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Ultra-processed foods and coronary artery disease severity: a cross-sectional study of at-risk normal-weight and overweight patients undergoing elective angiography

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Abstract

Introduction There is growing interest in the connection between ultra-processed food (UPF) and cardiovascular diseases. This study explores how UPF intake relates to the severity of coronary artery disease (CAD) in at-risk patients undergoing elective angiography.

Methods Data covering demographic, and clinical details, and dietary intakes (using a validated food frequency questionnaire) were gathered from the Nutrition Heshmat Registry (NUTHER) in Rasht, Iran. UPF consumption was evaluated using the NOVA food classification system, with the exception of core grain foods. The study comprised 1,015 participants, who were classified based on the severity of CAD using the Gensini score (severe-CAD = Gensini score ≥ 60). Logistic regression was used to analyze the odd ratio (OR) and 95%confidence interval (95%CI) for severe-CAD across UPF quartiles (percentage of energy), and for each 10% increase in UPF intake. Restricted cubic spline (RCS) regression was employed to explore nonlinear relationships between UPF and severe-CAD.

Results Following controlling for potential confounders, normal-weight participants in the highest quartile of UPF exhibited about 5 times greater odds of severe-CAD than those in the lowest category (OR(95%CI): 5.01 (1.89, 13.29); P-for-trend = 0.002). Overweight/obese participants in the higher UPF quartiles had approximately 2-3.5 times greater odds for severe-CAD than those in the 1st quartile (ORs (95%CIs): 3rd quartile 1.91 (1.14, 3.21); and 4th quartile: 3.53 (2.07, 5.99); P-for-trend < 0.001). Each 10% increase in daily energy intake from UPF was associated with about 1.6-2 times increased severe-CAD risk among overweight/obese and normal-weight individuals (ORs (95%CIs) of 1.64 (1.28, 2.11), and 2.24 (1.24, 4.05), respectively). RCS analysis showed an upward trend toward higher UPF intake in relation to increased risk of severe-CAD (P-for-overall-trend < 0.0001; P-for-nonlinearity = 0.005).

Conclusion The findings obtained underscore a direct association between UPF and the risk of CAD progression among at-risk patients, independent of BMI. However, further prospective studies are essential to confirm these results and better understand this relationship.

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Keywords Severe coronary artery disease (CAD), Obesity, Packaged snacks, Ready-to-eat meals, Sweets

Introduction

Cardiovascular diseases (CVD) have emerged as a leading contributor to death around the world [1]. Coronary artery disease (CAD), as one of the leading and significant types of CVD, significantly influences the mortality rates in developed and developing countries [2, 3]. CAD is recognized by atherosclerosis and associated with a wide range of clinical manifestations, including heart attack, stable and unstable angina, and sudden death [4, 5]. Emerging evidence revealed that CAD is responsible for approximately 129 million disabilities and 7 million deaths every year worldwide and leads to around 50% of annual deaths among Iranian individuals [6, 7].

Hypertension, dyslipidemia, smoking, obesity, diabetes, a sedentary lifestyle, and an unhealthy diet are underlying risk factors for CAD, which can elevate the risk of CAD progression [4, 8–10]. Implementing medical therapies to control such significant risk factors alongside encouraging lifestyle change, including increased physical activity, non-smoking, and a healthy diet, has been proven to be an effective strategy to prevent or improve CAD [6]. The American Heart Association (AHA) suggested diet has a valuable role in achieving cardiovascular health [11]. Previously published studies have demonstrated that adhering to healthy diets is correlated with a 50% lower risk of heart disease [12]. Similarly, the classification of ultra-processed foods (UPF) as defined by the NOVA [13, 14] may negatively impact overall diet quality and impact cardiometabolic health.

Over the past decades, considering its expanded availability, hyperpalatable and inexpensive UPF intake has drastically increased around the world [15, 16]. UPF comprised more than 50% of the total dietary energy consumption of individuals in high-income countries and one-fifth to one-third in middle-income countries [13]; however, this assessment depends on the definition used, with some debate as to the classification of whole grain breads and breakfast cereals and indications that whole grain foods should not be considered ultra-processed [17]. Many UPF have high amounts of energy, salt, sugars, and unhealthy fats, while they have a low amount of protein, dietary fiber, vitamins, and minerals. Furthermore, UPF may contain hydrolyzed protein, hydrogenated oils, modified starches, and additives and such substances may result in the formation of compounds which might have an influence on cardiometabolic health [18–20]. In order to be cardio-protective, diets need to optimize intake of vegetables, fruits, nuts, whole grain foods and legumes [21–24]. UPF contributes approximately 8–20% of the total energy intake in the Iranian diet [25, 26], yielding results that differ somewhat from those reported in other regions.

Thus, over the past years, there has been considerable interest in investigating the relationship between UPF consumption, cardiometabolic risk factors, and CVDs. For instance, Canhada et al. [27] found that a 15% increase in the intake of UPF as a proportion of total daily energy was related to a 20–30% increase in weight and the prevalence of obesity and overweight [27]. Recently, a prospective cohort study performed on 5257 Brazilian adults for four years found a remarkable association between UPF intake (25–32% of total energy consumption) and dyslipidemias, which is identified as one of the major cardiovascular risks [28]. Moreover, a report from another cohort study in France conducted on 105,159 individuals revealed that there was a direct relationship between consumption of UPF and higher risk of CVD, type 2 diabetes mellitus, and all-cause mortality [29–31]. A meta-analysis of 39 eligible prospective studies with 63,573,312 participants evaluated the relationship between consumption of UPF and the likelihood of cardio-cerebrovascular diseases (CCVDs). This study illustrated a 7% increase in the odds of CCVDs in individuals who consumed UPF more than one serving per day [32].

These studies emphasize an essential area for public health research, intervention, and dietary guidance; however, the issues with miss-classification of specific food types, primarily whole grain foods requires further consideration [33]. Notably, there exists a dearth of studies that have specifically examined the correlation between UPF intake and CAD severity using the Gensini scoring system. Consequently, this study aims to investigate the relationship between the consumption of UPF and the severity of CAD, employing the Gensini scoring system [34] among at-risk patients referred to the elective angiography department of Heshmat Hospital in Rasht, Iran. In this research, the Gensini score, a reliable tool for grading stenosis severity in patients with CAD, was utilized to assess the prognosis and progression of this condition [34, 35]. To deepen our understanding of this association, analyses were conducted separately for normal-weight and overweight/obese patients.

Methods

Study population and recruitment

A cross-sectional study design utilized dietary intake data of patients at risk for CAD from the Nutrition Heshmat Registry (NUTHER) in Guilan province. The study took place from January 21, 2022, to June 22, 2023, during which data based on habitual dietary intake were collected from eligible, consenting participants aged older

than 20 years who were admitted to the Elective Angiography Department at Dr. Heshmat Hospital, affiliated with Guilan University of Medical Sciences (GUMS) in Rasht, Iran. Each patient underwent evaluations by expert cardiologists to confirm CAD diagnoses. The diagnostic process involved initial medical examinations, measurement of laboratory and clinical indicators of angina pectoris or atherosclerosis, including non-invasive tests, exercise stress tests, echocardiography, and angiographic data. CAD diagnoses were validated by angiographic results consistent with "*ESC 2019 Guidelines for the Diagnosis and Management of Chronic Coronary Syndromes*" [36]. Study participants were excluded from the study if they were under 20 years of age, individuals with body mass indexes (BMIs) below 18.5 or above 40 kg/m², and those with a history of cardiovascular events, such as percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), or myocardial infarction. Subjects with chronic liver dysfunction, chronic kidney disease, immune system disorders, AIDS, chronic obstructive pulmonary disease (COPD), cancer, thyroid dysfunction, or gout were also excluded. Moreover, individuals who adhered to special diets or declined to participate did not meet the inclusion criteria. After completing the data collection process, individuals with more than 10% missing information, whether clinical or dietary, were excluded from the analysis. As a result, data from 1,200 subjects were collected and entered into the NUTHER database.

