Diabetes, Metabolic Syndrome and Obesity

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ORIGINAL RESEARCH

Assessment of the Association Between Cardiac Metabolic Markers and Carotid Atherosclerosis, and the Role of Insulin Resistance

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Background: Obesity is a growing global health concern. The cardiometabolic index (CMI), a novel marker of fat distribution, has been proposed as a potential risk indicator. This study investigates the association between CMI and carotid atherosclerosis (CAS), as assessed by carotid intima-media thickness (cIMT), and explores whether insulin resistance (IR) mediates this relationship.

Methods: This cross-sectional study enrolled type 2 diabetes mellitus (T2DM) patients hospitalized at Cangzhou People's Hospital between September 2024 and March 2025. Logistic regression models, restricted cubic spline (RCS) analysis, and subgroup analysis were used to examine the CMI-CAS relationship. The predictive ability of CMI was assessed using receiver operating characteristic (ROC) curves, and its incremental value beyond traditional risk factors was evaluated by integrated discrimination improvement (IDI) and net reclassification improvement (NRI). Mediation analysis assessed the role of IR.

Results: After adjustment, higher CMI was significantly associated with increased odds of CAS (OR = 1.48, 95% CI: 1.21–1.81, $P < 0.001$). RCS analysis showed a nonlinear relationship between CMI and CAS. ROC analysis indicated moderate predictive power (AUC = 0.65, 95% CI: 0.61–0.68). Including CMI improved prediction with an IDI of 0.04 ($P < 0.001$) and an NRI of 0.26 ($P < 0.001$). Subgroup analysis revealed a significant interaction with T2DM duration ($P = 0.013$). Mediation analysis showed that metabolic score for insulin resistance (METS-IR) partially mediated the CMI-CAS relationship, explaining 12.92% of the total effect.

Conclusion: Elevated CMI is independently associated with higher risk of CAS in T2DM patients, and insulin resistance partially mediates this relationship. CMI may be a valuable marker for early vascular risk stratification in diabetic populations.

Keywords: atherosclerosis, carotid intima-media thickness, cardiometabolic index, obesity, insulin resistance

Introduction

The global prevalence of obesity has become a significant public health issue. A study by Afshin A et al (2017) indicates that the prevalence of obesity has doubled since 1980 in over 70 countries and continues to rise in most other nations.[1] Obesity is not just a simple issue of weight gain; it is considered a complex, multi-system disease associated with various comorbidities, including type 2 diabetes mellitus (T2DM), cardiovascular diseases (CVD), chronic kidney disease, certain types of cancer, and more.[2,3] The body mass index (BMI) is the most widely used indicator of obesity. Extensive evidence shows that BMI is associated with hypertension, T2DM, asthma, carotid intima-media thickness (cIMT), metabolic syndrome, and CVD risk.[4–7] However, when assessing body fat distribution, BMI measurements cannot accurately differentiate between visceral fat and subcutaneous fat, and anatomical fat distribution is considered important because it produces different metabolic effects.[8] The Cardiometabolic index (CMI) is a relatively new obesity index proposed by Ichiro Wakabayashi in 2015, which combines clinical measurements of triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and waist-to-height ratio (WHtR) to accurately reflect lipid levels and the degree of obesity.[9] Evidence suggests that CMI is closely related to several diseases, including metabolic syndrome, non-alcoholic fatty liver disease, liver fibrosis, chronic kidney disease, heart failure, hypertension, stroke, and peripheral artery disease.[10–16]

Received: 8 May 2025
Accepted: 8 August 2025
Published: 15 August 2025

T2DM is a serious chronic disease characterized by elevated blood glucose levels due to β-cell dysfunction, which affects insulin action.[17] Insulin resistance (IR) is a common phenomenon in diabetic patients, not only affecting blood glucose regulation but also being closely related to the occurrence of various complications. Studies show that IR affects not only metabolic function but also vascular function, thus increasing the risk of CVD.[18] In T2DM patients, IR is closely associated with cardiovascular autonomic dysfunction, which further exacerbates the development of CVD.[19] Additionally, IR is associated with inflammatory responses, which may increase CVD risk by affecting endothelial function and promoting the development of atherosclerosis.[20] Individuals with higher CMI values tend to have a higher risk of IR, which may be due to the close relationship between CMI and dyslipidemia as well as abdominal obesity. In a study based on the National Health and Nutrition Examination Survey (NHANES) data, researchers found a nonlinear relationship between CMI, IR, impaired fasting glucose, and T2DM.[21]

cIMT is a sensitive and non-invasive method widely used to assess subclinical atherosclerosis and is considered an effective predictor of cardiovascular events. However, the relationship between CMI and carotid atherosclerosis (CAS) in T2DM patients has not been thoroughly studied. This study aims to explore the relationship between CMI and CAS in T2DM patients and further elucidate whether IR indicators play a potential role in mediating these associations. Through this study, we hope to provide new theoretical evidence for early screening and intervention of atherosclerosis in T2DM patients and offer scientific support for the early diagnosis and treatment of CVD.

Methods

Study Population

This study consecutively selected 1190 patients with type 2 diabetes (T2DM) who were admitted to Cangzhou People's Hospital, China, between September 2024 and March 2025. After applying the exclusion criteria, a total of 961 patients were included in the study. Exclusion criteria included age < 18 years; no carotid ultrasound examination; lack of necessary data related to CMI, Metabolic score for insulin resistance (METS-IR), and Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) such as BMI, fasting TG, HDL-C, fasting plasma glucose (FPG), and fasting insulin (FINS) levels. This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Cangzhou People's Hospital (K2024-094-01). All participants provided written informed consent.

