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RESEARCH

Higher Dietary Insulinemic Potential, and Triglyceride-Glucose (TyG)-BMI Index may Contribute to Coronary Artery Disease Severity: a Cross-Sectional Study

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Abstract

Background Emerging evidence suggests that insulin resistance (IR) may influence coronary artery disease (CAD) progression. However, the relationship between dietary insulinemic potential and IR surrogate markers and CAD severity remains unclear.

Methods This cross-sectional study utilized data from the Nutrition Heshmat Registry (NUTHER) in Guilan, Iran, including 930 patients at risk for CAD. CAD severity was assessed using the Gensini score based on angiographic findings. Dietary intake was evaluated using a validated 168-item food frequency questionnaire (FFQ), with energy-adjusted dietary insulin load, and dietary insulin index calculated accordingly. The triglyceride-glucose (TyG)-BMI index was derived as a surrogate marker of insulin resistance.

Results Of the 930 patients analyzed, 565 were categorized as having less severe CAD (Gensini score < 60) and 365 as severe CAD (Gensini score ≥ 60). Multiple regression models adjusted for various confounding factors showed that participants in the highest quartile of the TyG-BMI index had a 1.98-fold higher odds of severe CAD (OR (95%CI) = 1.98 (1.31–2.99); P-for-trend = 0.001), while those in the highest quartile of energy-adjusted dietary insulin load, and dietary insulin index had 2.41-fold and 2.22-fold increased odds of severe CAD, respectively (Q4 ORs (95%CIs) = 2.41 (1.41–4.12) for e.a.IL, and 2.22 (1.29–3.82) for e.a.II; P-for-trend < 0.001).

Conclusion Our significant findings suggest that higher TyG-BMI, dietary insulin load, and insulin index are likely associated with an increased odds of severe CAD. Monitoring and modifying dietary insulinemic potential and improving metabolic health may serve as practical strategies for reducing CAD severity in at-risk populations.

Keywords Coronary artery disease · Dietary insulin load · Dietary insulin index · Insulin resistance

1 Introduction

As the leading cause of death and disability worldwide, coronary artery disease (CAD) presents a major challenge to public health including in Iran where it accounts for about half of all annual deaths [1, 2]. CAD pathogenesis involves inflammation resulting from complex processes like atherosclerosis and the formation of blood clots in the coronary arteries. Its development is influenced by both unchangeable factors (e.g., age, genetics) and modifiable factors (e.g., obesity, smoking) [3–7]. Since preventing CAD needs to be affordable, adopting a healthier lifestyle remains a crucial strategy to reduce the overall burden of the disease [8, 9]. These changes primarily aim to prevent or lessen the

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development of chronic metabolic conditions like metabolic syndrome and type 2 diabetes mellitus (T2DM) through diet, exercise, and smoking cessation [3–7, 10].

Identifying reliable indices to assess metabolic health and insulin-related parameters is useful for prevention and therapeutic approaches [11]. Various indices have been developed to assess metabolic dysfunction, including the triglyceride-glucose (TyG) index, which is calculated from fasting triglyceride and glucose levels, and its extended version, that incorporates body mass index (BMI). These indices have emerged as valuable indicators for insulin resistance and cardiometabolic risk [10, 12–14].

Given its simplicity and strong correlation with hyperinsulinemic-euglycemic clamp-derived insulin resistance, the TyG index has been extensively studied in relation to metabolic disorders [10, 15, 16]. Several studies have demonstrated its predictive value for the development of T2DM, metabolic syndrome, and cardiovascular disorders (CVDs). However, due to the important role of BMI in metabolic disturbances, an extended version of the TyG index, known as the TyG-BMI index, has been introduced. The TyG-BMI index integrates fasting triglycerides, glucose levels, and BMI, providing a more comprehensive assessment of metabolic status, highlighting its potential utility in both clinical and research settings [10, 12, 17–19]. The TyG-BMI index represents a simple, clinically useful, non-invasive, accessible, and cost-effective method for assessing insulin resistance [20]. In contrast to Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), it does not require measurement of fasting insulin, thereby enhancing its feasibility and affordability in both clinical and research settings [10, 20]. Additionally, while HOMA-IR primarily reflects hepatic insulin resistance, the TyG-BMI index provides a more comprehensive evaluation of peripheral insulin resistance, lipid metabolism, and adiposity. Consequently, TyG-BMI may offer superior predictive utility for CVDs, particularly in populations affected by obesity or metabolic syndrome [21].

Beyond these indices, metabolic health is largely influenced by dietary patterns and their impact on insulin secretion. Dietary insulin load represents an individual's insulin response to dietary intake which is influenced by dietary composition and glycemic load. Excessive insulin secretion in response to high-carbohydrate and high-glycemic diets has been implicated in the pathogenesis of insulin resistance, obesity, and T2DM [22–26]. The excessive exposure to insulin, due to the elevated dietary insulin load, has been implicated in vascular inflammation, dyslipidemia, and the progression of atherosclerosis [27]. On the other hand, elevated TyG and TyG-BMI indices, indicative of heightened insulin resistance, have been associated with endothelial dysfunction, arterial stiffness, and subclinical atherosclerosis as well [28]. Although dietary insulin load is of increasing interest, research exploring its associations with CVDs, especially alongside serum insulin resistance surrogate markers like the TyG-BMI index, remains limited to the best of our knowledge.

Clarifying the interrelationships between the dietary insulinemic potential, metabolic insulin resistance, and the progression of CVDs seems crucial for advancing risk assessment and developing targeted preventive strategies, particularly for CAD. In this study, we examine the associations between surrogate markers of insulin resistance and nutritional indices that estimate the cumulative insulin response to dietary intake, indices that are increasingly recognized as important indicators of metabolic health. Specifically, the energy-adjusted dietary insulin load, and dietary insulin index, as well as the TyG-BMI are evaluated for their potential roles in risk stratification and prediction of CAD severity. These associations are investigated within a cross-sectional cohort of 930 patients undergoing coronary angiography.

2 Methods and Materials

2.1 Study Population and Recruitment

This cross-sectional study analyzed dietary intake data from patients at risk for CAD enrolled in the Nutrition Heshmat Registry (NUTHER) in Guilan Province, Iran. Data collection occurred between January 20, 2022, and June 22, 2023. Eligible participants, aged 20 to 80 years, were recruited from the Elective Angiography Department at Dr. Heshmat Hospital, affiliated with Guilan University of Medical Sciences (GUMS) in Rasht, Iran. CAD diagnoses were determined based on angiographic results, following the "*ESC 2019 Guidelines for the Diagnosis and Management of Chronic Coronary Syndromes*." [29]. Figure 1 illustrates the study design and timeline, as well as inclusion and exclusion criteria. A more thorough account of the methodology and results can be found in our previous publications, which employed the same extensive databank [30–32].

