Original Research

The association between serum uric acid levels and 10-year cardiovascular disease incidence: results from the ATTICA prospective study

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Limited data suggests possible gender-specific association between serum uric acid (SUA) and cardiovascular disease (CVD) incidence. The aim of the present analysis was to evaluate the association between SUA levels and 10-year CVD incidence (2002–2012) in the ATTICA study participants. Overall, 1687 apparently healthy volunteers, with SUA measurements, residing in the greater metropolitan Athens area (Greece), were included. Multivariable Cox-regression models were used to estimate the hazard ratios for SUA in relation to 10-year CVD incidence. Receiver operating curve analysis was conducted to detect optimal SUA cut-off values. Participants in the 2nd and 3rd SUA tertile had 29 and 73% higher 10-year CVD incidence compared with those in the 1st tertile ($p < 0.001$). In gender-specific analysis, only in women SUA was independently associated with CVD incidence; women in the 3rd SUA tertile had 79% greater 10-year CVD event risk compared to their 1st tertile counterparts. Obese in the 3rd SUA tertile had 2-times higher CVD incidence compared to those in the 1st tertile. Similar findings were observed in metabolically healthy (vs. unhealthy) and metabolically healthy obese. SUA thresholds best predicting 10-year CVD incidence was 5.05 and 4.15 mg/dL (0.30 and 0.25 mmol/L) in men and women, respectively. In conclusion, increased SUA levels were independently related to 10-year CVD event rate in women, obese and metabolically healthy individuals. SUA could predict 10-year CVD incidence even at low levels. Further studies are warranted to identify SUA cut-off values that may improve the detection of individuals at higher CVD risk in clinical practice.

Keywords

Serum uric acid; Cardiovascular disease; ATTICA study; Gender; Metabolic health status

1. Introduction

Serum uric acid (SUA), the final oxidation product of purine metabolism, has been traditionally associated with gout arthritis/arthropathy and nephrolithiasis [1]. During the last decades, there is accumulating evidence linking increased SUA levels with cardiovascular disease (CVD) [2–4], chronic kidney disease [5–7] and several metabolic disorders, such as diabetes and its complications [8–13], metabolic syndrome (MetS) [14, 15] and non-alcoholic fatty liver disease [16–18]. Furthermore, hyperuricemia has been related to increased total and CVD mortality [19–22]. Apart from these diseases, SUA levels are influenced by gender [23], age [24] and drug therapy (e.g., antihypertensive, antidiabetic and hypolipidemic) [25–30]. It should be noted that the latest (2018) guidelines of the European Society of Cardiology (ESC)/European Society of Hypertension (ESH) included SUA among CVD risk factors that should be evaluated to stratify individual's risk [31, 32]. There has been some discussion regarding the possible effect of gender on the association between SUA and CVD risk, the latter being stronger in women [33–36]. However, available data is limited.

SUA cut-off levels that define hyperuricemia [i.e., >7 mg/dL (0.42 mmol/L) in men and >6 mg/dL (0.36 mmol/L) in women] are based on the saturation point of SUA [37]. However, there is some evidence suggesting that CVD risk may be increased at even lower SUA levels [e.g., ≤5.7 mg/dL (0.34 mmol/L)] [37]. Similar findings have been reported for the links between SUA, all-cause and CVD mortality with SUA cut-off values ranging from 4.7 to 5.7 mg/dL (from 0.28 to 0.34 mmol/L) [38–40]. Overall, there is a need for further evidence to identify CVD SUA thresholds that may improve the detection of patients at higher CVD risk.

Obese patients in the absence of metabolic disorders are characterized as metabolically healthy obese (MHO) [41]. Although a unified definition of MHO is lacking, the features of the MetS (i.e., abnormal glucose, blood pressure, high-density lipoprotein and triglycerides) are the most frequent used criteria [42]. MHO individuals may be at an increased risk for CVD [43–45]. There are only a few studies reporting that elevated SUA levels may affect CVD risk in MHO individuals [46, 47].

The aim of the present study was to evaluate the association between SUA levels and 10-year CVD incidence in the ATTICA cohort study, as well as the potential synergistic effects of gender and metabolic health status on this association. SUA cut-off values predicting CVD incidence were also identified.

2. Methods

2.1 Design

The ATTICA study is a prospective, observational cohort investigation which was initiated in 2001 and had two follow-up examinations, on 2006 and 2012 [48].