Data Collection

A standardized questionnaire survey was conducted by trained staff to collect demographic characteristics (such as age, gender), lifestyle risk factors (such as smoking), and medical history data (such as hypertension and T2DM duration). The questionnaire used in this study was validated for reliability and internal consistency before use. Its construct validity was also assessed using confirmatory factor analysis to ensure it accurately measured the intended variables. Laboratory measurements included total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), TG, HDL-C, FPG, FINS, serum creatinine (Scr), serum uric acid (SUA), estimated glomerular filtration rate (eGFR), and glycated hemoglobin (HbA1c). Additionally, BMI and WHtR were measured. BMI = weight (kg) / height (m^2). WHtR = waist circumference (cm) / height (cm). Other calculated indices are as follows:

$\mathrm{CMI} = \mathrm{TG}(\mathrm{mmol/L})/\mathrm{HDL}-\mathrm{C}(\mathrm{mmol/L})\times\ \mathrm{WHtR}$;[9]

$\mathrm{METS}-\mathrm{IR} = \mathrm{Ln}[2\times\ \mathrm{FPG}(\mathrm{mg/dL})+\mathrm{TG}(\mathrm{mg/dL})]\times\ \mathrm{BMI}/\mathrm{Ln}\ \mathrm{HDL}-\mathrm{C}(\mathrm{mg/dL})$;[22]

$\mathrm{HOMA}-\mathrm{IR} = [\mathrm{FPG}(\mathrm{mmol/L})\times\ \mathrm{FINS}(\mu\ \mathrm{U/mL})]/22.5$.[23]

Ultrasound Measurements

Each participant underwent carotid Doppler ultrasound. The carotid ultrasound was performed by two experienced sonographers according to a standard protocol. All participants were examined in a supine position with the head at a 45-degree angle to the scanning site. The sonographers examined and recorded the bilateral common carotid artery, internal carotid artery, external carotid artery, subclavian artery, and vertebral arteries. cIMT measurements were taken using a 10.0 MHz linear transducer. According to the Mannheim consensus, the area of interest for cIMT measurement was the distal common carotid artery region on both sides of the carotid bifurcation. The diagnosis of CAS is based on cIMT thickening, specifically defined as a left/right cIMT ≥1.0 mm.[24]

Statistical Analysis

The study population was stratified by CMI quartiles. Descriptive statistical analysis was first conducted. Since the measurement data were not normally distributed, continuous variables were described using the median (M) and interquartile range (IQR), while categorical variables were presented as frequencies (n) and percentages (%). Comparisons between the four groups for continuous variables were performed using the Kruskal–Wallis *H*-test, and categorical variables were compared using the chi-square test. Logistic regression models were then used to estimate the odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) to evaluate the relationship between CMI and CAS. Model 1 was univariate logistic regression, Model 2 adjusted for age, gender, hypertension, smoking history, and T2DM duration. Model 3 further adjusted for Scr, SUA, HDL-C, LDL-C, FPG, HbA1c, eGFR, METS-IR, and HOMA-IR. To avoid multicollinearity issues, highly correlated variables (such as BMI, TC, TG, WHtR, and FINS) were not included in Model 3. The restricted cubic spline (RCS) regression model was used to further explore the nonlinear relationship between CMI and CAS. The receiver operating characteristic (ROC) curve and its area under the curve (AUC) were used to evaluate the ability of CMI to predict CAS and its improvement over traditional risk factors (age, hypertension, smoking history, T2DM duration, SUA, and LDL-C). The improvement was assessed using the integrated discrimination improvement (IDI) and net reclassification improvement (NRI) indices. Subgroup analyses were performed based on age, gender, smoking status, hypertension, BMI, and T2DM duration. Additionally, this study assessed the mediating effect of METS-IR on the relationship between CMI and CAS, with the mediation analysis adjusted based on Model 3. All statistical analyses were performed using R software (version 4.1.3). Statistical significance was defined as a *P*-value < 0.05.

Results

Baseline Characteristics of Participants According to CMI Quartiles

Table 1 shows the characteristics of participants according to CMI quartiles. In the higher CMI groups, the proportion of females was higher, and the levels of BMI, FPG, HbA1c, FINS, SCr, SUA, eGFR, TC, TG, LDL-C, METS-IR, and HOMA-IR were significantly elevated. Additionally, the prevalence of cIMT was higher, while HDL-C levels were lower (all *P* < 0.05).

Table 1 Baseline Characteristics of Participants According to CMI Quartiles

Variables	Overall (N=961)	Q1 (<0.50)	Q2 (0.50–0.86)	Q3 (0.86–1.47)	Q4 (≥1.47)	*P*-Value
Age [years, M (IQR)]	53.00 (46.00–61.00)	53.00 (43.00–61.00)	53.00 (45.00–61.00)	53.00 (44.50–62.00)	54.00 (48.00–61.00)	0.275
Gender[n (%)]						0.003
Female	363 (37.77%)	77 (31.95%)	79 (32.92%)	95 (39.58%)	112 (46.67%)	
Male	598 (62.23%)	164 (68.05%)	161 (67.08%)	145 (60.42%)	128 (53.33%)	
BMI [kg/m^2, M (IQR)]	26.96 (24.89–29.41)	25.72 (23.99–28.32)	26.77 (24.69–28.73)	27.33 (25.28–30.05)	28.30 (25.87–30.57)	<0.001
WHtR[M (IQR)]	0.53 (0.49–0.57)	0.51 (0.47–0.55)	0.52 (0.49–0.56)	0.53 (0.49–0.58)	0.55 (0.51–0.59)	<0.001
Smoking History [n (%)]						0.087
No	746 (77.63%)	178 (73.86%)	188 (78.33%)	181 (75.42%)	199 (82.92%)	
Yes	215 (22.37%)	63 (26.14%)	52 (21.67%)	59 (24.58%)	41 (17.08%)	
Hypertension [n (%)]						0.956
No	497 (51.72%)	124 (51.45%)	127 (52.92%)	125 (52.08%)	121 (50.42%)	
Yes	464 (48.28%)	117 (48.55%)	113 (47.08%)	115 (47.92%)	119 (49.58%)	
T2DM Duration [n (%)]						0.252
<1 year	190 (19.77%)	37 (15.35%)	52 (21.67%)	52 (21.67%)	49 (20.42%)	
1-5 years	226 (23.52%)	69 (28.63%)	61.00 (25.42%)	50 (20.83%)	46 (19.17%)	
5-10 years	194 (20.19%)	45 (18.67%)	47.00 (19.58%)	53 (22.08%)	49 (20.42%)	
≥10 years	351 (36.52%)	90 (37.34%)	80 (33.33%)	85 (35.42%)	96 (40.00%)	

(*Continued*)

Table 1 (Continued).

