscle. This damage may further exacerbate gallbladder peristalsis dysfunction. In diabetic patients, dysregulated glucose metabolism, often accompanied by insulin resistance, impairs gallbladder smooth muscle function due to microvascular damage, ultimately leading to impaired gallbladder emptying[49–51]. In addition, changes in bile composition may be one of the important mechanisms for GS formation in diabetic patients. In diabetic patients, the synthesis and secretion of bile acids may be reduced due to altered liver function. Inadequate bile acid secretion decreases cholesterol solubility and increases the risk of cholesterol crystal formation[52,53]. Insulin resistance is often accompanied by a chronic low-grade inflammatory state, which may promote GS formation through several mechanisms. Chronic inflammation leads to structural and functional changes in the gallbladder wall, such as thickening and reduced contractile function. In addition, inflammatory factors may affect the composition of bile, indirectly promoting GS formation.

The findings of this study offer substantial evidence for a correlation between the cardiovascular marker CMI and GS, with diabetes mellitus serving as a partial mediator in the relationship. As WHtR and lipid parameters can be obtained through routine physical examinations and blood tests, the assessment of CMI in clinical practice is feasible. These results imply that healthcare providers should not neglect blood glucose levels while regulating lipids in patients with high CMI levels, and that co-management of the two may be a proven way to reduce GS risk.

Strengths and limitations

Several noteworthy strengths of this study should be highlighted. Primarily, it stands as the original study to comprehensively assess the correlation between CMI levels and the prevalence of GS within a U.S. demographic, uncovering a potential mediating influence of diabetes and enriching the body of existing literature. Secondly, the large sample size sampling methodology and sensitivity analyses based on U.S. adults add to the persuasiveness and generalisability of the findings. Finally, this study enhances the understanding of CMI as a viable predictor of individuals susceptible to GS, highlighting the importance of cardiovascular markers and lipid metabolism disorders in the pathogenesis of GS. However, there are some limitations to our study. Due to the homogeneous nature of the NHANES database survey method, the diagnosis of GS in this study was obtained based on subjects' questionnaire interviews and self-reports, which may introduce recall bias, thus affecting the accuracy of the diagnosis. Additionally, due to its observational cross-sectional design, this study is limited in its ability to establish causal relationships, highlighting the necessity for future prospective cohort studies to confirm its findings. Finally, despite adjusting for many covariates based on previous studies and clinical experience, residual or omitted confounders may affect the associations observed in the results.

Conclusion

In summary, this large-scale original investigation suggests that elevated CMI is strongly associated with an increased risk of GS and that diabetes plays a key mediating role in the pathogenesis of both. This indicates that healthcare professionals should not neglect blood glucose levels while addressing dyslipidemia and that co-management of the two may be a proven approach to reducing GS risk.

Data availability

The data utilized in this study were sourced from NHANES, with the original dataset accessible through the corresponding author upon inquiry.

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Author contributions

Y.Z., X.Q.G., H.L.: conception and design, information provision, software, manuscript writing. H.L., Y.L.W., D.W.W.: interpretation, drawing, review, data analysis. D.W.W., J.W.: review, proofreading, financial support. All authors reviewed and agreed to the final manuscript for publication.

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Declarations

Competing interests

The authors declare no competing interests.

Ethical approval

The survey protocols were approved by the Ethics Review Board of the NCHS, and all participants provided written informed consent prior to their involvement in the study.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-025-93908-3.

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