2.2 Setting

Apparently healthy individuals, aged 18 and over, randomly and stratified selected from the greater metropolitan Athens area, Greece, were participated. All participants were free of CVD and other chronic diseases, according to study protocol [48].

2.3 Sample

At baseline examination (2001–2002), n = 3042 men and women agreed to participate. Of the enrolled participants, n = 1514 (49.8%) were men (mean age: 46 $\pm$ 13 years) and n = 1528 (50.2%) were women (mean age: 45 $\pm$ 14 years). A detailed clinical evaluation was performed by trained physicians. During 2011–2012, the 10-year follow-up was performed by the ATTICA study's investigators group. The combined endpoint studied was the development of a fatal or non-fatal CVD event, defined as the development of: acute myocardial infarction, or unstable angina, or other identified forms of ischemia (WHO-ICD coding 410–414.9, 427.2, 427.6), or heart failure of different types and chronic arrhythmias (WHO-ICD coding 400.0–404.9, 427.0–427.5, 427.9–) or stroke (WHO-ICD coding 430–438). For participants who died during the follow-up, information was retrieved from relatives and death certificates. Of the initially enrolled participants, n = 2563 were found at follow-up evaluation and n = 2020 of them had accurate data regarding CVD outcomes.

For the present analysis, another n = 333 participants with missing SUA measurements at baseline, were excluded. Thus, the working sample consists of n = 1687 individuals; n = 825 men (mean age: 46 $\pm$ 13 years) and n = 862 women (mean age: 45 $\pm$ 14 years).

2.4 Bioethics

The ATTICA study was approved by the Bioethics Committee of Athens Medical School (#017/1.5.2001). The study was carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association. All participants were informed about the study aims and procedures and provided written informed consent.

2.5 Measurements

2.5.1 Biochemical measurements

Biochemical evaluation was carried out in the biochemistry laboratory of the First Cardiology Clinic of University of Athens School of Medicine, following the criteria of the World Health Organization Reference Laboratories [49, 50]. SUA was measured only at baseline in mg/dL (1 mg/dL = 59.48 μmol/L) using an enzymatic colorimetric test with the uricase-peroxidase method (UA plus, Roche Diagnostics, Mannheim, Germany). The measuring range was 0.2–25 mg/dL (0.01–1.49 mmol/L) and the inter- and intra-assay variability was 0.5 and 1.7%, respectively. In the present work, participants were categorized according to gender-specific SUA tertiles.

2.5.2 Sociodemographic and lifestyle characteristics

Age, gender, education, adherence to the Mediterranean diet [52, 53], physical activity [54], smoking, body mass index (BMI) and metabolic health status were recorded. In details, BMI was calculated as weight (in kg) divided by height (in m squared). Normal weight was defined as BMI between 18.5 and 25 kg/m^2, overweight as BMI between 25 and 29.9 kg/m^2 and obesity as BMI $\geq$30 kg/m^2. Underweight was defined as BMI $<$18.5 kg/m^2. Metabolic health status was defined using the criteria suggested by Lavie *et al.* [51]. Healthy metabolic status was defined as the absence of hypertension, dyslipidemia and dysglycemia. For the scope of the present analysis, participants were divided in four groups as follows: (a) metabolically healthy non-obese (MHN) defined as BMI $<$30 kg/m^2 and healthy metabolic status; (b) metabolically healthy obese (MHO) defined as BMI $\geq$30 kg/m^2 and healthy metabolic status; (c) metabolically unhealthy non-obese (MUN) defined as BMI $<$30 kg/m^2 and unhealthy metabolic status; (d) metabolically unhealthy obese (MUO) defined as BMI $\geq$30 kg/m^2 and unhealthy metabolic status.

2.5.3 Statistical analysis

Categorical variables are presented as absolute (n) and relative frequencies (%). Continuous variables are presented as mean $\pm$ standard deviation. Associations between normally distributed variables and SUA tertiles were evaluated by one-way ANOVA. Whether these variables were normally distributed was tested through P-P plot and equality of variances by Levene's test. For non-normally distributed variables, the Kruskal-Wallis test was used. Associations between categorical variables and SUA tertiles were evaluated with the chi-squared test. Hazard ratios (HR) and their corresponding 95% confidence intervals (CI) for SUA tertiles in relation to the examined endpoint (i.e., 10-year fatal/non-fatal CVD incidence) were assessed through multivariable Cox-

Table 1. Baseline sociodemographic, clinical, anthropometric, biochemical and lifestyle characteristics of men and women from the ATTICA study according to serum uric acid tertiles (n = 1687).