Variables	Overall (N=961)	Q1 (<0.50)	Q2 (0.50–0.86)	Q3 (0.86–1.47)	Q4 (≥1.47)	*P*-Value
FPG [mg/dl, M (IQR)]	159.66 (126.68–214.44)	142.18 (115.15–192.45)	158.94 (121.82–213.00)	160.47 (131.82–206.96)	177.95 (142.36–235.25)	<0.001
HbA1c [%, M (IQR)]	8.50 (7.20–10.20)	8.00 (7.00–10.00)	8.50 (7.20–10.00)	8.50 (7.20–9.90)	9.20 (7.30–10.60)	0.006
FINS [uU/mL, M (IQR)]	9.00 (5.60–14.50)	6.50 (3.50–10.20)	8.60 (4.95–13.55)	10.05 (6.70–15.05)	11.30 (8.10–17.60)	<0.001
SCr [umol/L, M (IQR)]	63.00 (53.00–72.00)	60.00 (51.00–71.00)	60.00 (51.00–72.00)	65.00 (54.00–72.00)	65.50 (55.50–73.00)	0.001
SUA [umol/L, M (IQR)]	293.00 (242.00–358.00)	256.00 (207.00–302.00)	284.00 (239.50–343.00)	304.00 (264.00–366.00)	333.50 (284.00–402.00)	<0.001
eGFR [mL/min, M (IQR)]	110.20 (88.56–133.72)	101.55 (81.72–121.20)	109.65 (89.80–130.46)	109.00 (89.74–134.12)	123.14 (98.22–147.68)	<0.001
TC [mg/dl, M (IQR)]	179.43 (153.13–211.14)	170.92 (145.40–199.15)	176.15 (146.37–204.95)	180.59 (152.75–212.30)	193.74 (167.83–220.81)	<0.001
TG [mg/dl, M (IQR)]	148.76 (98.28–224.02)	81.46 (67.29–93.86)	123.08 (106.25–142.56)	180.64 (155.40–206.76)	322.31 (243.06–462.65)	<0.001
HDL-C [mg/dl, M (IQR)]	40.60 (34.80–49.11)	53.36 (45.24–60.71)	41.77 (37.12–47.56)	38.67 (34.42–43.12)	33.64 (30.36–38.67)	<0.001
LDL-C [mg/dl, M (IQR)]	107.89 (82.75–133.80)	102.09 (79.47–127.61)	104.41 (81.21–130.32)	113.69 (87.01–136.12)	114.85 (86.82–138.64)	0.004
METS-IR [M (IQR)]	45.03 (40.19–51.32)	39.03 (34.89–42.70)	43.18 (39.96–46.84)	47.14 (43.19–52.46)	52.50 (47.26–57.84)	<0.001
HOMA-IR [M (IQR)]	3.75 (2.13–6.39)	2.29 (1.23–4.57)	3.14 (1.97–6.02)	4.13 (2.75–6.69)	5.18 (3.29–9.27)	<0.001
cIMT [n (%)]						<0.001
No	459 (47.76%)	166 (68.88%)	111 (46.25%)	103 (42.92%)	79 (32.92%)	
Yes	502 (52.24%)	75 (31.12%)	129 (53.75%)	137 (57.08%)	161 (67.08%)	

Abbreviations: BMI, Body Mass Index; WHtR, Waist-to-Height Ratio; T2DM, Type 2 Diabetes Mellitus; FPG, Fasting Plasma Glucose; HbA1c, Glycated Hemoglobin; FINS, Fasting Insulin; SCr, Serum Creatinine; SUA, Serum Uric Acid; eGFR, Estimated Glomerular Filtration Rate; TC, Total Cholesterol; TG, Triglycerides; HDL-C, High-Density Lipoprotein Cholesterol; LDL-C, Low-Density Lipoprotein Cholesterol; METS-IR, Metabolic Score for Insulin Resistance; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; cIMT, Carotid Intima-Media Thickness.

Correlation Between CMI and the Prevalence of CAS

The association between CMI and the prevalence of CAS was evaluated using logistic regression analysis, and the results are shown in Table 2. In the fully adjusted model, an increase in CMI was significantly associated with an increased risk of CAS (OR = 1.48, 95% CI: 1.21–1.81, $P < 0.001$). Additionally, we used the Restricted Cubic Spline (RCS) method to flexibly model and visualize the association between CMI and CAS (Figure 1 – 3). After adjusting for all covariates in the main analysis model 3, the results revealed a significant nonlinear relationship between CMI and CAS (*P*-overall < 0.001, *P*-nonlinear < 0.001).

Predictive Value of CMI for the Prevalence of CAS

The ROC curve showed that CMI has modest diagnostic performance for CAS (AUC: 0.65, 95% CI: 0.61–0.68), with METS-IR having an AUC of 0.62 (95% CI: 0.59–0.65) and HOMA-IR an AUC of 0.59 (95% CI: 0.55–0.62) (Table 3 and Figure 4). Finally, we assessed whether including CMI further increased the predictive value of traditional risk

Table 2 Correlation Between CMI and CAS in T2DM Patients

Variable	Model	OR (95% CI)	*P*-Value
CAS	Model 1	1.67 (1.44–1.96)	<0.001
	Model 2	1.61 (1.38–1.89)	<0.001
	Model 3	1.48 (1.21–1.81)	<0.001

Notes: Model 1: Unadjusted; Model 2: Adjusted for age, gender, hypertension, smoking history, and T2DM duration; Model 3: Adjusted for age, gender, hypertension, smoking history, T2DM duration, Scr, SUA, HDL-C, LDL-C, FPG, HbA1c, eGFR, METS-IR, and HOMA-IR.

Abbreviations: CMI, Cardiometabolic Index; CAS, Carotid Atherosclerosis; OR, Odds Ratio; CI, Confidence Interval; T2DM, Type 2 Diabetes Mellitus; FPG, Fasting Plasma Glucose; HbA1c, Glycated Hemoglobin; SCr, Serum Creatinine; SUA, Serum Uric Acid; eGFR, Estimated Glomerular Filtration Rate; HDL-C, High-Density Lipoprotein Cholesterol; LDL-C, Low-Density Lipoprotein Cholesterol; METS-IR, Metabolic Score for Insulin Resistance; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance.

