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Serum uric acid and coronary artery disease risk: a 10-year prospective cohort study in healthy adults

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Abstract

Background The role of serum uric acid (SUA) as an independent risk factor for coronary artery disease (CAD) remains controversial, particularly in understudied Middle Eastern populations with distinct metabolic and dietary profiles.

Objective To investigate the association between SUA levels and 10-year CAD incidence in a healthy Iranian cohort, adjusting for cardiometabolic confounders and exploring sex-specific relationships.

Methods A 10-year prospective cohort study was conducted using data from the Yazd Healthy Heart Project. Cluster-random sampling recruited adults aged 20–74 years free of baseline cardiovascular disease. Participants with existing coronary artery disease, insufficient data, or loss to follow-up were excluded. Serum uric acid levels were stratified into quartiles, and Cox proportional hazards models adjusted for demographic, lifestyle, and metabolic variables were analyzed using SPSS (version 27.0).

Results Over 15,420 person-years, 225 incident CAD cases occurred (14.5% cumulative incidence). In crude analysis, the highest SUA quartile (Q4: > 5.2 mg/dL) was associated with increased CAD risk (HR = 1.66, 95% CI: 1.14–2.43). However, this association attenuated after adjustment for confounders (fully adjusted HR = 1.03, 95% CI: 0.62–1.69). Sex-stratified analysis revealed a transient association in women (crude HR = 2.13, 95% CI: 1.14–3.96), which dissipated post-adjustment, while no significant association was observed in men.

Conclusion Elevated SUA levels were not independently associated with CAD risk in this healthy Middle Eastern cohort. Initial associations were attributable to confounding by metabolic factors such as obesity, dyslipidemia, and hypertension. These findings underscore the importance of contextualizing SUA's role within population-specific risk profiles and highlight the need for nuanced risk stratification strategies.

Keywords Serum uric acid, Coronary artery disease, Cohort study, Metabolic risk factors, Middle East

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Introduction

Coronary artery disease (CAD) is the largest cause of morbidity and mortality worldwide, accounting for about 19 million deaths annually and imposing a tremendous burden on healthcare systems globally [1, 2]. In the Middle East, the prevalence of CAD has reached epidemic levels, with age-standardized rates surpassing global averages. Regional studies indicate a prevalence of CAD ranging from 5.4% to 8.1% among adults aged 30 to 70 years [2]. This prevalence is influenced by a combination of increasing cardiometabolic risk factors, including diabetes (18% to 25%), obesity (35% to 45%), and dyslipidemia (40% to 60%) [2, 3]. Contributing factors also include rapid urbanization, sedentary lifestyles, and genetic predispositions, such as variants of familial hypercholesterolemia [2–4]. Acute coronary syndromes in this population typically present a decade earlier than in Western cohorts, with premature coronary artery disease constituting 30–40% of cases [5, 6]. Despite these concerning trends, epidemiological studies on non-traditional biomarkers, such as serum uric acid (SUA), are limited in Middle Eastern populations [7]. These populations display unique dietary patterns, such as high refined carbohydrate intake, and metabolic profiles that may specifically influence SUA's role in atherogenesis [8, 9].

While established risk factors like high blood pressure, abnormal cholesterol levels, and diabetes are well-recognized, growing attention is being paid to non-traditional markers, such as SUA, in the development of cardiovascular disease [2, 10, 11]. However, the association between SUA and CAD risk is still debatable [10, 12]. Some studies suggested that SUA may be an independent risk factor [13, 14], while several others remarked that the link may simply be attributed to the presence of other confounding metabolic comorbidities [10, 12]. This inconsistency underscores the need for longitudinal research studies across varied populations to clarify SUA's role in CAD pathogenesis.

Hyperuricemia is mechanistically associated with endothelial dysfunction, oxidative stress, and systemic inflammation, which are processes integral to the development of CAD [15–18]. However, SUA's dual function as an antioxidant at physiological levels and a pro-oxidant at pathological concentrations complicates its interpretation in clinical studies [19]. Numerous prior studies have been carried out on high-risk groups or populations with existing cardiometabolic disorders, where confounding by overlapping risk factors may obscure the direct effects of SUA [10]. Additionally, data from Middle Eastern populations, characterized by distinct dietary and genetic profiles that affect uric acid metabolism, are notably scarce [20, 21]. Since the prevalence of coronary artery disease in the region has increased the inconsistency is worth investigating [22].

To address these uncertainties, we conducted a 10-year prospective cohort study examining the association between SUA levels and incident CAD in a large, initially healthy Iranian population. By excluding individuals with baseline cardiovascular disease and rigorously adjusting for confounders, we aimed to disentangle SUA's independent contribution to CAD risk while exploring sex-specific associations. Our findings provide novel insights into SUA's role in CAD pathogenesis within an understudied demographic, offering implications for risk stratification and personalized prevention strategies in diverse global populations.