Baseline characteristics	Gender-specific SUA tertiles			
Men	1st tertile	2nd tertile	3rd tertile	*p*-value
n	248	286	291	
SUA, mg/dL	3.71 (0.55)	4.81 (0.27)	6.35 (0.89)	<0.001
Age, years	44 (13)	42 (11)	46 (13)	<0.001
Body mass index, kg/m^2	26.5 (3.6)	26.8 (3.2)	28.5 (4.4)	<0.001
Waist circumference, cm	94 (12)	97 (12)	100 (12)	<0.001
Obesity, %	16	14	29	<0.001
Physical activity, %	49	39	40	0.37
Metabolically unhealthy status, %	36	47	66	<0.001
Current smoking, %	46	50	44	0.21
History of hypertension, %	37	32	42	0.02
Antihypertensive treatment, %	20	27	25	0.12
History of diabetes mellitus, %	8	5	9	0.05
Antidiabetic treatment, %	3	3	4	0.27
HOMA-IR	3.57 (2.63)	3.27 (1.85)	3.53 (2.31)	0.13
History of hypercholesterolemia, %	33	41	45	<0.001
Hypolipidemic treatment, %	20	31	32	<0.001
LDL-C, mg/dL	108 (33)	117 (35)	129 (36)	<0.001
CRP, mg/L	1.58 (1.97)	1.90 (2.24)	2.38 (2.48)	<0.001
Alanine transaminase, U/L	22 (10)	21 (8)	29 (18)	0.004
Aspartate transaminase, U/L	27 (13)	26 (8)	28 (13)	0.53
eGFR, mL/min/1.73 m^2	113 (24)	113 (24)	116 (29)	0.16
Family CVD history, %	22	26	30	0.12
Women	1st tertile	2nd tertile	3rd tertile	*p*-value
n	252	317	293	
SUA, mg/dL	2.46 (0.38)	3.38 (0.24)	4.48 (0.97)	<0.001
Age, years	39 (12)	42 (13)	48 (18)	<0.001
Body mass index, kg/m^2	23.1 (3.8)	24.8 (4.5)	27.3 (5.1)	<0.001
Waist circumference, cm	76 (10)	81 (13)	89 (14)	<0.001
Obesity, %	6	15	27	<0.001
Physical activity, %	41	37	41	0.01
Metabolically unhealthy status, %	57	57	77	<0.001
Current smoking, %	43	37	38	0.18
History of hypertension, %	15	19	33	<0.001
Antihypertensive treatment, %	9	8	19	<0.001
History of diabetes mellitus, %	2	4	9	<0.001
Antidiabetic treatment, %	1	1	3	0.07
HOMA-IR	2.52 (1.12)	2.70 (1.86)	2.87 (1.51)	0.008
History of hypercholesterolemia, %	28	36	52	<0.001
Hypolipidemic treatment, %	17	18	27	<0.001
LDL-C, mg/dL	119 (35)	121 (34)	133 (40)	<0.001
C-Reactive Protein, mg/L	1.19 (1.81)	1.99 (2.59)	2.68 (2.96)	<0.001
Alanine transaminase, U/L	16 (6)	18 (9)	20 (13)	0.001
Aspartate transaminase, U/L	23 (13)	23 (9)	25 (11)	0.30
eGFR, mL/min/1.73 m^2	99 (15)	100 (23)	104 (26)	0.12
Family CVD history, %	35	27	26	0.05

Data are presented as mean ± standard deviation (SD) or median (Interquartile Range) if normality was not met. *p*-values were obtained using one-way ANOVA for the normally distributed variables (age, body mass index), Kruskal Wallis test for the rest quantitative variables and chi-squared test for categorical variables.

Abbreviations: SUA, serum uric acid; CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; HOMA-IR, homeostatic model assessment of insulin resistance.

Table 2. Unadjusted 10-year cardiovascular disease incidence rate in men and women from the ATTICA study according to gender-specific serum uric acid tertiles.

Statistical metrics	Overall sample	Gender-specific SUA tertiles			*p*-value
		1st tertile	2nd tertile	3rd tertile	
Men, n/cases	825/157	248/42	286/46	291/69	0.04
CVD incidence rate per 100 participants	19.0	16.9	16.1	23.7	
Women, n/cases	862/96	252/20	317/30	293/46	0.008
CVD incidence rate per 100 participants	11.1	7.9	9.5	15.7	
Overall, n/cases	1687/253	500/62	603/76	584/115	<0.001
CVD incidence rate per 100 participants	15.0	12.4	12.6	19.7	
Man-to-woman CVD incidence rate ratio	1.72	2.13	1.69	1.50	

p-values were obtained using chi-squared test.