2.2 Ethical Considerations

The current research conducted within NUTHER databank, following the ethical principles outlined in the 2013 Declaration of Helsinki and was approved by the Institutional Review Board of GUMS (Research ID:

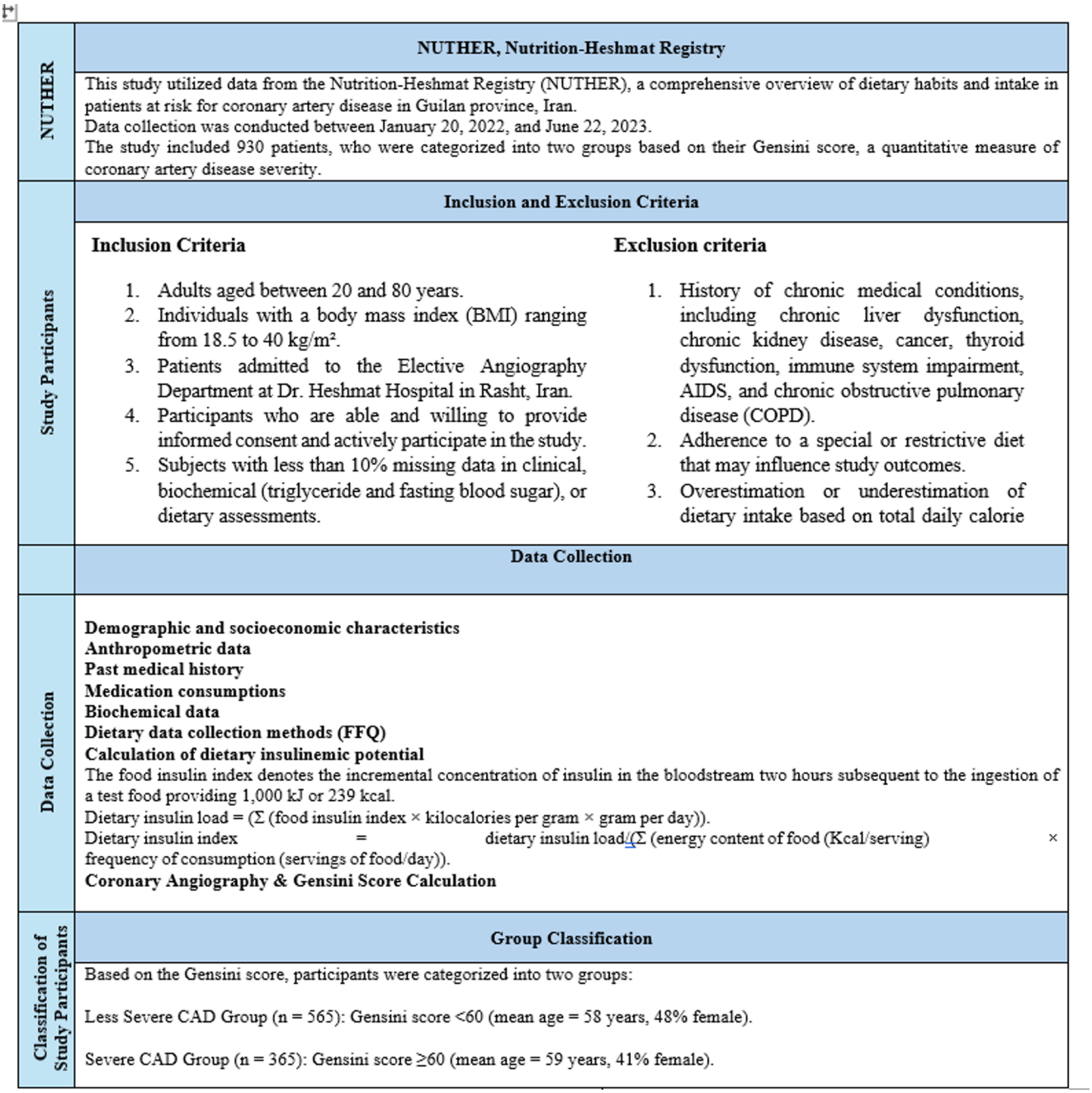

Fig. 1 Study Recruitment Procedure and Data Collection. NUTHER. Nutrition-Heshmat Registry

1404022222) as well as the GUMS Ethics Committee (Ethics Approval Code: IR.GUMS.REC.1404.177). All participants provided both verbal and written informed consent in the initial recruitment process.

2.3 Data Collection and Measurements

Upon admission, the study objectives were explained, and participants provided informed consent. Structured interviews, conducted by four trained researchers, collected demographic and socioeconomic data, including age, sex, employment, education level, smoking habits, opiate use, and medical history. Medical records were reviewed to verify chronic conditions and medication use.

Anthropometric assessments included height and weight measurements. Weight was recorded using a Seca 755 medical scale (accuracy: 0.5 kg), and height was measured with a stadiometer (precision: 0.1 cm). BMI was calculated as weight (kg) divided by height squared (m^2) with bare foot for all measures and shoulders in

neutral position. Physical activity was assessed using a validated questionnaire, with results expressed in minutes per day [33].

2.4 Coronary Angiography and Gensini Score Calculation

On the day of admission, two cardiologists assessed the severity of atherosclerosis using the Judkin technique with a femoral approach. Cardiologists blinded to the study details interpreted the angiograms and if discrepancies arose, a third interventional cardiologist, also blinded to the study, reviewed the findings. The classification of CAD severity was based on the number of affected major coronary arteries. Left main coronary artery lesions were considered equivalent to triple-vessel disease.

The Gensini score, which assesses the severity of coronary artery disease (CAD), was computed based on coronary angiography results, following previously established methods [34–37]. The final score for each individual was derived from the cumulative adjusted values. Based on the calculated scores, patients were divided into two categories: non-severe CAD (Gensini score < 60) and severe CAD (Gensini score ≥ 60), as described in earlier reports [30–32].

2.5 Analyses of Echocardiographic Data

Left ventricular systolic function was evaluated using echocardiographic assessments conducted upon hospital admission with a commercial ultrasound system. Left ventricular ejection fraction (LVEF) was estimated by a certified echocardiographer and verified by two cardiologists using the Simpson method. Participants were categorized based on LVEF into two groups: ≥50% or 40–49% [38].

2.6 Laboratory Analyses

For laboratory analyses, fasting venous blood samples were collected after at least eight hours of fasting. Blood samples were stored in sodium citrate tubes at −20 °C before processing. Total cholesterol and fasting blood glucose (FBS) were measured via enzymatic colorimetric methods. Triglycerides were measured using glycerol phosphate oxidase and commercial kits from Bionic Corporation (MAN Co., Tehran, Iran).