Methods

Study setting

This prospective longitudinal cohort study utilized data from the Yazd Healthy Heart Project (YHHP), a population-based initiative investigating cardiovascular and metabolic health [23]. According to our previously published study, sampling was conducted using a cluster-random sampling method, and the required sample size was determined based on statistical sample size estimation techniques [24]. Participants were recruited using a stratified geographic sampling framework: 100 clusters across Yazd city were delineated, with 20 households randomly chosen per cluster. From each household, one adult aged 20–74 years was randomly selected, yielding a final cohort of 2,000 individuals (1,000 male, 1,000 female). The Yazd Cardiovascular Research Center (YCRC) conducted two waves of assessments: baseline evaluations during the study's initiation (2005–2006) and a follow-up evaluation a decade later (2015–2016) [23].

Ethical statement

This study received ethical approval from the Institutional Review Board at Shahid Sadoughi University of Medical Sciences (Approval Code: IR.SSU.MEDICINE.REC.1402.182) and strictly adhered to the ethical principles outlined in the Declaration of Helsinki [25]. Participants provided written informed consent during both the baseline and follow-up phases of the research. The methodology and reporting align with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines to ensure transparency and rigor in observational research design [26].

Included participants

Out of the original 2,000 participants, 17 were lost to follow-up during the second phase and removed from the study. Of the 1,983 individuals who completed the initial assessment, 62 were excluded for having coronary

artery disease (CAD) at baseline, 78 passed away during the follow-up period, and 308 had insufficient or missing data [27]. This left a final sample of 1,552 participants (including 804 men, average age 48.6 ± 14.7 years) who were fully analyzed in this study (Fig. 1). These individuals were assessed during both the initial and follow-up phases, as described below.

Clinical and biological data

Blood samples were collected after a 12-h fasting period. Glucose and triglyceride (TG) levels were quantified using commercial assay kits (Pars Azmoon Inc., Tehran, Iran) following centrifugation. Lipid parameters—total cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL)—were assessed with Bionic diagnostic kits (Bionic Company, Tehran, Iran) on a BT 3000 biochemical autoanalyzer (Italy) [23]. Prediabetes was classified based on fasting blood sugar (FBS) levels of 100–125 mg/dL, while diabetes was defined as FBS ≥ 126 mg/dL or physician-confirmed diagnosis. Dyslipidemia criteria included TG ≥ 150 mg/dL, LDL ≥ 130 mg/dL, HDL ≤ 40 mg/dL (men) or ≤ 50 mg/dL (women), total cholesterol ≥ 200 mg/dL, active lipid-lowering therapy, or physician-verified diagnosis.

Anthropometric features

Height was assessed using a wall-mounted stadiometer on an even surface. Participants stood barefoot with heels, hips, shoulders, and head in contact with the wall, maintaining a horizontal gaze. Measurements were recorded to the nearest 0.5 cm. Body weight was determined using a digital scale (Seca, Germany) during the baseline phase (precision: 0.1 kg) and a body composition analyzer (Omron BF511, Japan) at follow-up, with participants wearing light clothing. Waist circumference (superior iliac crest) and hip circumference (maximal gluteal protrusion) were measured to 0.1 cm accuracy using a rigid tape. Obesity was defined as meeting any of the following: BMI > 30 kg/m^2, waist circumference > 94 cm (men) or > 80 cm (women), or waist-to-hip ratio > 0.9 (men) or > 0.85 (women) [28].

Blood pressure measurements

Blood pressure measurements were obtained using an Omron M6 Comfort automated digital monitor (Osaka, Japan). Participants remained seated with their right arm positioned at heart level, and trained nursing staff recorded two sequential readings spaced 5 min apart. Prehypertension was defined as systolic blood pressure (SBP) levels of 120–139 mmHg or diastolic blood pressure (DBP) of 80–89 mmHg. Hypertension criteria included SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, or active use of antihypertensive medications.

Physical activity, education, awareness and medicine consumption

Trained interviewers administered structured questionnaires to collect demographic data, educational attainment, physical activity patterns, smoking behavior, and angina symptoms. Educational levels were stratified into three categories: primary, high school, or academic. Physical activity was assessed using the International Physical Activity Questionnaire (IPAQ) [29], which quantified participants' weekly frequency and duration of walking, moderate-intensity activities (e.g., cycling), and vigorous-intensity activities (e.g., running). Responses were translated into MET-hours per week (1 MET-hour = 1 kcal/kg/hour) [30], categorizing participants into