The study met the 2013 guidelines of the Declaration of Helsinki and the protocol received approval by the Institutional Review Board of the Cardiovascular Diseases Research Center at GUMS (research number 1402070311), and the GUMS Ethics Committee (ethics code IR.GUMS.REC.1402.393). Participants were informed about the study's objectives and provided both oral and written consent to participate.

Demographic and anthropometric data

On the day of admission, the study's aims and objectives were explained to the participants, who then signed informed consent forms to officially enroll in the study. Four trained researchers conducted structured interviews to gather data on demographic information, socioeconomic status, and various confounding and contextual factors, including gender, age, employment status, education level, opiate use, smoking habits, and medical history. Information on chronic conditions was derived from the patients' medical records and related prescriptions. Details regarding medication usage were also collected, encompassing angiotensin-converting enzyme (ACE) inhibitors, antihypertensive drugs (specifically thiazides, calcium channel blockers (CCBs), beta-blockers, and angiotensin II receptor blockers (ARBs)), antidiabetic medications (primarily sulfonylureas and/or metformin), antihyperlipidemic agents (mainly statins), anti-inflammatory drugs (including corticosteroids and non-steroidal options), and anticoagulants (such as clopidogrel, warfarin, enoxaparin, and rivaroxaban).

Anthropometric measurements, including height and weight, were taken. The assessment of weight was done using a Seca 755 medical scale with an accuracy of 0.5 kg, while the measurement of height was performed with a standard stadiometer with a precision of 0.1 cm. Shoes were removed for all measures and shoulders positioned neutrally. BMI was calculated by dividing weight in kilograms by the square of height in meters (kg/m^2).

Physical activity was measured using a valid and reliable questionnaire and expressed in metabolic equivalent minutes per day [37].

Angiography of the coronary arteries

On the day of admission, the visual assessment of severity of atherosclerosis was performed by two cardiologists using the Judkin technique and a femoral approach. Interpretation of normal angiograms with no signs of detectable atherosclerosis in the coronary arteries was conducted by cardiologists who were uninformed about the details of the research. In cases of disagreement, a third interventional cardiologist, also unaware of the laboratory results and study specifics, reviewed the angiograms and determined the stenosis degree. The condition as single-, double-, or triple-vessel coronary artery disease was classified based on the presence of stenosis in one, two, or three major coronary arteries. The presence of a major lesion in the left main coronary artery was deemed equivalent to triple-vessel coronary artery disease.

Gensini score calculation

We computed the Gensini score based on coronary angiography findings following the methodology established by Gensini et al. [34]. The Gensini score is utilized to assess the severity of CAD by measuring the extent of stenosis in coronary lesions. The utilization of coronary angiography was done in order to quantitatively analyze the most prominent stenotic lesions in each branch artery. The degrees of stenosis were classified as follows: ≤25%, 26–50%, 51–75%, 76–90%, 91–99%, and 100%, assigned scores of 1, 2, 4, 8, 16, and 32 points, respectively. These scores were then adjusted based on the specific coronary branches, using the following multipliers: Left Main artery (LM) ×5.0, proximal Left Anterior Descending artery (LAD) ×2.5, middle LAD ×1.5, distal LAD ×1.0, proximal Left Circumflex artery (LCX) ×2.5 (3.5), middle LCX ×1.0 (2.0), distal LCX ×1.0 (2), Obtuse Marginal branch (OM) ×1.0, Left Posterior Lateral branch (PL) ×0.5, Right Coronary Artery (RCA) ×1.0, and

Posterior Descending Artery (PDA) ×1.0. By summing such adjusted scores of all lesions, the overall Gensini score for each single patient was computed [38–40].

For this research, patients were categorized into two groups based on their Gensini scores: those with Gensini scores less than 60 were categorized as non-severe CAD subjects and those Gensini scores equal to or more than 60 were categorized as severe CAD cases.

Analyses of echocardiographic

Left ventricular systolic function was assessed by measuring the proportion of end-diastolic blood volume that is ejected with each heartbeat, utilizing echocardiographic reports obtained shortly after hospital admission with a standard commercial ultrasound machine. A certified echocardiographer estimated the left ventricular ejection fraction (LVEF), and this estimation was subsequently verified by two cardiologists using the international Simpson method. Based on their LVEF results, participants were categorized as follows: LVEF ≥ 50%, and LVEF between 40% and 49% [41].

Laboratory analyses

Prior to collecting venous blood, subjects had a period of fasting at least 8 h. To inhibit coagulation, sodium citrate was utilized to store samples in tubes at -20 °C before analyzing. Leucocyte counts, including white blood cells (WBC) (10^9/L) was determined using standard methods. According to the manufacturer's guideline, the measurement of total cholesterol and fasting blood glucose (FBS) was conducted in accredited laboratories using the method of enzymatic colorimetric [42]. High-density lipoprotein cholesterol levels (HDL-C) were determined using an enzymatic technique provided by MAN Co. in Tehran, Iran. An enzymatic method with glycerol phosphate oxidase and commercial kits from Bionic Corporation (MAN Co., Tehran, Iran) was applied to measure the levels of triglyceride. The measurement of low-density lipoprotein cholesterol levels (LDL-C) was carried out using the formula of Friedewald [43, 44].

Dietary assessments

Two trained researchers collected data on the usual dietary habits of study participants by utilizing a validated 168-item semi-quantitative food frequency questionnaire (FFQ) [45]. This FFQ aimed to evaluate the participants' eating patterns over the year leading up to the study, gathering information on their food consumption on a daily, weekly, or monthly basis using a validated method. To ascertain the portion sizes of the foods consumed, the study employed the standard portion sizes established by the US Department of Agriculture (USDA) (for example, dairy as 1 cup, bread as 1 slice, and an apple as 1 medium). In instances where these standard portion sizes were not applicable, household measurements were used instead (for instance, chicken meat as 1 leg or wing, rice as filled in a large or small plate, and beans as 1 tablespoon) [46]. Assuming a 30.5-day month and employing the reported portion sizes along with raw and cooked coefficients, the estimates were expressed in grams per day. The dietary energy and nutrient content—encompassing protein, carbohydrates, fats, animal fats, animal proteins, plant fats, and plant proteins—were calculated using USDA food composition tables (FCTs) and Nutritionist-4 software (Nutritionist IV). For local food items, including certain dairy products like Kashk, vetch, sweets, wild plum, and mint, Iranian FCTs were employed [47, 48]. When evaluating the nutrient and energy profiles of mixed dishes, such as pizza, standard recipes from restaurants were referenced. Dietary data often suffers from inaccuracies due to both underreporting and overreporting. Consequently, participants who reported energy intakes exceeding twice the interquartile range above the 75th percentile—specifically, over 3760.836 kcal/day for men and 3683.798 kcal/day for women—or those whose intake was below twice the interquartile range beneath the 25th percentile—less than 2017.344 kcal/day for men and 1028.198 kcal/day for women—were excluded from further analysis ($n = 185$).