2.6.1 Dietary Assessments

A validated 168-item semi-quantitative food frequency questionnaire (FFQ) was administered by nutrition professionals prior to angiography, as physical issues and the required recovery period made post-angiography data collection impractical [39]. This FFQ assessed food consumption over the previous year, with portion sizes determined using standard measurements from the USDA Food Composition Tables (FCTs). Local food items, such as Kashk, vetch, sweets, wild plum, and mint, were analyzed using Iranian FCTs. When evaluating nutrient profiles of mixed dishes, standard restaurant recipes were referenced. Dietary intake data were converted into daily grams using established conversion factors by trained nutrition professionals. Energy and nutrient intake (protein, carbohydrates, fats, and macronutrient subtypes) were calculated using Nutritionist-4 software [40–42]. To minimize reporting biases, participants with implausible energy intake estimates were excluded. Those reporting intakes above twice the interquartile range of the 75th percentile (>3760.8 kcal/day for men, >3683.8 kcal/day for women) or below twice the interquartile range of the 25th percentile (< 2017.3 kcal/day for men, < 1028.2 kcal/day for women) were removed from further analysis (n = 185).

The Insulin Index for specific food items was determined by measuring the insulin response over two hours following the consumption of a 1,000-kJ (239 kcal) portion of a given test food. This response was then compared to the insulin response generated by an equivalent portion of a reference food. Data for the insulin index of different food items were sourced from previous studies conducted by Bao et al. (50 items) [23], Bell et al. (13 items) [25], Holt et al. (5 items) [24] and Sadeghi et al. (120 items) [22]. Additionally, for foods such as tea, coffee, and salt, whose energy, carbohydrate, protein, and fat contents are negligible, their insulin index was assumed to be zero.

The total insulin load for an individual was then obtained by summing the insulin loads of all food items. Finally, the Dietary Insulin Index was derived by dividing the total Dietary Insulin load by the individual's overall energy intake.

Dietary insulin load = (Σ (food insulin index × kilocalories per gram × gram per day)) [22].

Dietary insulin index = dietary insulin load/(Σ (energy content of food (Kcal/serving) × frequency of consumption (servings of food/day)) [22].

2.7 Insulin resistance surrogate markers

Following established methodologies from earlier studies, the indices for insulin resistance were computed using the formulas below:

$$\text{Triglyceride glucose (TyG)} - \text{BMI index} = (\text{TyG index} \times \text{BMI})$$

$$\text{Triglyceride glucose (TyG) index} = Ln\left(\frac{\text{fasting triglyceride s}\left(\frac{\text{mg}}{\text{dL}}\right)\times\text{fasting glucose}\left(\frac{\text{mg}}{\text{dL}}\right)}{2}\right)$$

[43, 44].

2.8 Sample Size Statistical Methods

The method used for sample size determination has been described in detail elsewhere [30–32]. Initially, 1,235 participants were recruited for the study. During data cleaning and quality control procedures, 185 participants were excluded due to implausible energy intake values (defined in Sect. 2.7). An additional 120 participants were excluded due to having more than 10% missing data in key clinical or dietary variables. Consequently, the final analytical sample consisted of 930 participants.

Categorical variables were summarized using frequencies and percentages, with between-quartiles differences evaluated using chi-squared or Fisher's exact tests. Continuous variables were analyzed using linear regression to assess trends across quartiles of TyG-BMI index or energy-adjusted dietary insulin load, with results expressed as means and standard deviations (SD). Using multivariable logistic regression, we assessed the association between quartiles of: (1) the TyG-BMI index, (2) energy-adjusted dietary insulin load (calculated via residual method), and (3) energy-adjusted dietary insulin index (derived using residual adjustment) and severe CAD, defined as a Gensini score ≥ 60. The initial models were controlled for age and gender. Subsequent regression analyses of the TyG-BMI index incorporated additional covariates, including energy-adjusted dietary insulin load, demographic factors, clinical variables, and medical history. These encompassed established CAD risk indicators such as education level, smoking status, opium use, LVEF category, physical activity, hypertension, prediabetes/diabetes, dyslipidemia, and use of antidiabetic or antihyperlipidemic medications. In models examining energy-adjusted dietary insulin load and dietary insulin index, TyG-BMI was included as a covariate. The third set of regression models for energy-adjusted dietary insulin load and dietary insulin index were additionally adjusted for dietary factors such as total dietary fiber, fruits, vegetables, meat, dairy, total fat (grams/day), and total energy intake (kcal/day). Odds ratios (OR) with 95% confidence intervals (CI) were calculated. Median values of each quartile were used as continuous variables to evaluate linear trends (P-for-trend) across quartiles. Sensitivity analyses, employing alternative cut-offs for Gensini scores (≥ 50 vs. <50 and ≥ 70 vs. <70), were conducted to assess the robustness of the findings.

All statistical analyses were conducted using STATA version 17 (StataCorp LLC, College Station, TX, USA).

3 Results

Among the 930 patients investigated in the current analysis, 565 were categorized into the less severe CAD group (mean age: 58 years, 48% female) with a Gensini score of less than 60. In contrast, 365 patients were classified in the severe CAD group (mean age: 59 years, 41% female) with a Gensini score of 60 or higher (Fig. 1; Supplementary Table S1). Overall, individuals with severe CAD were more likely to be male and married and exhibited a higher prevalence of dyslipidemia as well as greater use of anticoagulant medications (P-value < 0.05). Furthermore, they demonstrated a less favorable cardiometabolic profile, characterized by higher fasting blood glucose and triglyceride levels, alongside lower HDL-C and total cholesterol concentrations (P-value < 0.05). In addition, dietary patterns differed significantly between the two groups. Participants with severe CAD reported higher intakes of total energy, protein, carbohydrates, meat, and dairy products, but lower total fat intake (P-value ≤ 0.009). Consistent with these findings, their diets were characterized by significantly higher energy-adjusted dietary insulin load and dietary insulin index values (P-value < 0.001). The baseline characteristics and dietary intakes of participants according to CAD severity are summarized in Supplementary Table S1. Median values (range) of the key indices were comparable between sexes: for the TyG-BMI index, 245.92 (range: 158.01–443.01) in males and 249.07 (range: 156.73–454.99) in females; for the energy-adjusted dietary insulin load, 574.64 (range: 394.99–671.33) in males and 574.09 (range: 393.38–666.55) in females; and for the energy-adjusted dietary insulin index, 42.41 (range: 30.05–49.66) in males and 42.32 (range: 31.02–50.00) in females.