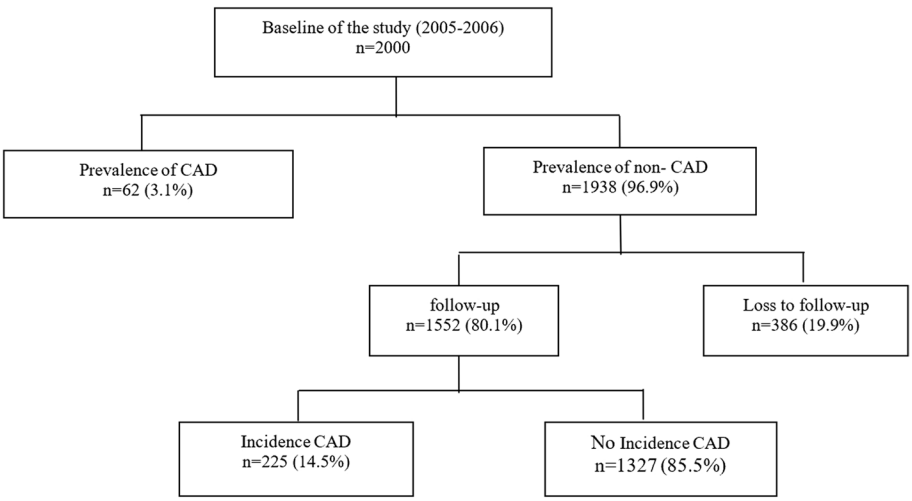

Fig. 1 Participant Flowchart

low-, moderate-, or high-activity groups. Smoking status was dichotomized into current smokers or non-smokers. A family history of premature coronary heart disease (CHD) was defined as the diagnosis of CHD in a father or brother prior to age 45, or in a mother or sister prior to age 55 [23]. Additionally, participants reported medical histories and treatments for diabetes, dyslipidemia, and hypertension, enabling evaluation of pre-existing risk factors and their therapeutic management.

Outcome definition

Coronary artery disease (CAD) events included fatal/nonfatal CAD, myocardial infarction (MI), percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), and new-onset angina. New angina diagnoses required confirmation via the Rose angina questionnaire [31] combined with supportive evidence: electrocardiogram (ECG) abnormalities, elevated cardiac enzymes, positive exercise tolerance tests, or angiographic findings. ECG interpretations underwent dual verification by a general practitioner and trained nurse, with unresolved discrepancies adjudicated by a cardiologist. Event timelines for outcomes (e.g., MI, CABG, PCI, abnormal biomarkers) were determined through retrospective review of medical records.

Statistical analysis

Analyses were executed in SPSS (version 27.0; IBM Corp., Armonk, NY), a statistical analysis software. Categorical data were expressed as frequency counts (percentages), with intergroup differences analyzed via chi-square tests. Continuous variables were reported as mean ± standard deviation and compared using independent samples t-tests. The 10-year incidence rate of CAD per 1,000 person-years was derived using the formula:

$$Incidence\ rate = (Number\ of\ new\ CAD\ cases \div [Total\ population\ at\ risk \times Follow-up\ duration\ in\ years]) \times 1{,}000$$

Advanced age was classified as exceeding 45 years for males and 55 years for females. Variables such as sex, smoking status, physical activity level, education, obesity, dyslipidemia, hypertension, and diabetes were treated as categorical (nominal) data. These variables were evaluated across the entire cohort and further stratified by gender.

A quartile-based analysis was performed by dividing the SUA into four equal parts, with the lowest quartile set as the reference point. The SUA quartiles' threshold levels were established in the following manner: quartile 1 (Q1) ≤3.5, 3.5 < quartile 2 (Q2) ≤4.3, 4.3 < quartile 3 (Q3) ≤5.2, and 5.2 < quartile 4 (Q4). Cox proportional hazards models were employed to quantify the association between baseline serum uric acid levels (as quartiles and continuous) and the 10-year CAD development, with outcomes reported as hazard ratios (HRs) and 95% confidence intervals (CIs). Three models were assessed: Model I: adjusted for age and sex; Model II: adjusted for age, sex, smoking, physical activity, education, and family history; Model III: Model II plus HDL, total cholesterol, BMI, Waist to hip ratio, SBP, DBP, LDL. A two-sided P-value of less than 0.05 was considered statistically significant.

Results

Characteristics of participants

Table 1 compares the baseline clinical and biological profiles of analyzed participants versus those excluded from analysis. Individuals excluded from the study were older on average and had a lower proportion of males compared to participants retained in follow-up.

Table 2 outlines baseline participant characteristics stratified by serum uric acid (SUA) quartiles. Individuals in the highest SUA quartile (Q4) were older, predominantly male, and demonstrated elevated smoking prevalence, blood pressure, fasting blood glucose (FBS), total cholesterol, low-density lipoprotein (LDL), and body mass index (BMI) relative to lower quartiles.

Incidence of coronary artery disease

As detailed in prior research [32], 225 incident CAD cases were documented over 15,420 person-years of follow-up. Male and female participants experienced 135 and 90 events, respectively. The 10-year cumulative incidence rate was 16.8 (95% CI: 14.4–19.2) per 1,000 person-years in men, compared to 12.0 (95% CI: 9.5–14.5) in women. Overall, 14.5% of participants developed new-onset CAD by the follow-up assessment.