The consumption of UPF was assessed by reviewing items classified within the NOVA system [13]. The study included a variety of UPF, such as sausages, ham, burgers, ice cream, chocolate milk, and creamy cheese, along with popular snacks like pufak, and potato chips, crackers, biscuits, and cakes. Sweet treats were also represented, including candies, and chocolates, while condiments like mayonnaise, hydrogenated fats and margarine were noted as well. Additionally, carbonated beverages were part of the selection. The overall intake of UPF was expressed as both grams per day and a percentage of the total daily caloric intake. To enhance our analysis of specific UPF types, we sub-divided the items into seven categories: (1) **Packaged Salty Snacks**: Includes potato chips, popcorn, and pufak; (2) **Processed or Ready-to-Eat Meats**: Includes ham, sausage, and burgers.; (3) **Dairy Products**: Includes ice cream, creamy cheese, chocolate milk.; (4) **Hydrogenated Fats**: Includes hydrogenated fats, mayonnaise and margarine.; (5) **Soft Drinks**: Includes a variety of soft drinks. (6) **Packaged Snacks and Sweets**: Includes cakes, biscuits, crackers, candies, and chocolates.; (7) **Ready-to-Eat or Heat Meals**: Includes pizza.

Since the FFQ does not distinguish between various types of commercially available packaged bread and bread from local bakeries, we did not categorize either as UPF in our analysis. Additionally, the FFQ does not include data on breakfast cereal consumption, as these products are generally less popular among middle-aged

individuals in our region. We assessed the contribution of energy rather than the weight of food, as UPF items impact total energy consumption differently.

Sample size calculation and statistical methods

The required sample size was determined to be 926 participants using the standard formula for estimating a proportion, with a 95% confidence interval (95%CI), a precision (d) of 0.03, and an estimated prevalence of severe CAD (≥3-vessel disease) of 31.75%, based on prior data from the same center [49]. To accommodate an anticipated 25% dropout rate—accounting for potential losses due to incomplete clinical histories or dietary intake data—the sample size was adjusted, yielding a final target of 1235 participants.

Frequencies and percentages were utilized to express categorical variables, and differences between groups were assessed using chi-squared or Fisher's exact tests. For continuous variables, mean differences were evaluated using independent samples t-tests, and results were reported as means and standard deviations (SD). To evaluate the risk of severe CAD, indicated by a Gensini score of 60 or greater, logistic regression was performed on the quartiles of UPF.

We initially performed multiple logistic regression analyses incorporating demographic and clinical factors, including age and biological sex. Subsequent models expanded to include additional covariates such as BMI, smoking status, physical activity levels, type of employment, LVEF category, medical histories (hypertension, prediabetes, dyslipidemia), medications (antidiabetic drugs, anti-inflammatories, antihypertensives, anticoagulants, opiates), biochemical data (triglycerides, cholesterol, LDL-C, HDL-C), and socioeconomic factors like education level. To mitigate the risk of overfitting due to the modest sample size and numerous covariates, we employed Least Absolute Shrinkage and Selection Operator (LASSO) regression, with the final model selected using the Extended Bayesian Information Criterion (EBIC) to balance model fit and complexity. This approach identified key predictors of severe CAD, including age, biological sex, BMI, education level, LVEF, anticoagulant use, biochemical markers (triglycerides and HDL-C), and dietary intakes of dairy and whole grains, ensuring a parsimonious and generalizable model.

Then, odds ratios (OR) with 95%CI were reported. The median values of each quartile were treated as continuous variables, allowing for the presentation of linear trends (P-for-trend) across UPF quartiles.

To assess potential multicollinearity among the dietary exposure (intake of UPFs), biochemical data, and physical activity levels, a post-hoc analysis was conducted using the variance inflation factor (VIF). All VIF values were below the standard threshold of 5, indicating that multicollinearity was not a concern in the dataset.

Restricted cubic spline (RCS) regression with three knots at the 5th, 50th, and 90th percentiles of UPF consumption, was employed to explore possible nonlinear relationships between UPF intakes and the risk of severe CAD, while controlling for relevant covariates. The findings were visualized to illustrate the estimated ORs and CIs from the spline model, highlighting the connection between UPF intake and the risk of severe CAD.

All statistical analyses were conducted using STATA version 17 software (StataCorp LLC. 4905 Lakeway Drive, College Station, TX 77845, USA).

Results

General characteristics of normal-weight and overweight/obese subjects are provided in Tables 1 and 2 according to the quartile of UPF consumption per total daily caloric intake (UPF consumption/Kcal). Among normal-weight individuals, there were no significant differences in general characteristic variables across quartiles of UPF consumption as percentage of total energy intake. In contrast, overweight/obese subjects in the highest quartile of UPF intake as percentage of total energy exhibited a higher BMI.

Dietary intakes of normal-weight and overweight/obese participants across quartiles of UPF consumption as percentage of total energy intake are shown in Tables 3 and 4. In comparison to the normal weight participants in the lowest quartile, those in the highest quartile of the UPF consumption/Kcal exhibited significantly lower intake of whole grains and dairy and higher consumption of UPF sources, including packaged salty snacks, processed or ready-to-eat meats, dairy products, hydrogenated fats, soft drinks, packaged snacks and sweets, and ready-to-eat or heat meals (P-value < 0.05). Furthermore, among overweight/obese individuals, there was a significant trend for higher intakes of UPF and lower consumption of whole grains, meat, dairy, vegetables, and fruits, as well as a higher intake of energy, fat, carbohydrate, saturated fatty acids and dietary fiber. In terms of UPF sources, packaged salty snacks, processed or ready-to-eat meats, dairy products, hydrogenated fats, soft drinks, and packaged snacks and sweets consumption of those classifies in the uppermost quartile of UPF consumption/Kcal was considerably greater than obese or overweight subjects in the first quartile (P-value < 0.05).

Table 5 shows the multivariable-adjusted ORs and 95%CIs for severe CAD across the quartiles of UPF consumption as percentage of total energy intake. Among normal weight subjects, we observed a significant inverse relationship between the highest quartile of UPF consumption (median (min, max) (% kcal) = 15.47 (19.57, 31.13)) and severe CAD risk (OR (95% CI): 4.30

Table 1 Characteristics of the normal-weight participants across quartiles of ultra processed food (UPF) consumption as percentage of total energy intake