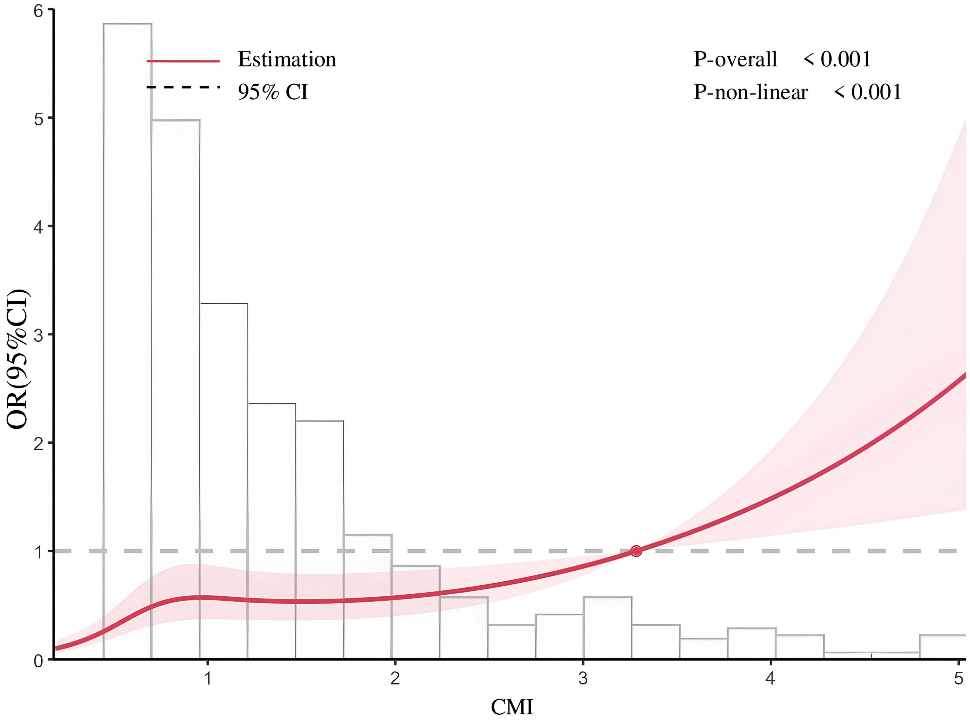

Figure 1 Unadjusted dose-response between CMI and CAS using RCS.
Abbreviations: CMI, Cardiometabolic Index; CAS, Carotid Atherosclerosis; OR, Odds Ratio; CI, Confidence Interval; RCS, Restricted Cubic Spline.

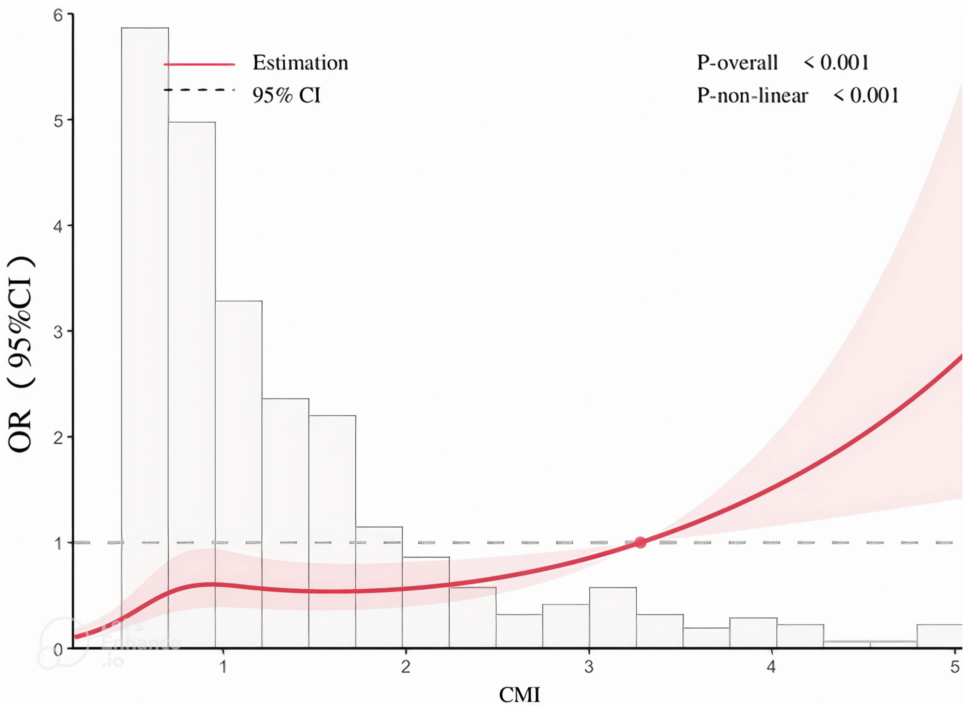

Figure 2 Dose-response between CMI and CAS based on Model 2 using RCS.
Abbreviations: CMI, Cardiometabolic Index; CAS, Carotid Atherosclerosis; OR, Odds Ratio; CI, Confidence Interval; RCS, Restricted Cubic Spline.

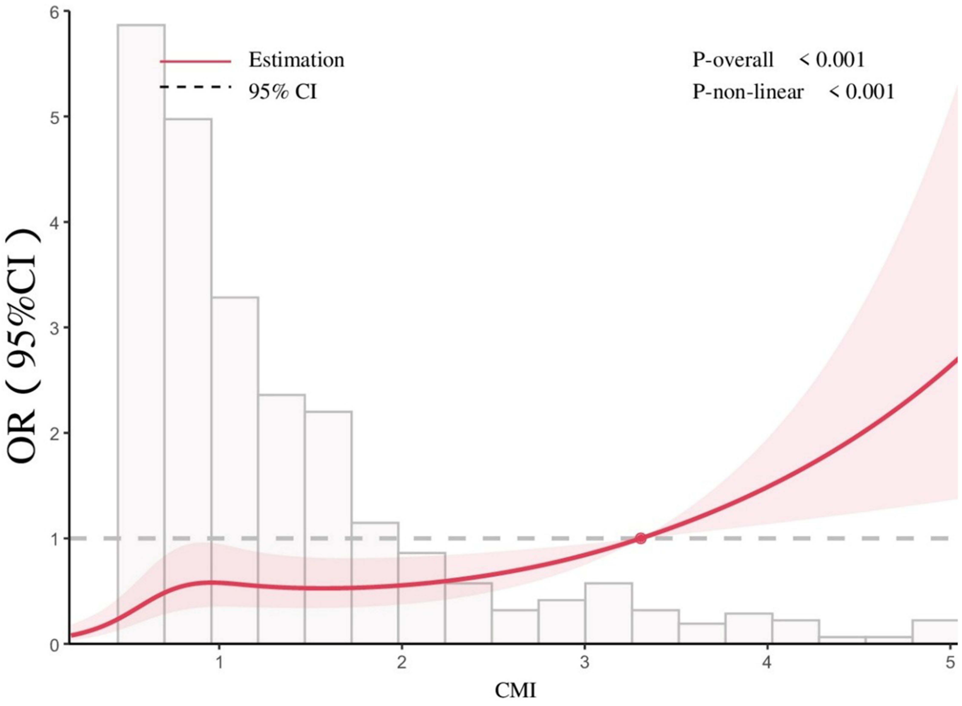

Figure 3 Dose-response between CMI and CAS based on Model 3 using RCS.
Abbreviations: CMI, Cardiometabolic Index; CAS, Carotid Atherosclerosis; OR, Odds Ratio; CI, Confidence Interval; RCS, Restricted Cubic Spline.