Survival analysis

Kaplan–Meier survival analysis was conducted to evaluate the association between survival probability and coronary artery disease (CAD) incidence over the 10-year follow-up period. Using R software (version 4.4.3), the overall survival curve (Fig. 2) demonstrated a sustained high survival probability of > 0.80 during the first 8 years, declining progressively to approximately 0.60 by year 12.

Sex-stratified analysis (Fig. 3) revealed significant disparities in survival outcomes. Women exhibited consistently higher survival probabilities compared to men, with a pronounced divergence in survival curves beginning at year 4 and widening thereafter. The log-rank test confirmed a statistically significant difference between sexes ($\chi^2 = 7.6$, $p = 0.0055$). At year 12, the survival probability for women (sex = 2) remained 15–20% higher than for men (sex = 1).

These findings underscore sex as a significant predictor of CAD-free survival in this cohort. Further multivariate Cox regression analyses (Table 3) corroborated these

Table 1 Baseline clinical characteristics and biological profiles of the participants according to the follow-up process

	Included	Excluded	p-value
Number of participants	1552	448	
Age (years)	48.6 ± 14.7	49.1 ± 16.8	< 0.001
Male (%)	804 (51.8)	193 (43.2)	0.01
Socioeconomic status (%)			0.09
Low	212 (30.2)	63 (34.6)	
Moderate	275 (39.2)	77 (42.3)	
High	215 (30.6)	42 (23.1)	
Education (%)			0.09
Primary	903 (59.8)	283 (64.3)	
High school	460 (30.4)	127 (28.9)	
Academic	148 (9.8)	30 (6.8)	
Anthropometry			
Weight (Kg)	71.3 ± 12.9	68.9 ± 13	0.96
Waist/hip ratio	0.9 ± 0.1	0.9 ± 0.1	0.73
Waist circumference (cm)	93.8 ± 12.1	92.4 ± 12.6	0.64
Body mass index (Kg/m^2)	26.2 ± 4.3	26 ± 4.9	0.64
Current smokers (%)	280 (18.1)	69 (15.6)	0.23
Physical activity (%)			0.44
Low	719 (67.9)	223 (71.7)	
Moderate	290 (27.4)	75 (24.1)	
Vigorous	50 (4.7)	13 (4.2)	
Blood pressure (mm Hg)			
Systolic	128.2 ± 15.5	127.9 ± 16.4	0.98
Diastolic	82.7 ± 8.8	82 ± 9.2	0.15
Diabetes (%)	264 (17.0)	93 (20.8)	0.60
Blood levels (mg/dL)			
Fasting glucose	103.1 ± 46	102 ± 44.2	0.92
Total cholesterol	199.3 ± 45.1	198.3 ± 93.9	0.23
LDL-cholesterol	109.2 ± 36.8	106.2 ± 35.1	0.40
HDL-cholesterol	54.1 ± 13.8	53.2 ± 13.2	0.41
Triglycerides	179.8 ± 109.2	170.7 ± 103.1	0.29
Uric acid	4.4 ± 1.3	4.7 ± 6.7	0.06

Results are expressed as number of participants (column percentage) for categorical variables and as average ± standard deviation for continuous variables. Between group comparisons performed using chi-square for categorical variables and by student's t-test for continuous variables

trends, demonstrating that traditional metabolic risk factors attenuated the crude associations observed in unadjusted models.

SUA levels and incidence of CAD

In the total study population, the crude Cox regression model revealed a significant association between the highest serum uric acid (SUA) quartile (Q4: > 5 mg/dL) and incident coronary artery disease (CAD), with a hazard ratio (HR) of 1.66 (95% CI: 1.14–2.43; p for trend = 0.003). However, this association attenuated progressively with sequential adjustment for confounders. In the fully adjusted model (Model III), which included age, sex, lifestyle factors, anthropometric measures, and cardiometabolic biomarkers, the HR for Q4 declined to 1.03 (95% CI: 0.62–1.69; p for trend = 0.79), indicating no independent relationship (Table 3).

Gender-stratified analyses demonstrated sex-specific disparities in Table 3. Among women, the crude model showed a significant 2.13-fold increased CAD risk in Q4 (95% CI: 1.14–3.96; p for trend = 0.03), but this association dissipated after adjustment for covariates (Model III HR = 1.65; 95% CI: 0.67–4.08; p for trend = 0.56). In contrast, men exhibited no significant association between SUA quartiles and CAD risk in any model (e.g., Model III HR for Q4 = 0.91; 95% CI: 0.49–1.70; p for trend = 0.63).

These findings suggest that elevated SUA levels are not independently predictive of CAD incidence in this cohort. The initial crude associations likely reflect confounding by interrelated metabolic and cardiovascular risk factors, such as obesity, dyslipidemia, and hypertension, which were accounted for in adjusted models.