	Quartiles				*P* value[†]
	Q1	Q2	Q3	Q4	
Number of normal-weight individuals	82	89	83	47	
Demographic data					
Age (y)	58.88 (11.35)	59.54 (9.84)	58.48 (11.20)	59.765 (11.08)	0.792
Gender (male, n (%))	44 (54%)	54 (61%)	51 (61%)	28 (60%)	0.735
Married (n (%))	72 (88%)	84 (94%)	77 (93%)	41 (87%)	0.333
Education					0.478
Illiterate or elementary school (n (%))	50 (60.98)	59 (66.29)	48 (57.83)	27 (57.45)	
Middle school (n (%))	26 (31.71)	19 (21.35)	21 (25.30)	16 (34.04)	
Diploma and Higher (n (%))	6 (7.32)	11 (12.36)	14 (16.86)	4 (8.51)	
Work type					0.645
Self-employed (n (%))	41 (50.00)	35 (39.33)	29 (34.94)	19 (40.43)	
Employee (n (%))	13 (15.85)	18 (20.22)	22 (26.51)	9 (19.15)	
Housewife (n (%))	16 (19.51)	16 (17.98)	18 (21.69)	11 (23.40)	
Farmer (n (%))	12 (14.63)	20 (22.47)	14 (16.87)	8 (17.02)	
Smoking (n (%))	18 (22%)	27 (30%)	20 (24%)	12 (26%)	0.632
Opium (n (%))	12 (15%)	19 (21%)	18 (22%)	13 (28%)	0.347
Physical activity (metabolic equivalent minutes/day)	31.83 (27.79)	25.62 (24.16)	33.79 (28.16)	27.13 (24.13)	0.492
Past medical history					
Dyslipidemia (n (%))	71 (87%)	70 (79%)	67 (81%)	37 (79%)	0.542
Hypertension (n (%))	58 (71%)	64 (72%)	61 (73%)	29 (62%)	0.534
Prediabetes (n (%))	53 (65%)	57 (64%)	50 (60%)	29 (62%)	0.933
FHDM (n (%))	24 (29%)	17 (19%)	19 (23%)	11 (23%)	0.478
FHHTN (n (%))	16 (20%)	18 (20%)	28 (34%)	9 (19%)	0.087
FHMI (n (%))	10 (12%)	18 (20%)	14 (17%)	6 (13%)	0.478
FH cancer (n (%))	7 (9%)	8 (9%)	4 (5%)	1 (2%)	0.354
FHCVDs (n (%))	27 (33%)	36 (40%)	40 (48%)	20 (43%)	0.257
Medication use					
Anti-inflammatory drugs (n (%))	63 (77%)	73 (82%)	69 (83%)	38 (81%)	0.752
Anticoagulant drugs (n (%))	5 (6%)	6 (7%)	7 (8%)	6 (13%)	0.558
Anti-hypertensive (n (%))	39 (48%)	45 (51%)	43 (52%)	22 (47%)	0.924
Anti-hyperlipidemic (n (%))	43 (52%)	51 (57%)	51 (61%)	26 (55%)	0.702
Antidiabetics (n (%))	42 (51%)	41 (46%)	38 (46%)	22 (47%)	0.888
Anthropometric and biochemical data					
BMI (kg/m^2)	22.99 (1.58)	22.50 (1.766)	22.97 (1.66)	23.11 (1.656)	0.360
Fasting blood sugar (mg/dL)	130.96 (67.61)	127.83 (51.08)	136.12 (63.21)	139.68 (59.69)	0.313
Cholesterol (mg/dL)	157.23 (36.82)	154.14 (44.20)	162.95 (46.91)	158.13 (43.51)	0.641
Triglyceride (mg/dL)	149.18 (86.39)	156.64 (112.11)	144.31 (68.60)	160.64 (68.50)	0.657
HDL-C (mg/dL)	40.40 (13.01)	42.60 (12.57)	46.17 (15.05)	41.51 (13.96)	0.414
LDL-C (mg/dL)	83.22 (27.77)	77.39 (29.11)	85.54 (31.12)	78.89 (24.86)	0.773
Angiographic and echocardiographic data					
Gensini Score	47.77 (30.89)	58.54 (37.72)	56.56 (45.14)	77.92 (46.36)	< 0.001
LVEF category					0.258
40–49 (n (%))	30 (37%)	43 (48%)	33 (40%)	24 (51%)	
≥ 50 (n (%))	52 (63%)	46 (52%)	50 (60%)	23 (49%)	

[*]All values are mean ± SD, unless indicated; †Linear regression for continuous variables and Chi-squared test for categorical variables. BMI: body mass index; FBS: fasting blood sugar; HDL: high-density lipoprotein; LDL: low-density lipoprotein; HLP: hyperlipidemia; HF: heart failure; FHDM: family history of diabetes; FHHTN: familial history of hypertension; FHMI: family history of myocardial infarction; FH cancer: family history of cancer; FHCVDs: family history of cardiovascular diseases; LVEF: left ventricular ejection fraction

Table 2 Characteristics of the overweight/obese participants across quartiles of ultra processed food (UPF) consumption as percentage of total energy intake

	Quartiles				*P* value[†]
	Q1	Q2	Q3	Q4	
Number of overweight/obese individuals	171	164	170	209	
Demographic data					
Age (y)	57.46 (9.12)	58.29 (10.08)	57.95 (11.78)	59.37 (10.89)	0.083
Gender (male, n (%))	100 (58.5%)	91 (55.5%)	93 (54.7%)	103 (49.3%)	0.331
Married (n (%))	145 (84.8%)	148 (90.2%)	157 (92.4%)	186 (89.0%)	0.149
Education					0.337
Illiterate or elementary school (n (%))	93 (23.54)	83 (21.01)	101 (25.57)	118 (29.87)	
Middle school (n (%))	26 (31.71)	19 (23.17)	21 (25.61)	16 (19.51)	
Diploma and Higher (n (%))	56 (24.55)	56 (24.11)	61 (25.00)	60 (26.34)	
Work type					0.098
Self-employed (n (%))	83 (26.77)	64 (20.65)	83 (26.77)	80 (25.81)	
Employee (n (%))	31 (24.41)	37 (29.13)	25 (19.69)	34 (26.77)	
Housewife (n (%))	35 (18.72)	43 (22.99)	39 (20.86)	70 (37.43)	
Farmer (n (%))	22 (24.44)	20 (22.22)	23 (25.56)	25 (27.78)	
Smoking (n (%))	33 (19.3%)	32 (19.5%)	31 (18.2%)	35 (16.7%)	0.894
Opium (n (%))	22 (12.9%)	26 (15.9%)	25 (14.7%)	33 (15.8%)	0.847
Physical activity (metabolic equivalent minutes/day)	31.02 (28.75)	34.54 (28.25)	32.10 (28.15)	30.74 (27.11)	0.996
Past medical history					
Dyslipidemia (n (%))	141 (82.5%)	132 (80.5%)	138 (81.2%)	171 (81.8%)	0.971
Hypertension (n (%))	128 (74.9%)	117 (71.3%)	116 (68.2%)	154 (73.7%)	0.529
Prediabetes (n (%))	126 (73.7%)	115 (70.1%)	120 (70.6%)	148 (70.8%)	0.884
FHDM (n (%))	46 (26.9%)	54 (32.9%)	51 (30.0%)	61 (29.2%)	0.684
FHHTN (n (%))	54 (31.6%)	51 (31.1%)	58 (34.1%)	67 (32.1%)	0.938
FHMI (n (%))	29 (17.0%)	33 (20.1%)	37 (21.8%)	50 (23.9%)	0.407
FH cancer (n (%))	15 (8.8%)	19 (11.6%)	13 (7.6%)	21 (10.0%)	0.641
FHCVDs (n (%))	75 (43.9%)	80 (48.8%)	81 (47.6%)	103 (49.3%)	0.733
Medication use					
Anti-inflammatory drugs (n (%))	133 (77.8%)	139 (84.8%)	134 (78.8%)	164 (78.5%)	0.352
Anticoagulant drugs (n (%))	11 (6.4%)	9 (5.5%)	19 (11.2%)	22 (10.5%)	0.139
Anti-hypertensive (n (%))	109 (63.7%)	101 (61.6%)	95 (55.9%)	114 (54.5%)	0.104
Anti-hyperlipidemic (n (%))	109 (26.01)	101 (24.11)	95 (22.67)	114 (27.21)	0.221
Antidiabetics (n (%))	91 (53.2%)	84 (51.2%)	86 (50.6%)	111 (53.1%)	0.945
Anthropometric and biochemical data					
BMI (kg/m^2)	28.91 (3.18)	28.62 (3.21)	28.96 (3.41)	31.66 (4.125)	< 0.001
Fasting blood sugar (mg/dL)	140.02 (64.03)	136.93 (61.75)	145.93 (91.03)	139.68 (64.18)	0.908
Cholesterol (mg/dL)	162.08 (47.35)	169.49 (55.13)	156.34 (39.57)	160.83 (49.44)	0.394
Triglyceride (mg/dL)	172.34 (121.57)	183.55 (121.26)	168.52 (94.33)	173.72 (101.58)	0.817
HDL-C (mg/dL)	42.61 (14.12)	42.74 (12.26)	40.53 (11.76)	39.75 (11.13)	0.009
LDL-C (mg/dL)	84.15 (31.15)	85.99 (29.76)	83.57 (31.02)	84.11 (30.70)	0.817
Angiographic and echocardiographic data					
Gensini Score	45.91 (34.61)	53.67 (37.96)	56.75 (37.85)	64.70 (42.38)	
LVEF category					0.478
40–49 (n (%))	58 (33.9%)	68 (41.5%)	59 (34.7%)	78 (37.3%)	
≥ 50 (n (%))	113 (66.1%)	96 (58.5%)	111 (65.3%)	131 (62.7%)	