In Table 1, the demographic, biochemical, and clinical characteristics of study participants are stratified by quartiles of the energy-adjusted dietary insulin load and TyG-BMI index. Among participants categorized by the quartiles of TyG-BMI index, no significant differences were observed in age, gender, marital status, or education levels, though prevalence of smoking decreased significantly in higher quartiles (P-value = 0.041). Physical activity levels also declined significantly in the highest quartile (P-value = 0.038). Data also indicated a significant rise in the prevalence of diabetes/prediabetes, and antidiabetic medications use, alongside a notable increase in family history of diabetes mellitus and hypertension across TyG-BMI quartiles (P-value ≤ 0.028).

Table 1 Characteristics of the studied participants across quartiles of energy-adjusted dietary insulin load and TyG-BMI index

	Energy-adjusted Insulin Load				P-value	TyG-BMI index				P-value
	Q1	Q2	Q3	Q4		Q1	Q2	Q3	Q4	
	N=233	N=232	N=233	N=232		N=233	N=232	N=233	N=232	
Demographic and socioeconomic data										
Age (y)	58.91 (10.12)	58.27 (10.80)	58.61 (10.92)	57.72 (10.35)	0.298	58.48 (11.14)	58.95 (10.89)	58.30 (9.45)	57.78 (10.66)	0.352
Gender (male, n (%))	128 (54.9%)	128 (55.2%)	122 (52.4%)	135 (58.2%)	0.661	138 (59.2%)	124 (53.4%)	130 (55.8%)	121 (52.2%)	0.443
Married (n (%))	198 (85.0%)	214 (92.2%)	211 (90.6%)	212 (91.4%)	0.060	213 (91.4%)	210 (90.5%)	211 (90.6%)	201 (86.6%)	0.352
Education					0.964					0.894
Illiterate or elementary school (n (%))	138 (59.2%)	130 (56.0%)	131 (56.2%)	133 (57.3%)		138 (59.2%)	131 (56.5%)	138 (59.2%)	125 (53.9%)	
High school (n (%))	67 (28.8%)	75 (32.3%)	69 (29.6%)	69 (29.7%)		69 (29.6%)	70 (30.2%)	66 (28.3%)	75 (32.3%)	
Higher Education (n (%))	28 (12.0%)	27 (11.6%)	33 (14.2%)	30 (12.9%)		26 (11.2%)	31 (13.4%)	29 (12.5%)	32 (13.8%)	
Smoking (n (%))	44 (18.9%)	48 (20.7%)	51 (21.9%)	45 (19.4%)	0.845	59 (25.3%)	52 (22.4%)	38 (16.3%)	39 (16.8%)	0.041
Opium (n (%))	43 (18.5%)	33 (14.2%)	41 (17.6%)	34 (14.7%)	0.519	48 (20.6%)	37 (15.9%)	33 (14.2%)	33 (14.2%)	0.211
Physical activity (min/day)	30.14 (27.50)	30.67 (26.58)	30.71 (27.28)	33.51 (28.98)	0.454	33.55 (28.34)	32.37 (26.87)	30.52 (27.62)	28.58 (27.40)	0.038
Past medical history										
Hypertension (n (%))	160 (68.7%)	161 (69.4%)	174 (74.7%)	168 (72.4%)	0.445	167 (71.7%)	166 (71.6%)	164 (70.4%)	166 (71.6%)	0.993
Dyslipidemia (n (%))	184 (79.0%)	187 (80.6%)	195 (83.7%)	189 (81.5%)	0.619	185 (79.4%)	181 (78.0%)	189 (81.1%)	200 (86.2%)	0.114
Diabetes/Prediabetes (n (%))	165 (70.8%)	154 (66.4%)	159 (68.2%)	163 (70.3%)	0.721	128 (54.9%)	155 (66.8%)	167 (71.7%)	191 (82.3%)	<0.001
Family history of diabetes (n (%))	58 (24.9%)	65 (28.0%)	71 (30.5%)	66 (28.4%)	0.603	43 (18.5%)	64 (27.6%)	76 (32.6%)	77 (33.2%)	<0.001
Family history of hypertension (n (%))	59 (25.3%)	73 (31.5%)	70 (30.0%)	70 (30.2%)	0.484	52 (22.3%)	76 (32.8%)	78 (33.5%)	66 (28.4%)	0.028
Family history of myocardial infarction (n (%))	40 (17.2%)	47 (20.3%)	46 (19.7%)	50 (21.6%)	0.678	40 (17.2%)	45 (19.4%)	40 (17.2%)	58 (25.0%)	0.123
Family history of cancer (n (%))	23 (9.9%)	21 (9.1%)	19 (8.2%)	21 (9.1%)	0.939	17 (7.3%)	19 (8.2%)	27 (11.6%)	21 (9.1%)	0.423
Family history of cardiovascular diseases (n (%))	108 (46.4%)	97 (41.8%)	111 (47.6%)	111 (47.8%)	0.527	97 (41.6%)	104 (44.8%)	111 (47.6%)	115 (49.6%)	0.342
Medication use										
Anti-inflammatory drugs (n (%))	193 (82.8%)	185 (79.7%)	181 (77.7%)	177 (76.3%)	0.322	192 (82.4%)	174 (75.0%)	190 (81.5%)	180 (77.6%)	0.167
Anticoagulant drugs (n (%))	17 (7.3%)	17 (7.3%)	20 (8.6%)	24 (10.3%)	0.618	14 (6.0%)	23 (9.9%)	20 (8.6%)	21 (9.1%)	0.442
Anti-hyperlipidemic (n (%))	130 (55.8%)	135 (58.2%)	136 (58.4%)	137 (59.1%)	0.904	130 (55.8%)	123 (53.0%)	144 (61.8%)	141 (60.8%)	0.183
Antidiabetics (n (%))	113 (48.5%)	116 (50.0%)	122 (52.4%)	120 (51.7%)	0.842	95 (40.8%)	108 (46.6%)	113 (48.5%)	155 (66.8%)	<0.001
Anti-hypertensive (n (%))	119 (51.1%)	130 (56.0%)	135 (57.9%)	134 (57.8%)	0.409	116 (49.8%)	132 (56.9%)	129 (55.4%)	141 (60.8%)	0.117
Angiographic and echocardiographic data										
LVEF category										
40–49 (n (%))	94 (40.3%)	91 (39.2%)	86 (36.9%)	80 (34.5%)	0.567	84 (36.1%)	82 (35.3%)	94 (40.3%)	91 (39.2%)	0.632
≥50 (n (%))	139 (59.7%)	141 (60.8%)	147 (63.1%)	152 (65.5%)		149 (63.9%)	150 (64.7%)	139 (59.7%)	141 (60.8%)	