Discussion

This prospective cohort study with a mean follow-up of 9.9 years contribute to the discussion on the relationship between serum uric acid (SUA) levels and the risk of coronary artery disease (CAD). Our analysis indicated no significant linear association between SUA levels and CAD incidence in a healthy Middle Eastern cohort. These findings align with prior observational studies reporting inconsistent associations [33, 34] and Mendelian randomization analyses questioning a causal role for serum uric acid (SUA) in cardiovascular disease [35, 36]. Epidemiological evidence further underscores that SUA is, at best, a weak predictor of cardiovascular risk in the general population after adjustment for confounding factors such as obesity, hypertension, and dyslipidemia [37, 38]. This underscores the importance of contextualizing SUA's role within specific physiological ranges (e.g., hyperuricemia thresholds) and subpopulations, where interactions with metabolic comorbidities or genetic predispositions may influence its clinical relevance.

Serum uric acid (SUA) demonstrates a dual physiological role, functioning as a protective antioxidant at lower concentrations but shifting toward a pro-oxidative, pathogenic agent when elevated [19]. This duality helps clarify the non-linear associations frequently observed in epidemiological and clinical studies. In human serum, UA exceeds the concentration of other endogenous antioxidants (e.g., melatonin, carotenoids) by more than tenfold and demonstrates superior antioxidant capacity [39]. At subclinical levels, Uric acid enhances the body's oxidative defense by scavenging reactive oxygen species (ROS) such as peroxynitrite, thereby mitigating damage

Table 2 Baseline clinical characteristics and biological variables of the participants according to serum uric acid quartiles

	First	Second	Third	Fourth	p-value
Number of participants					
Age (years)	45.8 ± 14.2	48.8 ± 14.6	49.7 ± 14.7	49.7 ± 15.0	0.001
Mean follow-up (years)	9.8 ± 1.0	9.9 ± 1.2	9.9 ± 1.0	9.9 ± 1.1	0.41
Male (%)	83 (23.7)	161 (40.8)	253 (62.3)	302 (76.6)	< 0.001
Socioeconomic status (%)					0.87
Low	44 (32.4)	55 (32.5)	58 (29.6)	54 (27)	
Moderate	49 (36)	62 (36.7)	80 (40.8)	84 (42)	
High	43 (31.6)	52 (30.8)	58 (29.6)	62 (31)	
Education (%)					0.04
Primary	219 (63.3)	242 (62.7)	229 (58)	209 (55.4)	
High school	104 (30.1)	106 (27.5)	116 (29.4)	131 (34.7)	
Academic	23 (6.6)	38 (9.8)	50 (12.7)	37 (9.8)	
Anthropometry					
Weight (Kg)	66.6 ± 12.7	69.5 ± 12.2	72.1 ± 12	76.6 ± 12.7	< 0.001
Weight/hip ratio	0.88 ± 0.11	0.9 ± 0.08	0.92 ± 0.07	0.93 ± 0.09	< 0.001
Waist circumference (cm)	90.7 ± 12.7	92.6 ± 11.6	93.9 ± 11.2	97.6 ± 12	< 0.001
Body mass index (Kg/m^2)	25.6 ± 4.6	26 ± 4.4	26.1 ± 4.3	26.9 ± 4	< 0.001
Current smokers (%)	34 (9.7)	63 (15.9)	90 (22.2)	63 (23.6)	< 0.001
Physical activity (%)					0.74
Low	134 (63.8)	182 (68.7)	202 (70.4)	196 (67.4)	
Moderate	66 (31.4)	69 (26)	71 (24.7)	83 (28.5)	
Vigorous	10 (4.8)	14 (5.3)	14 (4.9)	12 (4.1)	
Blood pressure (mm Hg)					
Systolic	124.1 ± 15.4	126.5 ± 15.4	130.3 ± 14.8	131.5 ± 15.4	< 0.001
Diastolic	80.6 ± 80.6	81.5 ± 8.4	84 ± 8.2	84.2 ± 9.3	< 0.001
Diabetes (%)	81 (23.1)	68 (17.2)	57 (14)	51 (12.9)	0.001
Family history of CAD	50 (14.4)	54 (14)	58 (14.6)	60 (15.5)	0.9
Blood levels (mg/dL)					
Fasting glucose	113.2 ± 62.2	104.7 ± 51.8	97.4 ± 32.7	98.2 ± 30.2	< 0.001
Total cholesterol	189.1 ± 42.1	198.7 ± 46.1	201.5 ± 42.3	206.6 ± 48	< 0.001
LDL	102.6 ± 35.4	109.6 ± 35.6	111.6 ± 36.7	112.2 ± 38.7	< 0.001
Triglycerides*	132 (125–186)	168 (135–208)	223 (160–225)	249 (179–264)	< 0.001
HDL	56.0 ± 13.6	55.6 ± 13.0	53.4 ± 14.3	51.7 ± 13.8	< 0.001