factors (age, hypertension, smoking history, T2DM duration, SUA, and LDL-C). With the inclusion of CMI, the AUC improved from 0.61 to 0.66 ($P < 0.001$), significantly enhancing the predictive performance of the traditional model (Table 4 and Figure 5). Further discriminative power and risk reclassification analysis showed an IDI of 0.04 (95% CI: 0.02–0.05, $P < 0.001$) and an NRI of 0.26 (95% CI: 0.14–0.38, $P < 0.001$), indicating significant improvement in both comprehensive discriminative ability and classification accuracy in the new model (Table 5). These findings support the clinical application value of CMI as an adjunctive risk prediction tool.

Subgroup Analysis

To further assess the association between CMI and the prevalence of CAS, a subgroup analysis was conducted (Table 6). The OR values were calculated using the Model 3 logistic regression model for each subgroup. The results for the specific subgroups were: males (OR = 1.54, 95% CI: 1.20–1.98); females (OR = 1.46, 95% CI: 1.04–2.07); age 45–60 years (OR = 1.57, 95% CI: 1.19–2.08); smoking history (OR = 1.62, 95% CI: 1.03–2.53); non-smoking history (OR = 1.44, 95% CI: 1.15–1.81); hypertension (OR = 1.50, 95% CI: 1.14–1.99); non-hypertension (OR = 1.48, 95% CI: 1.11–1.98); BMI ≥ 28 kg/m² (OR = 1.58, 95% CI: 1.17–2.13); BMI < 28 kg/m² (OR = 1.47, 95% CI: 1.10–1.97); and T2DM duration of 1–5 years (OR = 2.01, 95% CI: 1.18–3.42). Additionally, the interaction P-value between T2DM duration and CMI was 0.013, suggesting that the duration of diabetes may modulate the relationship between CMI and CAS.

Table 3 Predictive Performance of CMI, METS-IR, and HOMA-IR for CAS

Variables	AUC (95% CI)	Sensitivity	Specificity	Youden Index (J)	Related Criteria
CMI	0.65 (0.61–0.68)	85.06	36.82%	0.22	0.51
METS-IR	0.62 (0.59–0.65)	68.92%	50.76%	0.20	43.20
HOMA-IR	0.59 (0.55–0.62)	58.57%	57.95%	0.17	3.71

Abbreviations: CMI, Cardiometabolic Index; CAS, Carotid Atherosclerosis; AUC, Area Under the Curve; CI, Confidence Interval; METS-IR, Metabolic Score for Insulin Resistance; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance.

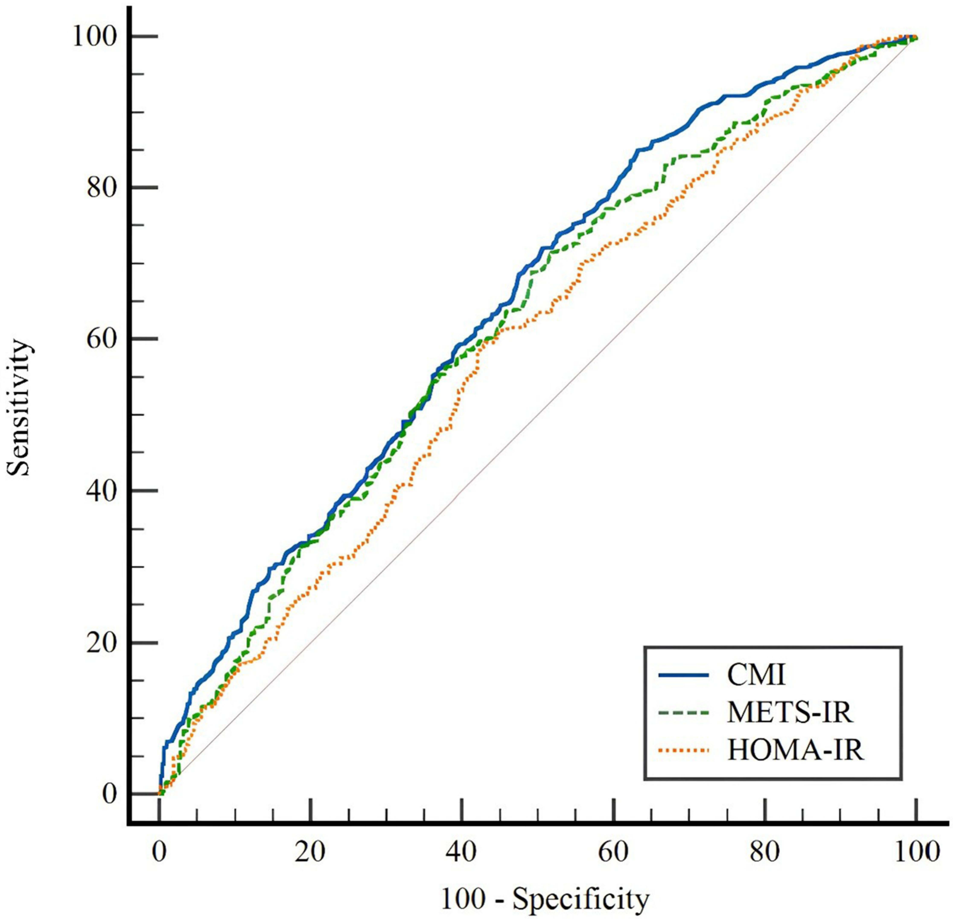

Figure 4 ROC curve of CMI, METS-IR, and HOMA-IR for predicting CAS.
Abbreviations: CMI, Cardiometabolic Index; CAS, Carotid Atherosclerosis; ROC, Receiver Operating Characteristic; METS-IR, Metabolic Score for Insulin Resistance; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance.