[*]All values are mean ± SD, unless indicated; †Linear regression for continuous variables and Chi-squared test for categorical variables. BMI: body mass index; FBS: fasting blood sugar; HDL: high-density lipoprotein; LDL: low-density lipoprotein; HLP: hyperlipidemia; HF: heart failure; FHDM: family history of diabetes; FHHTN: familial history of hypertension; FHMI: family history of myocardial infarction; FH cancer: family history of cancer; FHCVDs: family history of cardiovascular diseases; LVEF: left ventricular ejection fraction.

Table 3 Dietary intakes of normal-weight participants across quartiles of ultra processed food (UPF) consumption as percentage of total energy intake

	Quartiles				*P* value†
	Q1	Q2	Q3	Q4	
Number of overweight/obese individuals	82	92	84	47	
Energy (Kcal/day)	3323.23 (669.72)	3139.43 (739.50)	3088.89 (606.82)	3514.40 (662.26)	0.151
Protein (g/day)	103.48 (22.05)	98.825 (23.52)	94.41 (19.525)	103.73 (19.72)	0.828
Carbohydrate (g/day)	471.97 (127.275)	426.20 (139.460)	421.58 (104.75)	507.71 (125.30)	0.129
Fat (g/day)	104.79 (23.515)	106.35 (23.43)	105.62 (20.31)	109.42 (21.21)	0.297
Saturated fatty acid (g/day)	46.80 (11.61)	47.31 (11.72)	47.06 (10.68)	48.43 (10.86)	0.466
Dietary Fiber (g/day)	23.57(6.23)	21.985 (5.93)	21.37 (5.795)	24.36 (5.32)	0.562
Refined grain (g/day)	742.97 (247.76)	660.97 (266.23)	646.10 (210.06)	702.35 (197.98)	0.358
Whole grain (g/day)	68.10 (80.11)	55.24 (62.08)	42.07 (54.87)	42.98 (50.92)	0.018
Dairy (g/day)	471.43 (191.17)	475.51 (154.45)	478.20 (228.90)	396.46 (165.21)	0.036
Meat (g/day)	112.635 (40.78)	114.97 (38.78)	99.55 (30.54)	112.44 (35.39)	0.469
Vegetables (g/day)	307.64 (129.12)	305.78 (131.64)	255.50 (76.40)	307.07 (147.355)	0.488
Fruits (g/day)	353.82 (164.99)	355.81 (189.03)	315.085 (160.03)	375.94 (185.28)	0.771
UPF sources					
Packaged Salty Snacks (g/day)	9.27 (7.65)	14.19 (11.48)	16.78 (12.88)	31.52 (43.77)	< 0.001
Processed or Ready-to-Eat Meats (g/day)	4.935 (5.015)	7.19 (6.42)	10.86 (8.11)	11.57 (10.12)	< 0.001
Dairy Products (g/day)	15.785 (12.81)	26.15 (29.59)	40.86 (37.01)	50.74 (68.01)	< 0.001
Hydrogenated Fats (g/day)	3.75 (4.45)	5.65 (5.70)	7.115 (6.86)	9.07 (10.79)	< 0.001
Soft Drinks (g/day)	32.75 (39.45)	43.17 (40.77)	39.21 (41.44)	90.84 (202.86)	0.001
Packaged Snacks and Sweets (g/day)	14.24 (8.92)	22.70 (14.51)	34.21 (15.74)	82.06 (44.49)	< 0.001
Ready-to-Eat or Heat Meals (g/day)	9.86 (6.69)	10.68 (7.05)	11.29 (7.56)	14.19 (12.76)	0.004

*All values are mean ± SD. †Linear regression

Table 4 Dietary intakes of overweight/obese participants across quartiles of ultra processed food (UPF) consumption as percentage of total energy intake

	Quartiles				*P* value†
	Q1	Q2	Q3	Q4	
Number of overweight/obese individuals	174	164	172	209	
Energy (Kcal/day)	3177.905 (778.49)	3332.01 (625.66)	3232.81 (727.51)	3460.29 (801.38)	< 0.001
Protein (g/day)	99.30 (26.16)	103.49 (20.11)	98.66 (23.84)	102.465 (22.45)	0.393
Carbohydrate (g/day)	443.78 (129.69)	464.50 (115.53)	445.92 (127.47)	484.315 (140.425)	0.004
Fat (g/day)	103.185 (31.80)	108.90 (21.73)	108.89 (25.45)	118.46 (28.56)	< 0.001
Saturated fatty acid (g/day)	45.36 (14.46)	47.72 (10.415)	47.50 (12.58)	51.05 (13.58)	< 0.001
Dietary Fiber (g/day)	23.710 (6.70)	23.69 (6.18)	23.08 (6.44)	25.29 (6.94)	0.010
Refined grain (g/day)	681.90 (262.29)	697.18 (237.13)	663.36 (269.72)	680.06 (262.15)	0.764
Whole grain (g/day)	63.67 (65.59)	66.19 (70.83)	59.05 (69.84)	51.17 (59.40)	0.026
Dairy (g/day)	425.08 (211.85)	468.44 (188.73)	412.81 (184.89)	348.13 (184.43)	< 0.001
Meat (g/day)	113.17 (43.36)	109.16 (33.16)	107.69 (35.17)	98.70 (35.635)	< 0.001
Vegetables (g/day)	307.87 (123.38)	280.29 (98.40)	282.44 (111.82)	262.23 (106.45)	< 0.001
Fruits (g/day)	385.90 (208.79)	358.78 (178.34)	331.34 (173.51)	273.62 (155.48)	< 0.001
UPF sources					
Packaged Salty Snacks (g/day)	7.55 (7.10)	12.415 (11.45)	15.94 (19.72)	31.97 (56.95)	< 0.001
Processed or Ready-to-Eat Meats (g/day)	4.88 (4.71)	8.72 (6.90)	8.82 (7.65)	7.825 (8.22)	0.007
Dairy Products (g/day)	13.99 (13.14)	28.30 (27.69)	47.70 (47.80)	138.45 (150.00)	< 0.001
Hydrogenated Fats (g/day)	2.78 (3.40)	6.18 (6.03)	8.88 (7.98)	15.16 (13.875)	< 0.001
Soft Drinks (g/day)	26.155 (27.19)	36.74 (49.89)	38.87 (42.85)	39.385 (60.33)	0.021
Packaged Snacks and Sweets (g/day)	14.98 (9.57)	25.75 (13.05)	36.18 (20.08)	71.07 (51.80)	< 0.001
Ready-to-Eat or Heat Meals (g/day)	8.525 (6.505)	10.63 (7.10)	11.40 (8.50)	8.98 (7.48)	0.788