Table 1 (continued)

	Energy-adjusted Insulin Load				P-value	TyG-BMI index				P-value
	Q1	Q2	Q3	Q4		Q1	Q2	Q3	Q4	
	N=233	N=232	N=233	N=232		N=233	N=232	N=233	N=232	
Gensini Score	44.36 (33.02)	47.47 (37.18)	57.14 (38.91)	67.57 (40.50)	<0.001	48.04 (33.33)	54.22 (37.11)	56.80 (41.89)	57.46 (40.73)	0.009
Anthropometric and biochemical data										
Body mass index (kg/m^2)	28.56 (5.18)	27.25 (4.48)	27.30 (4.18)	27.37 (4.26)	0.520	22.86 (2.01)	25.99 (1.68)	28.30 (2.25)	33.35 (3.62)	<0.001
Fasting blood sugar (mg/dL)	142.13 (64.77)	138.30 (77.32)	143.34 (76.21)	140.53 (63.44)	0.688	112.03 (33.23)	127.66 (47.96)	151.22 (76.79)	173.48 (92.42)	<0.001
Cholesterol (mg/dL)	166.75 (52.99)	162.27 (49.35)	159.63 (43.77)	156.59 (42.60)	0.022	153.58 (39.21)	154.48 (43.93)	165.06 (47.39)	172.15 (55.51)	<0.001
Triglyceride (mg/dL)	186.76 (164.45)	171.48 (109.59)	174.75 (101.53)	177.93 (103.73)	0.850	124.91 (67.28)	151.67 (76.86)	190.32 (103.10)	244.22 (176.60)	<0.001

All data are presented as mean ± standard deviation (SD), unless otherwise specified. *Continuous variables were analyzed using linear regression, while categorical variables were assessed using the Chi-squared test

Table 2 Dietary macronutrients and fiber intake of the studied participants across quartiles of energy-adjusted dietary insulin load

	Energy-adjusted Dietary Insulin Load				P-value*	TyG-BMI index				P-value*
	Q1	Q2	Q3	Q4		Q1	Q2	Q3	Q4	
	N=233	N=232	N=233	N=232		N=233	N=232	N=233	N=232	
Energy (Kcal/day)	3310.47 (661.59)	3059.77 (601.39)	3190.07 (642.01)	3342.13 (675.42)	0.383	3200.84 (635.91)	3189.88 (646.87)	3252.60 (652.66)	3259.34 (681.96)	0.227
Protein (g/day)	101.02 (22.79)	94.90 (20.43)	99.17 (20.83)	102.56 (20.70)	0.239	98.83 (21.77)	98.19 (20.70)	100.20 (21.23)	100.43 (21.81)	0.287
Carbohydrate (g/day)	423.64 (114.49)	409.50 (103.46)	450.52 (106.81)	491.55 (115.76)	<0.001	437.01 (114.72)	440.20 (112.65)	450.03 (114.73)	447.90 (115.81)	0.239
Fat (g/day)	127.02 (25.16)	108.18 (19.33)	102.00 (21.84)	98.81 (22.42)	<0.001	108.83 (21.93)	107.28 (25.40)	108.32 (24.50)	111.64 (27.04)	0.146
Dietary Fiber (g/day)	24.51 (6.92)	22.47 (5.98)	23.30 (6.30)	23.89 (6.33)	0.492	22.73 (5.87)	22.54 (6.01)	23.68 (6.97)	25.23 (6.45)	<0.001
Fruits (g/d)	350.05 (194.23)	347.29 (169.82)	335.87 (171.60)	320.47 (172.39)	0.058	353.07 (177.56)	345.85 (176.90)	335.77 (162.41)	318.97 (190.94)	0.028
Vegetables (g/d)	302.11 (120.92)	281.70 (110.93)	275.66 (108.78)	285.16 (118.46)	0.077	301.53 (125.43)	276.97 (95.64)	284.69 (121.24)	281.41 (115.06)	0.140
Meat (g/d)	111.31 (46.23)	106.08 (37.21)	106.03 (31.63)	106.69 (33.88)	0.184	112.24 (41.79)	107.57 (35.12)	106.92 (33.56)	103.37 (39.29)	0.014
Dairy products (g/d)	414.29 (209.40)	447.35 (196.78)	425.37 (187.77)	417.55 (185.56)	0.932	461.66 (182.47)	466.55 (191.82)	423.46 (191.98)	352.70 (194.11)	<0.001
Total grain (g/d)	684.17 (260.14)	650.38 (219.39)	745.43 (220.01)	817.10 (268.13)	<0.001	729.75 (255.88)	705.80 (237.15)	740.89 (238.69)	720.46 (270.07)	0.996

All data are presented as mean ± standard deviation (SD), unless otherwise specified. *Analyzed using linear regression

Participants stratified by energy-adjusted dietary insulin load quartiles showed no significant differences in gender, marital status, educational status, physical activity levels, past medical history or smoking or opium use. An increase in Gensini scores was noted when either TyG-BMI or insulin load quartiles increased (P-value $\leq$ 0.009). Anthropometric and biochemical data demonstrated significant increases in BMI, FBS, cholesterol, and triglycerides across TyG-BMI quartiles (P-values $<$ 0.001). Cholesterol levels showed significant decreasing trend (P-values $\leq$ 0.05) across the increasing quartiles of energy-adjusted dietary insulin load (Table 1).

Table 2 presents the dietary intake patterns across quartiles of energy-adjusted dietary insulin load and the TyG-BMI index. For energy-adjusted dietary insulin load quartiles, carbohydrate, and total grains intake showed a significant increasing trend, while fat intake decreased progressively (P-value $<$ 0.001). However, protein, energy, dietary fiber, fruit, vegetable, meat or dairy intake consumption did not differ significantly across quartiles. For the TyG-BMI index quartiles, total energy intake showed minimal differences across quartiles, as did protein, carbohydrate and the majority of dietary factors. Dietary fiber intake increased progressively from Q1 to Q4, while fruits, meat, and dairy products

consumption showed a marked decline (P-value ≤ 0.028) (Table 2).