Results are expressed as number of participants (column percentage) for categorical variables and as average ± standard deviation or median (interquartile range) for continuous variables. Between group comparisons performed using chi-square for categorical variables and analysis of variance or nonparametric tests for continuous variables

to cellular macromolecules like lipids, proteins, and nucleic acids. Its antioxidant mechanisms include chelating transition metal ions, reducing lipid peroxidation, and preserving tetrahydrobiopterin activity, a critical factor in counteracting oxidative stress [40]. At physiological levels, UA scavenges approximately two-thirds of circulating free radicals, a critical defense against oxidative damage [39]. Clinical studies further support this protective role, demonstrating that exogenous uric acid administration in healthy individuals and athletes significantly reduces ROS generation, underscoring its capacity to maintain vascular health and cellular integrity [41]. Notably, epidemiological studies associate hyperuricemia with a markedly reduced risk of neurodegenerative disorders, including Parkinson's disease, suggesting UA's protective role extends beyond vascular health [42]. However, once SUA surpasses the clinically defined hyperuricemia thresholds (6.8 mg/dL in men; 6.0 mg/dL in women), it is increasingly linked to detrimental vascular effects, including endothelial dysfunction, low-grade inflammation, and arterial remodeling [43]. These effects are thought to be mediated by xanthine oxidase–driven oxidative stress and activation of the renin–angiotensin–aldosterone system [16, 44]. In our cohort,

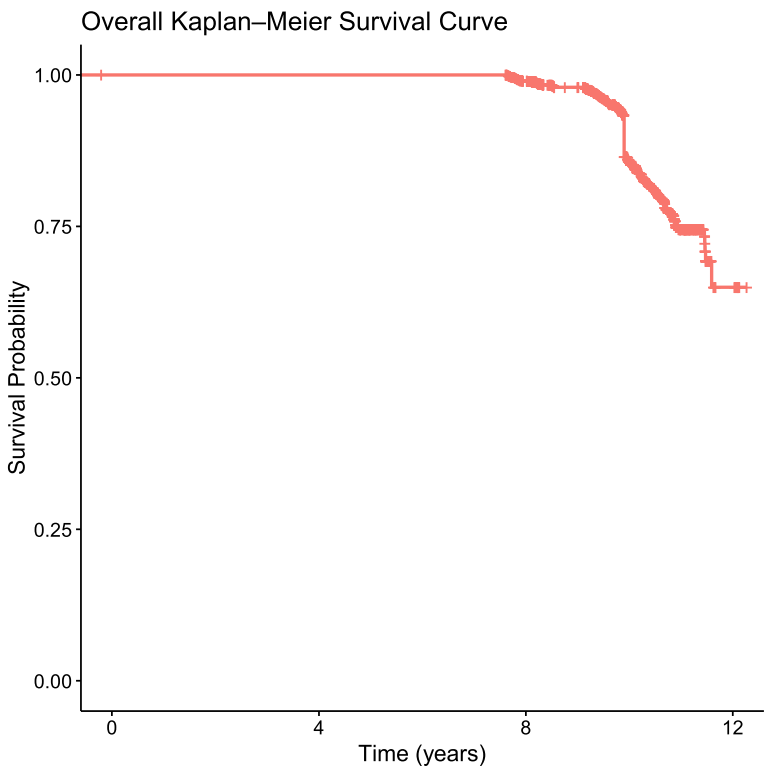

Fig. 2 Kaplan–Meier Survival Curve for 10-Year CAD Incidence

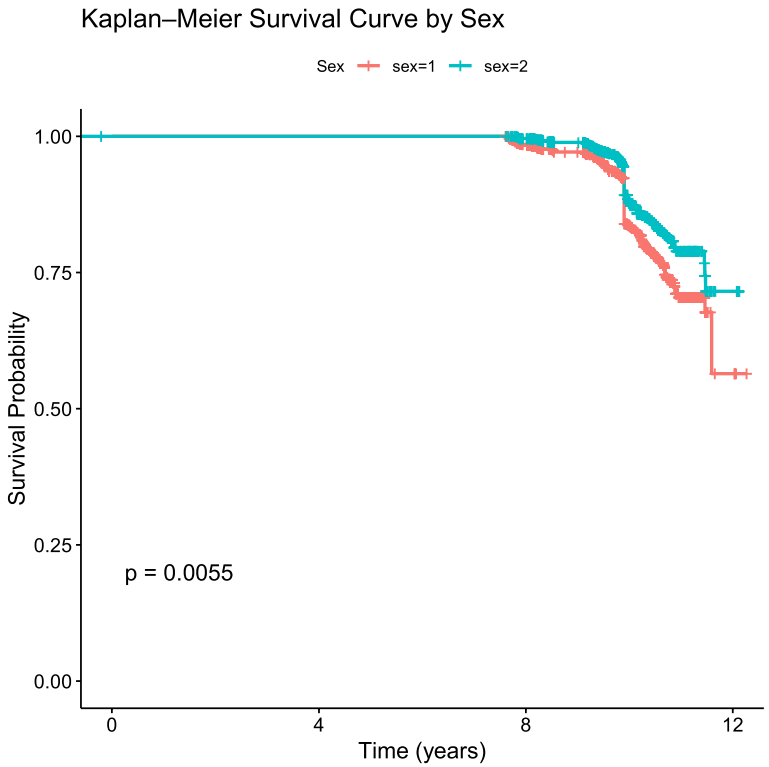

Fig. 3 Sex-Stratified Kaplan–Meier Survival Curves

Table 3 Risk of CAD according to quartiles of serum uric acid, overall and stratified by gender