*All values are mean ± SD. †Linear regression; UPF: Ultra processed food

Table 5 Odds ratios (ORs) and 95% confidence interval (95%CI) of severe coronary artery disease (CAD) according to quartiles of ultra-processed food (UPF) consumption as percentage of total energy intake

	Quartiles				*P* for trend	Each 10% increase in the daily energy intake from UPF
	Q1	Q2	Q3	Q4		
Normal-weight individuals						
Median (min, max) (% kcal)	0.66 (5.82, 7.73)	7.78 (9.17, 10.63)	10.65 (12.31,15.37)	15.47 (19.57, 31.13)		
Cases/non-cases	26 /56	41 / 48	36/47	31/16		
Model 1†	1.00	1.82 (0.96, 3.46)	1.70 (0.88, 3.27)	4.30 (1.96, 9.42)	0.001	2.38 (1.45, 3.90)
Model 2‡	1.00	1.78 (0.83, 3.79)	2.07 (0.95, 4.50)	4.95 (1.98, 12.38)	0.001	2.39 (1.36, 4.19)
Model 3¥	1.00	1.88 (0.84, 4.23)	1.79 (0.79, 4.03)	5.01 (1.89, 13.29)	0.002	2.24 (1.24, 4.05)
Overweight/obese individuals						
Median (min, max) (% kcal)	0.44 (5.72, 7.73)	7.76 (9.19, 10.64)	10.66 (12.71, 15.45)	15.50 (20.91, 48.41)		
Cases/non-cases	48 /123	64/100	71 /99	110 /99		
Model 1†	1.00	1.67 (1.05, 2.65)	1.88 (1.19, 2.96)	3.00 (1.94, 4.64)	< 0.001	1.51 (1.23, 1.84)
Model 2‡	1.00	1.66 (0.99, 2.78)	1.95 (1.18, 3.23)	3.73 (2.23, 6.23)	< 0.001	1.69 (1.33, 2.15)
Model 3¥	1.00	1.70 (1.00, 2.87)	1.91 (1.14, 3.21)	3.53 (2.07, 5.99)	< 0.001	1.64 (1.28, 2.11)

†Model 1: Adjusted for age, and gender

‡Model 2: Further adjusted for body mass index (BMI), education, left ventricular ejection fraction (LVEF), anticoagulant drugs, triglyceride, and HDL-C levels

¥Model 3: Further adjusted for dietary intakes of dairy, and whole grains

(1.96–9.42); P-for-trend = 0.001), as compared to the lowest quartile (median (min, max) (% kcal) = 0.66 (5.82, 7.73)), after adjusting for age and gender. This association strengthened further after adjusting for factors such as BMI, education, LVEF category, anticoagulants drugs, and levels of triglycerides, and HDL-C (4th quartile OR (95%CI): 4.95 (1.98, 12.38); P-for-trend = 0.001). After taking into account dietary intake (including dairy, and whole grains as grams per day), normal-weight participants categorized in the highest quartile of UPF consumption as percentage of total energy had about 5 times greater likelihood of severe CAD compared to those in the lowest consumption category (4th quartile OR (95%CI): 5.01 (1.89, 13.29); P-for-trend = 0.002). The findings also indicate that each 10% increase in daily energy intake from UPF is associated with about two-fold increase in the severe CAD risk (ORs (95%CIs) of 2.38 (1.45, 3.90) in the age and gender adjusted model, 2.39 (1.36, 4.19) in the second model, and 2.24 (1.24, 4.05) in the fully adjusted regression models).

In overweight/obese subjects, we found that the risk of severe CAD was significantly higher in those within the higher quartiles of UPF intake (median (min, max) (% kcal) for 2nd to 4th quartiles: 7.76 (9.19, 10.64); 10.66 (12.71, 15.45); and 15.50 (20.91, 48.41), respectively) vs. bottom quartile (median (min, max) (% kcal) = 0.44 (5.72, 7.73)), according to the age and gender adjusted model (ORs (95% CIs) for 2nd quartile: 1.67 (1.05, 2.65); 3rd quartile 1.88 (1.19, 2.96); and 4th quartile: 3.00 (1.94, 4.64) P-for-trend < 0.001). This relationship intensified further after considering additional factors, namely BMI, education, LVEF category, anticoagulants drugs, and levels of triglycerides, and HDL-C (ORs (95% CIs) for 3rd quartile 1.95 (1.18, 3.23); and 4th quartile: 3.73 (2.23, 6.23); P-for-trend < 0.001). When dietary intakes of dairy, and whole grains (in grams per day) were also considered in the regression models, overweight/obese participants in the higher quartiles of UPF consumption had approximately 2-3.5 times greater odds of experiencing severe CAD compared to those in the lowest quartile (ORs (95% CIs) for 3rd quartile 1.91 (1.14, 3.21); and 4th quartile: 3.53 (2.07, 5.99); P-for-trend < 0.001). Additionally, each 10% increase in daily energy intake from UPF was linked to approximately 1.5-1.6-fold increase in the risk of severe CAD, with ORs (95% CIs) of 1.51 ( ) in the age and gender-adjusted model, 1.69 (1.33, 2.15) in the second model, and 1.64 (1.28, 2.11) in the fully adjusted regression models.