Abbreviations: CVD, cardiovascular disease; SUA, serum uric acid.

Table 3. Nested Cox-regression analysis models to evaluate the association of serum uric acid with 10-year cardiovascular disease incidence (n = 1687).

Variables included in the model	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
SUA tertiles						
1st	Ref	Ref	Ref	Ref	Ref	Ref
2nd	1.29 (1.19, 1.40)	1.16 (1.07, 1.26)	1.12 (1.03, 1.21)	1.09 (1.00, 1.18)	1.05 (0.96, 1.15)	1.02 (0.95, 1.07)
3rd	1.73 (1.23, 2.42)	1.55 (1.11, 2.18)	1.51 (1.09, 2.11)	1.47 (1.05, 2.08)	1.42 (1.01, 1.99)	1.39 (0.98, 1.95)
Age, per 1 year	-	1.08 (1.07, 1.09)	1.08 (1.06, 1.09)	1.07 (1.05, 1.09)	1.07 (1.05, 1.09)	1.07 (1.05, 1.09)
Male gender	-	1.86 (1.41, 2.46)	1.82 (1.36, 2.45)	1.81 (1.17, 2.76)	1.66 (1.07, 2.61)	1.66 (1.07, 2.61)
Years of school, per 1 year	-	-	0.96 (0.92, 0.99)	0.97 (0.92, 1.02)	0.95 (0.90, 1.01)	0.95 (0.90, 1.01)
MedDietScore (range 0–55), per 1/55	-	-	0.98 (0.96, 0.99)	0.98 (0.94, 0.99)	0.97 (0.94, 1.01)	0.97 (0.94, 1.01)
Alcohol consumption, yes vs. no	-	-	0.90 (0.75, 1.10)	0.92 (0.76, 1.11)	0.92 (0.76, 1.11)	0.92 (0.76, 1.11)
Physical activity, yes vs. no	-	-	0.94 (0.70, 1.25)	1.32 (0.88, 1.98)	1.43 (0.94, 2.17)	1.43 (0.94, 2.17)
Current smoking, yes vs. no	-	-	1.27 (0.94, 1.71)	1.50 (1.00, 2.28)	1.45 (0.94, 2.23)	1.45 (0.94, 2.23)
LDL-C, per 1 mg/dL	-	-	-	1.01 (1.00, 1.03)	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)
Family history of CVD, yes vs. no	-	-	-	1.37 (0.90, 2.08)	1.39 (0.89, 2.17)	1.39 (0.89, 2.17)
ALT, per 1 U/L	-	-	-	1.01 (0.98, 1.04)	1.00 (0.97, 1.04)	1.00 (0.97, 1.04)
AST, per 1 U/L	-	-	-	0.99 (0.95, 1.02)	0.98 (0.94, 1.01)	0.98 (0.94, 1.01)
Waist circumference, per 1 cm	-	-	-	1.00 (0.98, 1.02)	1.00 (0.98, 1.02)	1.00 (0.98, 1.02)
HOMA-IR, per 1 unit	-	-	-	1.06 (0.98, 1.16)	1.06 (0.98, 1.16)	1.06 (0.98, 1.16)
CRP, per 1 mg/L	-	-	-	1.06 (0.98, 1.15)	1.06 (0.98, 1.15)	1.06 (0.98, 1.15)
eGFR, per mL/min/1.73 m^2	-	-	-	0.99 (0.98, 1.01)	0.99 (0.98, 1.01)	0.99 (0.98, 1.01)
Obesity, yes vs. no	-	-	-	-	1.65 (1.00, 2.92)	1.61 (0.89, 2.52)
Metabolic health status, healthy vs. unhealthy	-	-	-	-	-	0.43 (0.17, 0.99)

HRs and their corresponding 95% CIs were obtained from Cox regression analysis. Bold indicates statistically significant outcomes, i.e., $p < 0.05$.