	Q1	Q2	Q3	Q4	P for trend
All participants					
Crude	1	1.00 (0.66–1.51)	1.09 (0.73–1.65)	1.66 (1.14–2.43)	0.003
Model I	1	0.82 (0.54–1.24)	0.79 (0.52–1.20)	1.14 (0.77–1.70)	0.31
Model II	1	0.99 (0.60–1.62)	0.93 (0.56–1.53)	1.32 (0.82–2.14)	0.20
Model III	1	0.87 (0.52–1.45)	0.72 (0.43–1.21)	1.03 (0.62–1.69)	0.79
Men					
Crude	1	0.56 (0.30–1.06)	0.65 (0.37–1.13)	0.94 (0.56–1.58)	0.39
Model I	1	0.58 (0.31–1.08)	0.64 (0.36–1.12)	0.95 (0.57–1.58)	0.42
Model II	1	0.71 (0.34–1.47)	0.80 (0.42–1.54)	1.09 (0.59–2.02)	0.32
Model III	1	0.61 (0.29–1.30)	0.63 (0.32–1.23)	0.91 (0.49–1.70)	0.63
Women					
Crude	1	1.38 (0.79–2.40)	1.38 (0.74–2.57)	2.13 (1.14–3.96)	0.03
Model I	1	1.05 (0.60–1.85)	0.93 (0.49–1.73)	1.24 (0.66–2.34)	0.65
Model II	1	1.30 (0.66–2.56)	0.90 (0.40–2.03)	1.78 (0.81–3.90)	0.36
Model III	1	1.21 (0.58–2.51)	0.8 (0.33–1.92)	1.65 (0.67–4.08)	0.56

Results are expressed as hazard ratio and (95% confidence interval). Model I: adjusted for age and sex; Model II: Adjusted for age, sex, smoking, physical activity, education, and family history; Model III: adjusted for Model II variables plus HDL, total cholesterol, BMI, Waist to hip ratio, SBP, DBP, LDL. The SUA quartiles'threshold levels (mg/dL) were established in the following manner: (Q1) $\leq$ 3.5, 3.5 < (Q2) $\leq$ 4.3, 4.3 < (Q3) $\leq$ 5.2, and 5.2 < (Q4)

SUA levels were consistently below these pathological thresholds, implying that the antioxidant properties of uric acid may have played a protective role in attenuating oxidative stress and reducing early atherogenic risk. This threshold-dependent behavior is consistent with findings that associate high SUA levels with cardiovascular disease primarily in metabolically compromised populations, whereas minimal or inverse associations are typically observed in healthier cohorts [12]. The absence of baseline cardiovascular disorders and also the relatively low SUA level concentrations in our study population likely explain the divergence from trends seen in broader meta-analyses that involve high-risk groups. These findings underline the need for a more detailed stratified risk assessment when interpreting SUA's clinical relevance across diverse population profiles.

Our gender-stratified analysis revealed no statistically significant relationship between serum uric acid (SUA) levels and coronary artery disease (CAD) risk in either men or women after adjusting for confounding variables. One possible explanation involves the influence of estrogen, which promotes uric acid excretion and may protect women against its harmful vascular effects [45, 46]. As many women in our cohort were likely postmenopausal, the decline in estrogen levels could plausibly increase their vulnerability to the negative cardiovascular impact of elevated SUA. In parallel, in men, no distinct association emerged, implying that the contribution of SUA may be overshadowed by the predominance of traditional metabolic risk factors (for instance, central obesity, insulin resistance, and dyslipidemia) [47, 48] or might be neutralized by compensatory vascular mechanisms [49–51]. Also, residual confounding by unmeasured factors (e.g., muscle mass, dietary patterns) cannot be excluded. These findings underscore the necessity of sex-specific analyses in future studies and highlight the complexity of SUA's role in CAD pathogenesis.

Strengths and Limitations

This study's strengths include its prospective cohort design, which minimizes biases common in observational studies, and its rigorous outcome assessment combining physician evaluations with standardized diagnostic tools. By controlling for key confounders such as anthropometric and cardiometabolic variables, the analysis enhances both accuracy and clinical relevance. Unlike prior research limited to middle-aged and older populations, our cohort encompassed a broader age range, including younger participants, and featured an extended follow-up period to assess cumulative lifetime coronary artery disease (CAD) risk. However, the prolonged observation timeframe may have introduced biases due to unmonitored lifestyle changes or inconsistent health monitoring among participants over the study duration.