Mediating Role of IR

We conducted a Spearman correlation analysis to assess the relationship between CMI and METS-IR (Figure 6). The results showed a positive correlation between CMI and METS-IR ($r = 0.58$, $P < 0.001$). We also evaluated the mediating role of IR, including METS-IR and HOMA-IR. However, not all IR-related indices exhibited significant mediating effects. The mediation analysis only showed that the total effect of CMI on CAS was significant (β=0.09, 95% CI: 0.05–0.12, $P < 0.001$), with the mediating effect of METS-IR being significant (β=0.01, 95% CI: 0.00–0.03, $P = 0.034$), accounting for 12.92% of the mediation (95% CI: 0.64–35.95%). Meanwhile, the direct effect of CMI on CAS remained significant (β=0.08, 95% CI: 0.03–0.11, $P = 0.002$), indicating that METS-IR partially mediates the relationship between CMI and CAS (Figure 7).

Table 4 Evaluation of the Effect of Adding CMI to the Traditional Risk Prediction Model for CAS

Models	AUC (95% CI)	Sensitivity	Specificity	*P*-value for the Difference Between Traditional Model and AUC
Traditional model	0.61 (0.57–0.64)	59.76%	58.39%	-
Traditional model + CMI	0.66 (0.62–0.69)	64.14%	61.00%	< 0.001

Abbreviations: CMI, Cardiometabolic Index; CAS, Carotid Atherosclerosis; AUC, Area Under the Curve; CI, Confidence Interval.

https://doi.org/10.2147/DMSO.S539166

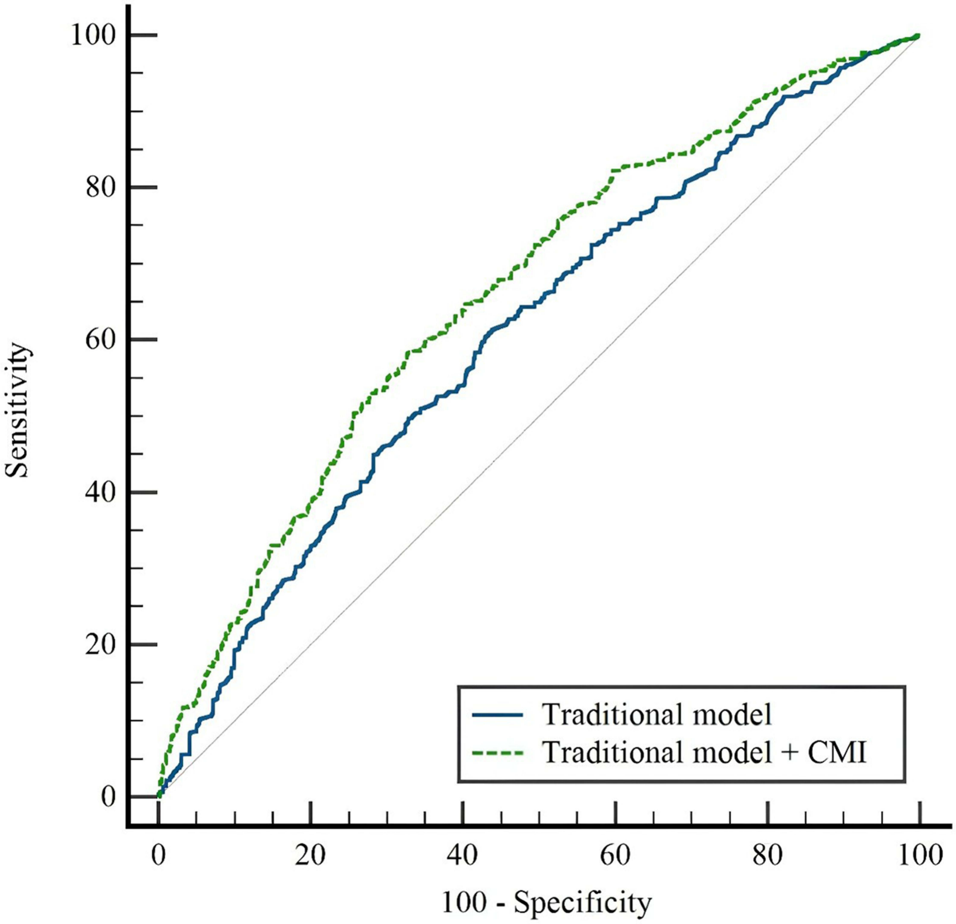

Figure 5 ROC curve after adding CMI to the traditional model for predicting CAS.
Abbreviations: CMI, Cardiometabolic Index; CAS, Carotid Atherosclerosis; ROC, Receiver Operating Characteristic.

Discussion

In our study, we found a positive correlation between CMI and CAS in T2DM patients, and this association may be partially mediated by IR. In the fully adjusted model, higher CMI was significantly associated with an increased risk of CAS in T2DM patients. The RCS curve further revealed a nonlinear relationship between CMI and CAS in T2DM patients. The ROC curve confirmed that CMI has predictive value for CAS, and its predictive ability outperformed traditional models. Our mediation analysis highlighted the important role of METS-IR in the relationship between CMI and CAS risk in T2DM patients, further suggesting that IR may be a potential mechanism underlying these associations. Therefore, monitoring CMI in patients provides a simple and effective method for early identification of CAS risk in T2DM patients.

Song et al estimated that in 2020, the prevalence of carotid artery plaque among individuals aged 30–79 years globally was approximately 21.1%, and the prevalence of significant cIMT was about 27.6%.[25] In China, the prevalence of CAS in the 30–79 age group reached 27.22%.[26] These data indicate that CAS imposes a significant burden on public

Table 5 Incremental Predictive Value of CMI Beyond Traditional Risk Factors

Models	NRI (95% CI)	*P*-Value	IDI (95% CI)	*P*-Value
Traditional model	References	-	References	-
Traditional model + CMI	0.26 (0.14–0.38)	< 0.001	0.04 (0.02–0.05)	< 0.001

Abbreviations: CMI, Cardiometabolic Index; NRI, Net Reclassification Improvement; IDI, Integrated Discrimination Improvement; CI, Confidence Interval.