The relationship between UPF intake, expressed as a percentage of daily energy intake, and the risk of severe CAD was also evaluated using RCS regression with three knots at the 5th (4.37%), 50th (0.66%), and 90th (21.75%)

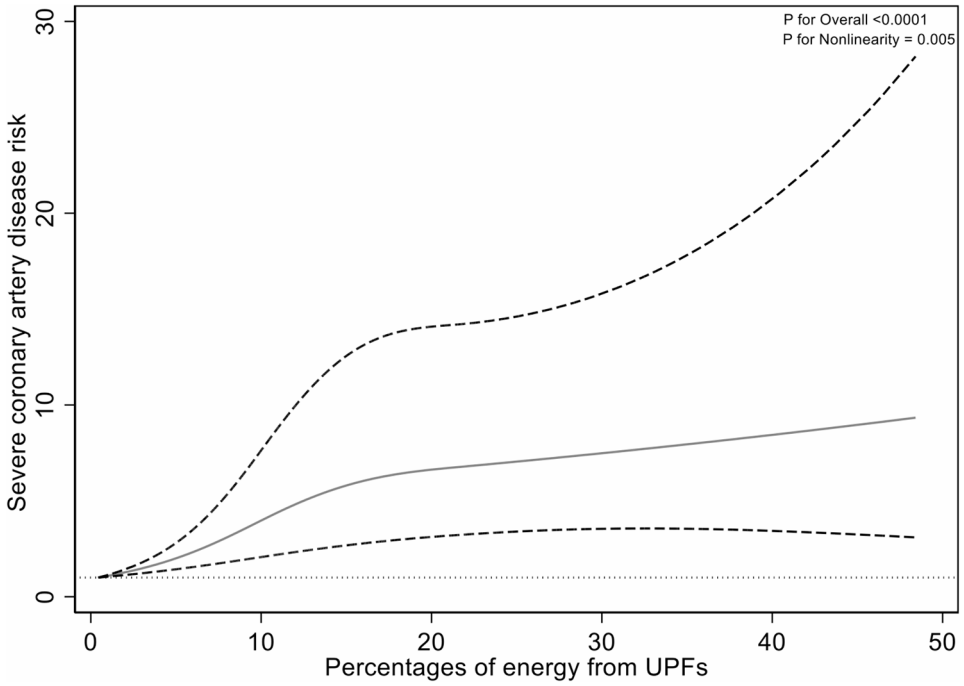

Fig. 1 Analysis of dose-response relationship between ultra processed food (UPF) consumption as percentage of total energy intake and severe coronary artery disease (CAD) risk. The restricted cubic spline (RCS) model accounts for factors such as age, biological sex, body mass index (BMI), educational level, left ventricular ejection fraction (LVEF), use of anticoagulant drugs, along with biochemical data (triglyceride, and HDL-C levels), in addition to dietary intakes of dairy, and whole grains. The spline model utilized cubic knots at the following percentiles: 5th (4.37%), 50th (0.66%), and 90th (21.75%). The plotted lines represent odds ratios (ORs) and 95% confidence intervals (95% CIs)

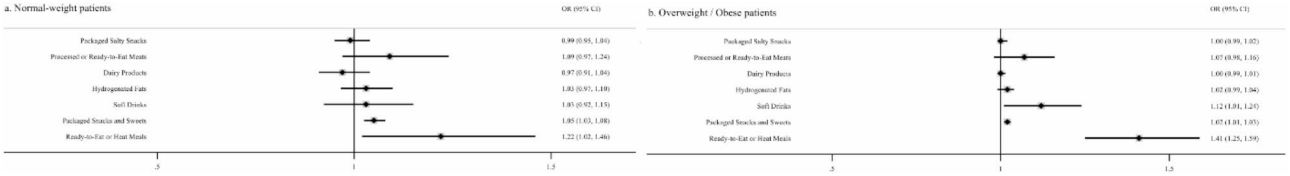

Fig. 2 Forest plot showing multivariable adjusted odds ratio (95% confidence interval) for association between each 10% increase in ultra-processed foods (UPF) consumption and severe coronary artery disease (CAD) risk in normal weight (**a**) and overweight/obese participants (**b**). Models were adjusted for age, biological sex, body mass index (BMI), educational level, left ventricular ejection fraction (LVEF), use of anticoagulant drugs, along with biochemical data (triglyceride, and HDL-C levels), in addition to dietary intakes of dairy, and whole grains

percentiles, as shown in Fig. 1. After adjusting for relevant covariates, an upward trend was noted, where higher percentages of UPF energy intake are associated with increased risk levels (P for overall trend < 0.0001; P for nonlinearity = 0.005). Specifically, as UPF intake rises from 4.37% of total calorie intake, the OR for severe CAD gradually increases, reflecting a persistent risk associated with higher UPF consumption (Fig. 1).

Figure 2**(a and b)** illustrates a multivariable adjusted OR (95%CI) for the relationship between 10% increase in daily energy intake from various types of UPF sources and severe CAD risk in normal weight and overweight/obese participants. After controlling for potential covariates in the fully adjusted regression model, with every 10% rise in proportion of energy consumption from packaged snacks and sweets, and ready-to-eat or heat meals was associated with 5% and 22% higher risk of having severe CAD, respectively (ORs (95% CIs): 1.05 (1.03, 1.08), and 1.22 (1.02, 1.46), respectively) in normal-weight individuals (Fig. 2 (a.)). In addition, overweight/obese participants had about 2–41% greater risk of having severe CAD with each 10% increase in soft drinks (OR (95% CI): 1.12 (1.01, 1.24)), packaged snacks and sweets (OR (95% CI): 1.02 (1.01, 1.03)), and ready to eat or heat meals (OR (95% CI): 1.41 (1.25, 1.59)). However, other UPF sources did not exhibit a significant association with the risk of severe CAD in either group (Fig. 2 (b.)).

Discussion

In this study, we found that overweight and obese individuals in the higher quartiles, who consumed about 10–15% of their total daily caloric intake from UPF, resulting in approximately 2- to 3.5-fold increase in the risk of severe CAD compared to those in the bottom

quartile, who consumed less than 0.5% of their daily total energy from UPF. The relationship was even more pronounced among normal-weight individuals in the highest quartile of UPF consumption—averaging about 15% of their daily total energy intake from UPF—were approximately 5 times more likely to develop severe CAD compared to those who consumed less than 1% of their energy from UPF. These associations remained significant after controlling for various demographic, clinical, biochemical, and dietary factors. It was also revealed that for each additional 10% of energy consumed from UPF, the risk of CAD progression increased by approximately 1.6-2 times among overweight/obese and normal-weight subjects, respectively. Packaged snacks, sweets, and ready-to-eat or heat meals were identified as the primary sources of UPF linked to an increased risk of severe CAD in normal-weight individuals. Additionally, soft drinks were significantly associated with severe CAD risk among overweight and obese participants, alongside these UPF sources. Furthermore, RCS analysis revealed a noteworthy nonlinear dose-response relationship between UPF intake (as a percentage of daily energy consumption) and the risk of severe CAD, with a significant overall trend. This suggests that an increase in energy derived from UPFs correlates with a heightened risk of severe CAD, underscoring a troubling association.

Aligned with our results, other published studies demonstrated that consumption of foods categorized as ultra-processed might be directly associated with the risk of CVDs and atherosclerosis progression [12, 32, 50–54]. In a cross-sectional study conducted by Jesus Santana et al. in 2020 [50], a significant relationship was observed between higher UPF intake (1068 g/day) and increased cardiometabolic risk factors such as abdominal obesity [50]. In addition, in another case-control study conducted on female patients under 70 years and male patients under 60 years, the risk of premature CAD, which is defined as stenosis of 75% or greater in at least one coronary artery or a stenosis of 50% or more in the left main coronary artery, was explored. It was revealed that in subjects with greater daily intake of UPF (430 g/day), the risk of premature CAD was elevated by about two times compared to participants who had lower daily UPF consumption (404 g/day) [12]. Also, within a cohort study from Atherosclerosis Risk in Communities (ARIC) in the USA, Du et al. [51]. demonstrated that middle-aged American participants who consumed more than four servings per day of UPF had a greater chance of having CAD compared to those who had UPF intake of fewer than four servings per day. Moreover, this study reported that among subjects consuming more than 4 servings of UPF per day, each additional serving increased the incidence of CAD by 3.2% [51]. Another study performed by da Silva et al. [52] on 2,357 participants with an average UPF intake of about 18% of their total energy intake, reported that a straightforward link was identified between UPF intake and odds of peripheral arterial disease in women and whole cohort participants. However, such a relationship was not observed among men [52]. Furthermore, among type 2 diabetes patients, the study found that daily intake of 117 g of UPF significantly increased the risk of the development of CVDs compared to those with consuming 18 g of UPF per day [53]. In a cohort study, investigators found that participants who consumed 500 g/day of UPF had a twofold increase in the likelihood of developing coronary atherosclerosis compared to those who consumed 100 g/day of UPF [54].