This study has several limitations. First, detailed data on medications influencing coronary artery disease (CAD) risk—such as urate-lowering agents and diuretics—were unavailable [52], and creatinine levels to assess kidney function in relation to uric acid excretion were not collected [53]. Second, the exclusive focus on a

single urban center restricts generalizability and introduces urban-specific bias. Reliance on a single baseline assessment of risk factors may fail to capture intraindividual variability over time, while self-reported categorical variables (e.g., physical activity, smoking) are prone to misclassification, reporting bias, and non-response bias. However, prior studies using objective measures (e.g., accelerometers) reported similar findings, supporting the validity of our methodology [54]. Third, despite a 20% attrition rate during follow-up, comparative analyses revealed no significant differences between retained and excluded participants, substantially mitigating attrition bias concerns. Finally, this study did not include measurements of inflammatory biomarkers (e.g., CRP, IL-6), which may have offered more detailed insights into the mechanistic pathways connecting hyperuricemia with vascular dysfunction and cardiovascular outcomes.

Clinical and public health implications

In healthy individuals, routine measurement might not help to better estimate the risk of coronary artery diseases. But the possible correlation implies SUA as a marker of metabolic imbalance among high-risk subgroups (those with comorbidities like hypertension, diabetes, chronic renal disease), who were underrepresented in our analysis. Targeted interventions in these patients, like xanthine oxidase inhibitors or dietary changes (e.g., lowering fructose intake), should be taken under consideration to see whether SUA lowering offers cardiovascular advantages. Public health policies in areas with increasing CAD incidence, such as the Middle East, should prioritize established risk factors (e.g., hypertension, diabetes) while monitoring SUA's role in secondary prevention.

Conclusion

In a study involving healthy individuals, serum uric acid (SUA) may not exhibit a direct, independent correlation with coronary artery disease (CAD). It indicates that the association may be more complex and could involve certain thresholds. The dual role of SUA as both an antioxidant and pro-oxidant depending on the serum concentrations, along with variations related to sex and diet, complicates interpretation in large population studies. Future research should investigate these details through more nuanced analytical methods and concentrate on elucidating the underlying biological mechanisms in individuals with diverse metabolic profiles. This approach may enhance cardiovascular risk assessment and facilitate the development of personalized prevention strategies, which are essential for addressing the global burden of CAD.

Abbreviations

BMI	Body Mass Index
CAD	Coronary Artery Disease
CI	Confidence Interval
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
FBS	Fasting Blood Sugar
HDL	High-Density Lipoprotein
IPAQ	International Physical Activity Questionnaire
LDL	Low-Density Lipoprotein
ROS	Reactive Oxygen Species
SBP	Systolic Blood Pressure
SD	Standard Deviation
SUA	Serum Uric Acid
TG	Triglyceride
YHHP	Yazd Healthy Heart Project

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Authors' contributions

M.S. conceptualized the study, designed the methodology, conducted data analysis, and drafted the manuscript; S.M. collected data, performed literature reviews, and contributed to manuscript drafting; P.M. supervised the research, executed statistical analyses, and critically revised the manuscript for intellectual rigor; S.R.M. interpreted data, reviewed the manuscript, and approved the final version; S.M.N. curated datasets, edited the manuscript, and ensured quality control; H.M. acquired data, developed visualizations, and supported manuscript preparation; A.M.1 administered project logistics, validated results, and endorsed the final manuscript; A.M.2 (corresponding author) co-conceptualized the study, supervised its execution, finalized edits, and submitted the manuscript. All authors assumed full responsibility for the analytical framework, interpretation of findings, and conducted critical revisions of the manuscript. Each contributor independently accessed and validated the underlying data, reviewed and endorsed the final manuscript prior to submission. A.M.2, as the corresponding author, assumes full responsibility for the integrity of the dataset and the precision of statistical analyses, serving as the guarantor of data integrity and analytical accuracy. In this capacity, A.M.2 retains unrestricted access to all study datasets and oversees methodological rigor.
All authors assumed full responsibility for the analytical framework, interpretation of findings, and conducted critical revisions of the manuscript. Each contributor independently accessed and validated the underlying data, reviewed and endorsed the final manuscript prior to submission. A.M.2, as the corresponding author, assumes full responsibility for the integrity of the dataset and the precision of statistical analyses, serving as the guarantor of data integrity and analytical accuracy. In this capacity, A.M.2 retains unrestricted access to all study datasets and oversees methodological rigor.

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Data availability

The datasets produced and/or analyzed in this study are accessible from the corresponding author upon formal request, subject to ethical and privacy guidelines.

Declarations

Ethics approval and consent to participate

This study received ethical approval from the Institutional Review Board at Shahid Sadoughi University of Medical Sciences (Approval Code: IR.SSU.

MEDICINE.REC.1402.182) and strictly adhered to the ethical principles outlined in the Declaration of Helsinki. Participants provided written informed consent during both the baseline and follow-up phases of the research. The methodology and reporting align with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines to ensure transparency and rigor in observational research design.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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