Table 6 Subgroup Regression Analysis Between CMI and the Prevalence of CAS

Variables	OR (95% CI)	*P*-Value	Interaction *P*-Value
Age			0.972
< 45years	1.47 (0.91–2.38)	0.117	
45-60years	1.57 (1.19–2.08)	0.001	
≥ 60years	1.35 (0.91–2.01)	0.135	
Gender			0.799
Male	1.54 (1.20–1.98)	0.001	
Female	1.46 (1.04–2.07)	0.031	
Smoking History			1.000
Yes	1.62 (1.03–2.53)	0.036	
No	1.44 (1.15–1.81)	0.002	
Hypertension			0.755
Yes	1.50 (1.14–1.99)	0.004	
No	1.48 (1.11–1.98)	0.008	
Obesity			0.487
BMI≥ 28kg/m^2	1.58 (1.17–2.13)	0.003	
BMI< 28kg/m^2	1.47 (1.10–1.97)	0.010	
T2DM Duration			0.013
< 1 year	1.51 (0.98–2.33)	0.063	
1-5 years	2.01 (1.18–3.42)	0.010	
5-10 years	1.55 (0.94–2.57)	0.085	
≥ 10 years	1.35 (0.98–1.85)	0.064	

Abbreviations: CMI, Cardiometabolic Index; CAS, Carotid Atherosclerosis; OR, Odds Ratio; CI, Confidence Interval; T2DM, Type 2 Diabetes Mellitus; BMI, Body Mass Index.

health. Therefore, it is crucial to develop and implement effective prevention strategies, strengthen early screening and intervention, and especially focus on monitoring and managing disease progression. CMI is a novel obesity index that combines waist circumference with TG and HDL-C. This index not only reflects the characteristics of fat distribution but also indicates the potential link between metabolic disorders and CVD, and has been proposed as a predictive tool for assessing the risk of T2DM and CVD. Given that CMI is closely associated with metabolic disorders and cardiovascular events, exploring its role in the prevention and control of atherosclerosis is of great significance for formulating public health strategies. Several studies have shown that CMI has high accuracy in identifying metabolic syndrome.[12,27] Furthermore, the predictive value of CMI for systemic diseases has gained increasing recognition. Yan et al found a positive correlation between CMI and non-alcoholic fatty liver disease and fibrosis.[28] A cross-sectional study involving 2732 elderly individuals found that CMI is an independent risk factor for microalbuminuria.[29] Li et al demonstrated that elevated CMI is significantly negatively correlated with the prevalence of osteoporosis in the elderly population in the United States.[30] Additionally, Guo et al found a significant association between increased CMI and the prevalence of hypertension in a cross-sectional study including 45,250 participants (OR=1.30, 95% CI: 1.25–1.35, $P < 0.01$), with this relationship following a non-linear L-shaped curve.[31] In this study, logistic regression analysis showed that higher CMI was significantly independently associated with the prevalence of CAS. We observed a positive and robust association between CMI and CAS, which was not influenced by multiple confounding factors. ROC analysis further demonstrated that CMI performs well in diagnosing CAS, with an AUC of 0.65 (95% CI: 0.61–0.68). Moreover, CMI further enhanced the predictive value of traditional risk factors (age, hypertension, smoking history, T2DM duration, SUA, and LDL-C). These findings suggest that CMI provides a simple and effective alternative method for early identification of CAS.

A large number of studies have demonstrated that IR participates in the onset and progression of atherosclerotic diseases through various mechanisms. IR refers to the decreased ability of peripheral tissues to respond to insulin stimulation and is commonly found in metabolic diseases such as obesity, metabolic syndrome, hypertension, and T2DM.[32,33] IR leads to reduced glucose uptake and utilization by peripheral tissues, initially triggering compensatory

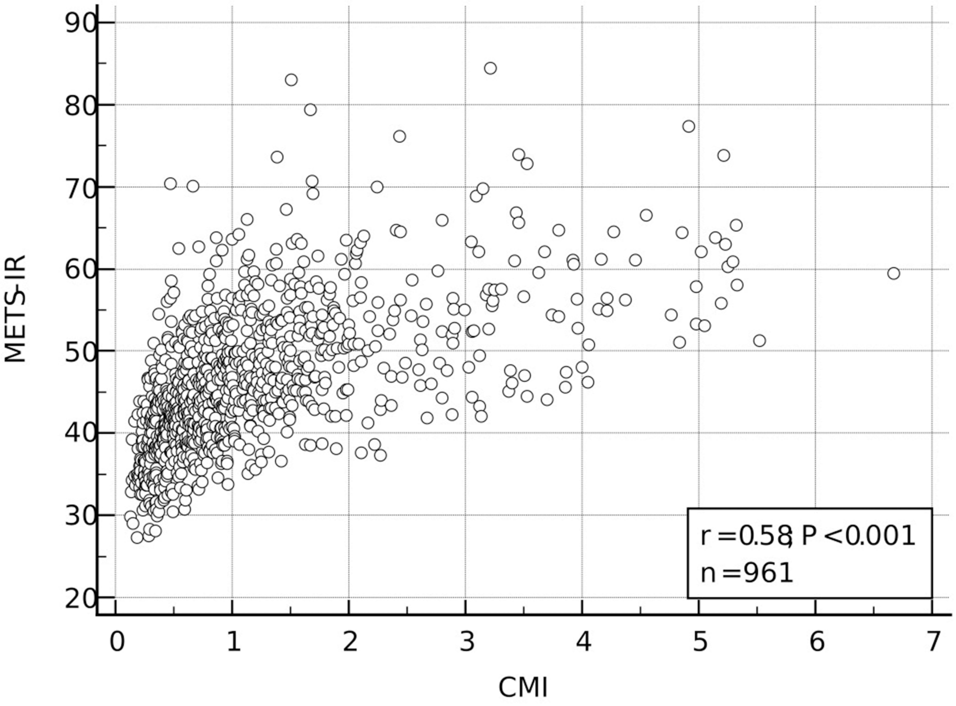

Figure 6 Spearman correlation coefficient between CMI and METS-IR.
Abbreviations: CMI, Cardiometabolic Index; METS-IR, Metabolic Score for Insulin Resistance.