Several biological explanations have been proposed for the potential relationship between UPF consumption and risk of CAD. The nutrient profile of UPF is often skewed, characterized by high levels of added sugars, salts, and unhealthy fats (such as trans fats and saturated fats) while being low in dietary fiber. This makes UPF more appealing and delicious, promoting overconsumption and leading to the displacement of healthier food options [55–59]. UPF contributes to changes in atherogenic and anti-atherogenic lipid profiles, including increased triglycerides and LDL-C levels and decreased HDL-C levels, which may elevate the risk of atherosclerosis [10, 59, 60]. UPF is also known to induce high glycemic responses and provide low satiety, which can result in increased calorie intake and subsequent weight gain—both of which are significant risk factors for CAD [55–59]. Interestingly, the current results align with previous research showing that individuals who consume more UPF have higher energy intakes than those who do not [55–59]. Furthermore, the processing of these foods adversely affects their dietary fiber and fat intake, which can disrupt gut microbiota composition. Diets rich in UPF have been associated with decreased microbial diversity and a rise in harmful bacteria, ultimately fostering an inflammatory gut environment linked to various cardiometabolic issues [55–59, 61].

Strengths and limitations of the study

This research presents several key strengths alongside identifiable limitations. One notable strength is that the nutritional intake of the participants was assessed through a validated 168-item FFQ, which underlies the estimations of the UPF intakes, but by excluding whole grain foods from this categorization we better estimate the impact of problematic foods and drinks. Furthermore, all individuals in the study underwent coronary angiography, and two cardiologists with no information about study details assessed the conditions of participants. This process ensured reliable diagnoses based on angiogram results, including the intensity of atherosclerosis and the degree of stenosis. The severity CAD was

rigorously measured using the validated Gensini scoring system. Additionally, both regression and ROC analyses were performed, accounting for various potential confounders to investigate the nonlinear relationship between UPF and the risk of severe CAD.

On the other hand, several limitations must be recognized when interpreting these findings. Although a validated FFQ was employed, there is a possibility of recall bias affecting the accuracy of dietary data, particularly in relation to underreporting. Additionally, data information on food processing methods was not uniformly available in the NUTHER databank for all food items, which could lead to slight overestimations or underestimations of UPF consumption, that is a known issue [62]. Furthermore, the study's cross-sectional and single-center design also limits the ability to establish causal relationships between UPF, and severe CAD risk. To confirm the associations observed, further prospective investigations involving long-term follow-up duration are warranted.

Implications for clinicians and dietitians

The current findings indicate that even modest increases in UPF sources—particularly packaged snacks, sweets, ready-to-eat or heat-and-eat meals, and soft drinks—are associated with the progression of severe CAD in both normal-weight and overweight/obese individuals, regardless of BMI. These increases can significantly hinder dietary control. Therefore, it is essential to prioritize dietary strategies aimed at reducing these UPF sources for both groups. Healthcare professionals should emphasize the reduction of UPF intake in dietary counseling, encouraging patients to replace UPFs with whole, minimally processed foods such as fruits, vegetables, whole grains, and lean proteins [20]. Public health campaigns should raise awareness about the risks associated with UPF consumption and promote healthier dietary patterns through educational programs and community-based initiatives. Policymakers should consider implementing measures such as revising food labeling to clearly identify UPFs, restricting the marketing of UPFs to vulnerable populations, and incentivizing the production and consumption of healthier food options. These strategies can help mitigate the adverse effects of UPF consumption on cardiovascular health and support broader efforts to reduce the burden of CAD.

Conclusion

In conclusion, the results of this study confirm that higher intakes of UPF, particularly packaged snacks, sweets, ready-to-eat or heat meals, and soft drinks, are linked to the progression of severe CAD in both normal-weight and overweight/obese participants. Specifically, normal-weight individuals who consumed over 15% of their daily total energy intake from UPF exhibited a fivefold increase in the risk of severe CAD. Similarly, overweight and obese individuals consuming 10–15% or more of their total daily caloric intake from UPF also demonstrated a 2-3.5-fold higher risk of severe CAD. Each 10% increase in daily energy intake from UPF was also associated with about 1.6-2 times increased severe-CAD risk among overweight/obese and normal-weight individuals, respectively. To translate these findings on the dose-response associations between UPF and CAD progression into practice, we recommend encouraging patients to limit their intake of these products and adopt diets rich in whole, and minimally processed foods. While these findings indicate a direct association between UPF intake and the risk of CAD progression, independent of BMI, further prospective studies are needed to validate these results and explore the mechanisms underlying this relationship.

Abbreviations

CVD	Cardiovascular diseases
CAD	Coronary artery disease
AHA	The American Heart Association
UPF	Ultra-processed foods
CCVDs	Cardio-cerebrovascular diseases
NUTHER	Nutrition Heshmat Registry
GUMS	Guilan University of Medical Sciences
BMIs	body mass indexes
PCI	Percutaneous coronary intervention
CABG	Coronary artery bypass grafting
COPD	Chronic obstructive pulmonary disease
ACE	Angiotensin-converting enzyme inhibitors
CCBs	Calcium channel blockers
ARBs	Angiotensin II receptor blockers
BP	Blood pressure
LM	Left Main artery
LAD	Left Anterior Descending artery
LCX	Left Circumflex artery
OM	Obtuse Marginal branch
PL	Posterior Lateral branch
RCA	Right Coronary Artery
PDA	Posterior Descending Artery
LVEF	Left ventricular ejection fraction
FBS	Fasting blood glucose
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
FFQ	Food frequency questionnaire
USDA	US Department of Agriculture
FCTs	Food composition tables
SD	Standard deviations
OR-CI	odds ratios with 95% confidence intervals
RCS	Restricted cubic spline
ARIC	Atherosclerosis Risk in Communities

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Author contributions

MMR, and ZGh: Conceived and designed the research. ZGh, MMR, FD, and SA: played an important role in data collection and reviewing the patients' documents. ZGh, and MMR: Acquired data and performed data analysis. ZGh, FD, SG, SA, AS, and MMR: Played an important role in results interpretation. ZGh, MMR, FD, and SG: Drafted and revised the manuscript. All authors reviewed and approved the final version of the submitted manuscript.

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

Declarations

Ethics approval and consent to participate
The research adhered to the 2013 guidelines of the Declaration of Helsinki. The study protocol received approval from the Institutional Review Board of the Cardiovascular Diseases Research Center, affiliated with GUMS (research number 1402070311). Additionally, the GUMS Ethics Committee approved the study (ethics code IR.GUMS.REC.1402.393). Participants were informed of the study objectives and provided both oral and written consent to participate.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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