The analysis of severe CAD odds across quartiles of the TyG-BMI index, energy-adjusted dietary insulin load, and energy-adjusted dietary insulin index reveals significant associations, showing that higher values of these metabolic and dietary markers of insulin resistance are consistently linked to increased odds of CAD. For the TyG-BMI index, individuals in the highest quartile (Q4, median = 313.84) had a 1.64-fold higher odds of severe CAD compared to the lowest quartile (Q1, median = 202.81) in Model 1 (adjusted for age and gender; OR (95% CI): 1.64 (1.12–2.39); P for trend = 0.011), which increased to a 1.98-fold higher odds in Model 2 (further adjusted for education, smoking, opium use, LVEF category, physical activity, hypertension, prediabetes/diabetes, dyslipidemia, antidiabetic medication, antihyperlipidemic medication, and energy-adjusted dietary insulin load; OR (95% CI): 1.98 (1.31–2.99); P for trend = 0.001) (Table 3). Similarly, for energy-adjusted dietary insulin load, the odds of severe CAD increased sharply across quartiles. In the age- and gender-adjusted regression model (Model 1), participants in third to fourth quartiles (Q3 to Q4, median = 589.56, and 625.64, respectively) showed approximately 2.03 to 3.63 times higher odds compared to the lowest quartile (Q1, median = 514.72) (Q3: OR (95% CI) = 2.03 (1.37–3.00); Q4: OR (95% CI) = 3.63 (2.45–5.37); P for trend < 0.001). After adjusting for additional covariates such as education, smoking, opium use, LVEF category, physical activity, hypertension, prediabetes/diabetes, dyslipidemia, antidiabetic medication, antihyperlipidemic medication, and TyG-BMI index, participants in the higher quartiles (Q3-Q4) of energy-adjusted dietary insulin load exhibited progressively increased odds of severe CAD, ranging from about 2.19 to 4.28 times compared to those in Q1 (Q3: OR (95% CI) = 2.19 (1.45–3.33); Q4: OR (95% CI) = 4.28 (2.81–6.51); P for trend < 0.001). Additional adjustment of the regression models for dietary factors (total fiber, fruits, vegetables, meat, dairy, total fat (grams/day), and total energy intake (kcal/day)) revealed that only those in the highest quartile of energy-adjusted dietary insulin load exhibited significant linked higher odds of severe CAD by about 2.4 times (Q4: OR (95% CI) = 2.41 (1.41–4.12); P for trend < 0.001) (Table 3). Likewise, the energy-adjusted dietary insulin index showed a consistent link to the severity of CAD. In both analytical models, higher quartiles of the energy-adjusted dietary insulin index were associated with significantly increased odds of severe CAD. Patients in the higher quartiles (Q3-Q4, median = 43.53, and 46.17, respectively) had roughly 2 to 3.4 times greater odds of severe CAD compared to those in the lowest quartile (Q1, median = 37.81) in the age- and gender-adjusted model (Q3: OR (95% CI) = 2.31 (1.56–3.41); Q4: OR (95% CI) = 3.40 (2.30–5.04); P for trend < 0.001). This strong association remained significant even after adjusting for additional factors in the second multiple adjusted model (Q3: OR (95% CI) = 2.59 (1.70–3.94); Q4: OR (95% CI) = 4.03 (2.64–6.14); P for trend < 0.001). Further controlling for dietary factors demonstrated similar findings with those in the third to fourth quartiles of energy-adjusted dietary insulin index showing roughly 1.6 to 2 folds higher severe CAD

Table 3 Odds Ratios (ORs) and 95% Confidence Interval (95% CI) of severe coronary artery disease (CAD) according to quartiles of TyG-BMI index, dietary insulin load, and dietary insulin index

Variable	Q1	Q2	Q3	Q4	P for trend
Triglyceride-glucose (TyG)-body mass index (BMI) Index					
Median	202.81	234.70	263.61	313.84	
Cases/non-cases	80/153	89/143	91/142	105/127	
Model 1	1.00	1.21 (0.83–1.77)	1.24 (0.85–1.82)	1.64 (1.12–2.39)	0.011
Model 2	1.00	1.16 (0.78–1.73)	1.33 (0.89–1.99)	1.98 (1.31–2.99)	0.001
Energy-adjusted Dietary Insulin Load					
Median	514.72	557.99	589.56	625.64	
Cases/non-cases	63/170	71/161	99/134	132/100	
Model 1	1.00	1.20 (0.80–1.80)	2.03 (1.37–3.00)	3.63 (2.45–5.37)	<0.001
Model 2*	1.00	1.32 (0.86–2.02)	2.19 (1.45–3.33)	4.28 (2.81–6.51)	<0.001
Model 3**	1.00	1.05 (0.65–1.68)	1.47 (0.89–2.42)	2.41 (1.41–4.12)	<0.001
Energy-adjusted Dietary Insulin Index					
Median	37.81	41.13	43.53	46.17	
Cases/non-cases	61/172	74/158	104/129	126/106	
Model 1	1.00	1.32 (0.88–1.98)	2.31 (1.56–3.41)	3.40 (2.30–5.04)	<0.001
Model 2*	1.00	1.51 (0.98–2.33)	2.59 (1.70–3.94)	4.03 (2.64–6.14)	<0.001
Model 3**	1.00	1.22 (0.76–1.95)	1.65 (1.01–2.72)	2.22 (1.29–3.82)	0.002

Model 1: Adjusted for age and gender

Model 2 (TyG-BMI): Additionally adjusted for education, smoking, opium use, LVEF category, physical activity, hypertension, prediabetes/diabetes, dyslipidemia, antidiabetic medication, antihyperlipidemic medication, and energy-adjusted dietary insulin load

Model 2* (Dietary Indices): Additionally adjusted for education, smoking, opium use, LVEF category, physical activity, hypertension, prediabetes/diabetes, dyslipidemia, antidiabetic medication, antihyperlipidemic medication, and TyG-BMI index

Model 3**: Further adjusted for total fiber, fruits, vegetables, meat, dairy, total fat (all in grams/day), and total energy intake (Kcal/day)

odds (Q3: OR (95% CI) = 1.65 (1.01–2.72); Q4: OR (95% CI) = 2.22 (1.29–3.82); P for trend = 0.002) (Table 3).

To assess the robustness of our findings, further sensitivity analyses using alternative cut-offs for Gensini scores (≥50 vs. <50 and ≥70 vs. <70) were conducted and consistently confirm the current findings of an increased risk of severe CAD in association with higher energy-adjusted dietary insulin load and insulin index (Supplementary Tables S2 and S3).

4 Discussion

The current findings show that both metabolic and dietary indicators of insulin resistance, reflected in elevated levels of the TyG-BMI index, energy-adjusted dietary insulin load, and energy-adjusted dietary insulin index, appeared to be linked to heightened odds of severe CAD. Specifically, individuals in the highest quartile of energy-adjusted dietary insulin load (median: 625.64) exhibited approximately 2.4-fold increased odds of severe CAD relative to the subjects in the first quartile (median: 514.72), after adjusting for potential confounders, and dietary factors. Similarly, those in the higher quartiles of energy-adjusted dietary insulin index (Q3 median: 43.53; Q4 median: 46.17) faced a 1.6–2.6-fold greater odds relative to the lowest quartile (median: 37.81). The persistence of significant, albeit attenuated, associations for both the energy-adjusted dietary insulin load and index after further adjustment for key dietary factors suggests that while these measures share variance with other aspects of an unhealthy diet, they also capture a unique dimension of dietary insulinemic potential that remains independently linked to the odds of severe CAD.