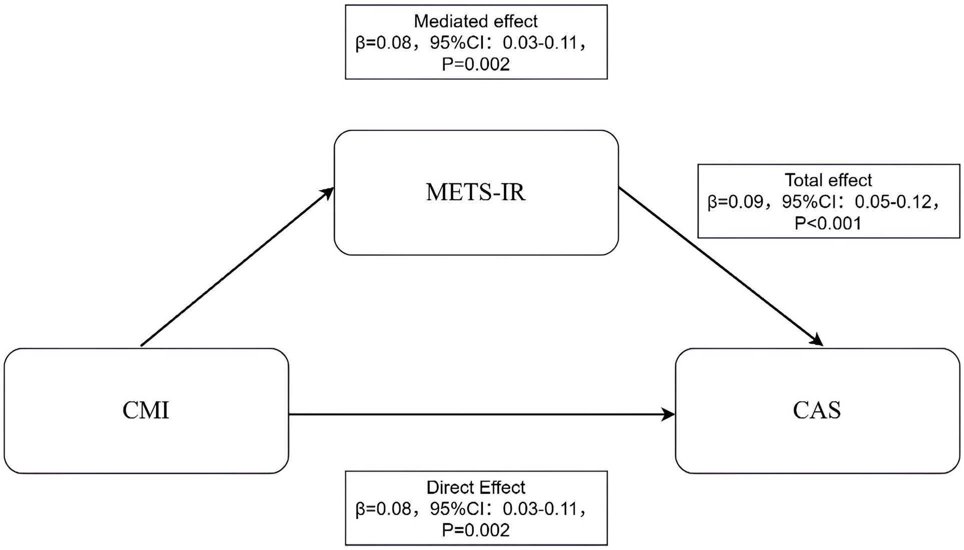

Figure 7 Mediation analysis of IR mediating the relationship between CMI and CAS.
Abbreviations: CMI, Cardiometabolic Index; CAS, Carotid Atherosclerosis; METS-IR, Metabolic Score for Insulin Resistance.

hyperinsulinemia. As the function of pancreatic β-cells gradually declines, it eventually progresses to persistent hyperglycemia.[34] Persistent hyperglycemia increases reactive oxygen species generation and activates pro-inflammatory pathways, such as the NF-κB signaling pathway, through metabolic routes like the polyol pathway, protein kinase C pathway, hexosamine pathway, and self-oxidative reactions, inducing oxidative stress and chronic inflammation, ultimately leading to cellular damage.[35] Meanwhile, hyperinsulinemia can activate the sympathetic nervous system and promote renal sodium retention, thus elevating blood pressure.[36] In a hyperglycemic environment, the excessive production of advanced glycation end products binds to vascular receptors, stimulating the proliferation of vascular smooth muscle cells and collagen deposition, promoting vascular remodeling and arteriosclerosis.[37] Moreover, IR weakens the inhibitory effect of insulin on lipolysis in adipose tissue, leading to elevated plasma free fatty acids, which in turn promote increased TG, decreased HDL-C, and increased small dense low-density lipoprotein, forming a typical lipid profile characteristic of atherosclerosis.[38–40] Under IR conditions, endothelial cells show a reduced response to shear stress and metabolic signals, and the PI3K/Akt/eNOS pathway is impaired, leading to decreased nitric oxide production and resulting in endothelial dysfunction. This endothelial dysfunction is recognized as an early marker of atherosclerosis.[41] Additionally, IR can enhance platelet adhesion, activation, and aggregation, increasing the tendency for thrombosis, and by activating vascular inflammation and further impairing endothelial function, it indirectly reduces vascular elasticity, thus accelerating the development of arterial stiffness.[42] In summary, IR promotes atherosclerosis and vascular dysfunction through multiple mechanisms, working synergistically to advance the disease process.

The most accurate methods for evaluating are the hyperinsulinemic-euglycemic clamp test and the hyperglycemic clamp test. However, due to their complex preparation, time-consuming procedures, and high costs, these methods are difficult to apply in clinical practice and large-scale population studies. Therefore, researchers have proposed various alternative methods, among which the HOMA-IR reflects insulin compensatory responses by measuring FPG and FINS levels. Higher HOMA-IR values indicate more severe IR.[43] According to a meta-analysis by Li et al, elevated HOMA-IR levels were significantly associated with the progression of coronary artery calcification.[44] Additionally, González-González et al demonstrated that HOMA-IR is linked to an increased risk of diabetes, hypertension, and non-fatal adverse cardiovascular events.[45] In recent years, METS-IR, a composite index that does not require direct measurement of insulin levels, has also been proposed for the convenient assessment of IR and has gained wider clinical application. Existing studies have shown that METS-IR is closely related to cardiovascular events,[46] cardiovascular mortality,[47] and arterial stiffness,[48] suggesting its important potential value in assessing metabolic disorders and cardiovascular risk. This study further reveals the mediating role of IR in the relationship between CMI and atherosclerotic diseases. Our analysis indicates that the mediating effect of IR through CMI significantly impacts the prevalence of CAS. Specifically, the total effect of CMI on CAS was significant ($\beta=0.09$, $P<0.001$), and the mediating effect of METS-IR was 12.92% ($P=0.034$), suggesting that IR plays a partial mediating role in this process. IR exacerbates the progression of atherosclerosis through multiple pathways, including promoting endothelial dysfunction, enhancing oxidative stress, increasing inflammation, and altering lipid metabolism. These mechanisms collectively accelerate changes in the vascular wall, leading to the aggravation of arteriosclerosis. These results support the use of CMI as an effective clinical screening tool that can better assess cardiovascular risk through the integration of metabolic indicators. This finding provides a new theoretical basis for the potential application of IR in cardiovascular disease risk assessment.

Limitations

This study has several limitations. First, as an observational study, although we identified an association between CMI and CAS, a causal relationship could not be established. Second, despite adjusting for multiple confounding factors, the influence of unmeasured or residual confounding factors could not be completely ruled out. Third, this study was conducted at a single center with a limited sample size of T2DM patients, which may restrict the generalizability of the results.

Conclusion

This study suggests that CMI could serve as an effective predictive tool for assessing the risk of CAS occurrence, while also highlighting the important mediating role of IR in this relationship.

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of Cangzhou People's Hospital. All patients provided consent for the record review associated with the research. The research was conducted in accordance with the principles of the Declaration of Helsinki, ensuring the ethical treatment of all participants.

Data Sharing Statement

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Funding

Medical Science Research Project of Hebei (20261340).

Disclosure

The authors declare no competing interests.

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