The TyG-BMI index, which serves as an indirect measure of insulin resistance, demonstrated a moderate yet statistically significant association with severe CAD. Participants in the top quartile (median value: 313.84) exhibited 1.9 times higher odds of severe CAD compared to those in the bottom quartile (median: 202.81). These results remained consistent in sensitivity analyses that employed different threshold values for severe CAD classification.

Current research increasingly focuses on the relationship between diet and CAD as well as its risk factors, with growing emphasis on the insulin-stimulating effects of various dietary patterns. In a cross-sectional study by Nimptsch et al. [45], involving 4,002 healthy adults from the "Nurses' Health Study and the Health Professionals Follow-Up Study", the dietary insulin index and dietary insulin load were analyzed in relation to several serum biomarkers of CVD risk. Higher values of the dietary insulin index (Q5 range: ≥858) were associated with significantly higher triglyceride levels, particularly in obese individuals as compared to those in the first quartile (Q1 range: <648). In obese participants, higher dietary insulin index (Q5 range: ≥46.2) was also linked to lower HDL-C levels when comparing to those in the first quartile (Q1 range: <38.3). Similar results were observed for dietary insulin load. However, none of these dietary indices was significantly related to C-peptide, glycosylated haemoglobin (HbA1c), Low density Lipoprotein- Cholesterol (LDL-C), C-reactive protein (CRP), or interleukine-6 [45]. However, contrary to our findings, a recent prospective cohort study involving 2,198 participants from the Tehran Lipid and Glucose Study [46], with a median follow-up of approximately 6.7 years and 76 incident CVD cases, failed to identify any significant association between dietary insulin index (Q4 median vs. Q1 median: 58.9 vs. 44.3) and insulin load (Q4 median vs. Q1 median: 340.6 vs. 142.6). Nonetheless, a non-significant trend towards a higher CVD risk with increased dietary insulin load was observed. Participants in the highest glycemic load (GL) quartile (Median Q4: 292.1) had a 2.67-fold greater risk of developing CVD compared to those in the lowest quartile (median: 120.6), with a statistically significant trend (Hazard Ratio (HR): 2.67; 95% CI: 1.00–7.69; P-trend = 0.033). The authors noted that the lack of significant findings might be partly attributable to the study's limited sample size and the small number of CVD cases within each quartile of dietary insulin load [46].

Although there is limited direct evidence connecting the insulin indices evaluated in this study to CAD, related glycemic measures exhibit more consistent associations with heightened cardiovascular risk. One of the earliest reports on the association between glycemic index (GI), GL, and CAD emerged from the "Nurses' Health Study", which indicated that a high dietary GL was linked to an increased risk of coronary heart disease (CHD) [47]. A systematic review and meta-analysis of fifteen prospective studies, encompassing a total of 438,073 participants, demonstrated a linear dose-response relationship between dietary GL and elevated CHD risk, particularly among overweight and obese individuals [48]. Additionally, other systematic reviews and meta-analyses have reported a higher relative risk of CHD associated with both GI [49, 50] and GL [49, 51]. Overall, GI measures how quickly carbohydrates in a particular food raise blood sugar levels, while GL assesses the overall impact of carbohydrate consumption on blood glucose after eating. However, because other nutrients besides carbohydrates also influence insulin release, the dietary insulin index and insulin load were introduced to provide a more comprehensive evaluation. The insulin index compares the insulin response triggered by a mixed meal (containing carbs, proteins, and fats) to that of a reference food. Meanwhile, insulin load accounts for both the insulinogenic effect of a food and its typical serving size and frequency of consumption [52].

The TyG-BMI index, a composite measure incorporating fasting triglyceride concentrations, glucose levels, and BMI, has been established as a robust indicator of both insulin resistance and cardiometabolic risk [53, 54]. TyG-BMI index was shown to be related to the CAD and CVD development and progression [55–59]. In a recent research by Yang et al. on 2,317 acute coronary syndrome (ACS) patients, multivariate logistic regression analysis of the overall population showed a statistically significant association between TyG-BMI index and the degree of complex CAD (mid/high SYNTAX score) (OR (95% CI): 1.0041 (1.0000–1.0079.0000.0079)), with more prominent findings among female patients. Overall, within those in the third tertile (median: 245.86 ≤), the risk of a mid/high SYNTAX score was 1.47 times greater odds compared to the first tertile (median: < 209.99) (OR (95% CI): 1.47 (1.01–2.14)) [55]. Also, in a single-center, prospective cohort study on 823 patients with CHD, a nonlinear association was observed between the TyG-BMI index and both all-cause mortality and heart failure re-hospitalization in patients with CHD [60]. Similarly, a recent retrospective study involving 2,306 patients with stable CAD who underwent percutaneous coronary intervention found that TyG-BMI is a significant indicator for assessing cardiovascular risk and predicting major adverse cardiovascular and cerebrovascular events (MACCE). Patients in the third tertile (>228.69) had a substantially higher risk (OR (95% CI): 2.47 (1.85–3.29)) compared to those in the first tertile (≤ 198.12) [57]. In our previous cross-sectional study of 1,170 cardiology outpatients stratified by CAD status, the link between insulin resistance surrogates and hyperuricemia, a potential independent risk factor for cardiovascular events, was explored. It was found that among patients with CAD, those in the highest tertile of the TyG-BMI index (median: 296.45) had 1.83 times higher odds of hyperuricemia compared to those in the lowest tertile (median: 217.61), both before and after adjusting for confounding factors (OR (95%CI): 1.83 (1.24–2.70)). However, no such association was found in patients without CAD [54].

Further, in the current research we found that individuals in higher TyG-BMI quartiles exhibited higher prevalence of prediabetes/diabetes, antidiabetics medication use. This finding suggests that excessive insulin secretion, possibly driven by dietary factors, may contribute to metabolic dysfunctions and increased CVD risk. In this regard, a recent retrospective study of 1537 hypertensive patients undergoing coronary angiography examined the relationship between TyG-BMI and multi-vessel CAD [61]. In accordance with the current findings, those in the third tertile of TyG-BMI (237.46 ≤ TyG-BMI index ≤ 360.86), experienced a 3.57-fold increased risk of developing multi-vessel CAD (OR (95%CI): 3.57 (2.24–5.69)), compared to the patients in the lowest tertile (119.34 ≤ TyG-BMI index ≤ 209.89). These findings were more pronounced among those suffering from T2DM. Thus, the TyG-BMI seems to be a predictor of CAD severity in hypertensive patients, particularly those with diabetes. The non-linear dose-response relationship between TyG-BMI and multi-vessel CAD in diabetic patients underscores its potential clinical utility [61].

It is important to note that our findings reveal distinct associations for CAD severity odds and the TyG-BMI index as well as the energy-adjusted dietary insulin load and index, underscoring their different pathophysiological implications. The TyG-BMI index, a marker of systemic metabolic dysfunction, demonstrated a robust and independent association with severe CAD that was stable across models. This suggests it represents an established, underlying insulin-resistant phenotype that is a primary driver of coronary atherosclerosis. In contrast, the nutritional indices, reflecting a dietary behavior that imposes a high postprandial insulin demand, showed a stronger initial association that was substantially attenuated after adjusting for other dietary components. Importantly, the persistence of significant, albeit attenuated, associations for both the energy-adjusted dietary insulin load and index after further adjustment for key dietary factors indicates that a diet eliciting a high postprandial insulin response, potentially independent of its overall nutrient profile, might be a significant contributor to the pathogenesis of coronary atherosclerosis.

Overall, it is important to emphasize that our study design identifies an association and does not establish causality or elucidate the underlying mechanisms. However, the observed relationship is biologically plausible and can be contextualized within existing mechanistic hypotheses from the literature. It is well-known that insulin resistance would result in disruptions in metabolism of glucose and lipotoxicity, induce a pro-inflammatory state, and exacerbate the atherosclerosis progression [53, 62–64]. However, the exact mechanisms by which diet-induced insulin responses may contribute to CAD risk remain unclear, consumption of a large high-carbohydrate meal, especially one rich in high-glycemic-index carbohydrates, is proposed to lead to a significant increase in postprandial blood glucose and insulin levels. This forces an insulin-driven reduction in blood glucose which can then induce hunger within a few hours post-meal, prompting additional food intake and potentially causing prolonged elevation of blood glucose levels and insulin resistance [65]. Persistent hyperinsulinemia and hyperglycemia are also thought to lead to sodium retention, peripheral vasoconstriction, and enhanced very-low-density lipoprotein (VLDL) production by the liver, all of which may play a role in the progression of atherosclerosis [65]. In particular, elevated triglyceride levels facilitate the formation of LDL-C, which promote atherosclerosis

while diminishing the protective effects of HDL-C [54, 64, 66]. Importantly, postprandial hyperglycemia has been implicated in increased oxidative stress [67], while hyperinsulinemia independently influences endothelial function, coagulation factors, blood pressure, and inflammatory responses, all of which contribute to elevated risk of CAD progression [54, 64, 67, 68]. However, the specific mechanistic role of the dietary insulin indices measured in our study remains to be directly tested in future experimental and longitudinal research.

4.1 Strengths and Limitations

The current study had several strengths. We utilized a well-defined cross-sectional design with data from the NUTHER, ensuring systematic data collection. The study employed strict inclusion and exclusion criteria to minimize confounders and enhance internal validity. CAD severity was objectively assessed using the validated Gensini scoring system, with coronary angiograms reviewed by blinded cardiologists to reduce bias. Dietary intake data were collected using a validated 168-item semi-quantitative FFQ, and anthropometric and biochemical assessments followed standardized protocols, ensuring measurement accuracy. Additionally, the incorporation of insulin resistance markers, including TyG-BMI, dietary insulin load, and dietary insulin index, provides novel insights into the metabolic dimensions of CAD risk.

Despite these strengths, our study has some limitations. The cross-sectional design prevents causal inferences, requiring longitudinal studies to confirm these associations over time. While our study population was fairly diverse, it may not fully represent the general population, which limits the generalizability of our findings. Additionally, despite adjusting for a comprehensive set of demographics, clinical, and lifestyle covariates, as well as key dietary factors, the potential for residual confounding persists. Unmeasured or imperfectly measured aspects of overall diet quality, socioeconomic status, and other lifestyle factors could still influence the observed associations. The attenuation of the effect estimates for the dietary insulin load and index after additional dietary adjustment suggests that these measures are correlated with broader dietary patterns, and the residual associations, while significant, should be interpreted with this context in mind.

4.2 Clinical Relevance of the Current Findings

The findings of this study underscore the clinical significance of metabolic and dietary factors in the severity of CAD. The strong associations observed between higher quartiles of the TyG-BMI index, energy-adjusted dietary insulin load, and energy-adjusted dietary insulin index with increased odds of CAD highlight the potential role of insulin resistance and diet-induced insulin response in cardiovascular health.

These results suggest that dietary interventions aimed at lowering insulin load and improving metabolic health may be beneficial in reducing CAD severity. Clinically, these findings emphasize the importance of assessing insulin-related dietary factors and metabolic indices in routine cardiovascular risk evaluations. Healthcare professionals can integrate practical dietary modifications, such as prioritizing education focused on appropriate meal and portion size, distribution of food across the day, reducing refined carbohydrates while emphasizing whole grain food choices, to help reduce glycaemic load and the hyperinsulinemic response. Given the observed relationships, incorporating dietary strategies that modulate insulin dynamics could be a valuable approach in CAD prevention and management.

However, considering the limitations inherent in the cross-sectional design of our study, the observed associations warrant verification through longitudinal studies to establish temporality and through randomized controlled trials to determine causality, which are crucial steps for developing evidence-based dietary guidelines for clinically high-risk individuals.

5 Conclusion

Our findings demonstrate that elevated levels of both metabolic (TyG-BMI index) and dietary (energy-adjusted insulin load/index) markers of insulin resistance are significantly associated with increased odds of severe CAD. These consistent associations underscore the importance of insulin resistance and diet-induced hyperinsulinemia in cardiovascular pathogenesis. The observed relationships suggests that clinical interventions targeting insulin-modulating dietary patterns may improve cardiovascular risk stratification and management. Specifically, dietary strategies focused on reducing insulinemic load and optimizing metabolic parameters could potentially attenuate CAD severity. However, the cross-sectional design of this study necessitates confirmation through prospective longitudinal studies and controlled trials to verify these associations and establish targeted dietary guidelines for high-risk individuals.

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Data Availability The datasets of the current study are available from the corresponding author on reasonable request.

Declarations

Ethical Approval and Consent The research adhered to the 2013 principles outlined in the Declaration of Helsinki, and the study protocol was approved by the Institutional Review Board of the Cardiovascular Diseases Research Center at GUMS (research number 1404022222). Additionally, the GUMS Ethics Committee granted ethical approval for this study (ethics code "IR.GUMS.REC.1404.177").

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Competing Interests The authors declare no competing interests.

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