Abbreviations: SUA, serum uric acid; ALT, alanine transaminase; AST, aspartate transaminase; CVD, cardiovascular disease; CI, confidence interval; CRP, C-Reactive Protein; eGFR, estimated glomerular filtration rate; HR, Hazard ratio; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; LDL-C, low density lipoprotein cholesterol.

regression analysis. Proportional hazards' assumption was graphically tested. Multicollinearity was evaluated through Variable Inflation Factors (VIF); VIF <4 indicated no multicollinearity. In this context, six models were constructed; Model 1 (crude model); Model 2 (age, sex); Model 3 (Model 2 plus years of school, MedDietScore, alcohol consumption, physical activity, current smoking); Model 4 (Model 3 plus low-density lipoprotein cholesterol (LDL-C), family history of CVD, aspartate transaminase (AST), alanine transaminase (ALT), waist circumference, homeostatic model assessment of insulin resistance (HOMA-IR), C-Reactive Protein (CRP), estimated glomerular filtration rate (eGFR)); Model 5 (Model 4 plus obesity); Model 6 (Model 5 plus metabolic status). Receiver operating curve (ROC) analysis was also performed and the area under the curve (AUC) was calculated to identify the discriminative effect of SUA on CVD incidence, as well as to detect the SUA cut-off point with the best discriminative ability for evaluating CVD events, separately for men and women. STATA software, version 14 (MP & Associates, Sparta, Greece) was used for all statistical analyses. Two-sided level of significance was set at $p < 0.05$.

Table 4. Nested Cox-regression analysis models to evaluate the dose-response association of serum uric acid with 10-year cardiovascular disease incidence (n = 1687).

Variables included in the model	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
SUA per 1 mg/dL	1.27 (1.16, 1.39)	1.14 (1.09, 1.25)	1.12 (1.06, 1.21)	1.10 (1.04, 1.18)	1.06 (0.99, 1.12)	1.04 (0.97, 1.10)
Age, per 1 year	-	1.09 (1.06, 1.11)	1.09 (1.07, 1.12)	1.09 (1.07, 1.12)	1.09 (1.07, 1.12)	1.09 (1.07, 1.12)
Male gender	-	1.87 (1.40, 2.45)	1.83 (1.35, 2.46)	1.83 (1.35, 2.46)	1.66 (1.07, 2.61)	1.65 (1.08, 2.60)
Years of school, per 1 year	-	-	0.96 (0.92, 0.99)	0.97 (0.92, 1.02)	0.95 (0.90, 1.01)	0.95 (0.90, 1.01)
MedDietScore (range 0–55), per 1/55	-	-	0.98 (0.96, 0.99)	0.98 (0.94, 0.99)	0.97 (0.94, 1.01)	0.97 (0.94, 1.01)
Alcohol consumption, yes vs. no	-	-	0.90 (0.75, 1.10)	0.92 (0.76, 1.11)	0.92 (0.76, 1.11)	0.92 (0.76, 1.11)
Physical activity, yes vs. no	-	-	0.94 (0.70, 1.25)	1.32 (0.88, 1.98)	1.43 (0.94, 2.17)	1.43 (0.94, 2.17)
Current smoking, yes vs. no	-	-	1.27 (0.94, 1.71)	1.50 (1.00, 2.28)	1.45 (0.94, 2.23)	1.45 (0.94, 2.23)
LDL-C, per 1 mg/dL	-	-	-	1.01 (1.00, 1.03)	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)
Family history of CVD, yes vs. no	-	-	-	1.37 (0.90, 2.08)	1.39 (0.89, 2.17)	1.39 (0.89, 2.17)
ALT, per 1 U/L	-	-	-	1.01 (0.98, 1.04)	1.00 (0.97, 1.04)	1.00 (0.97, 1.04)
AST, per 1 U/L	-	-	-	0.99 (0.95, 1.02)	0.98 (0.94, 1.01)	0.98 (0.94, 1.01)
Waist circumference, per 1 cm	-	-	-	1.00 (0.98, 1.02)	1.00 (0.98, 1.02)	1.00 (0.98, 1.02)
HOMA-IR, per 1 unit	-	-	-	1.06 (0.98, 1.16)	1.06 (0.98, 1.16)	1.06 (0.98, 1.16)
CRP, per 1 mg/L	-	-	-	1.06 (0.98, 1.15)	1.07 (0.99, 1.15)	1.07 (0.99, 1.15)
eGFR, per mL/min/1.73 m^2	-	-	-	0.99 (0.98, 1.01)	0.99 (0.98, 1.01)	0.99 (0.98, 1.01)
Obesity, yes vs. no	-	-	-	-	1.64 (1.01, 2.90)	1.60 (0.88, 2.50)
Metabolic health status, healthy vs. unhealthy	-	-	-	-	-	0.42 (0.19, 0.99)

HRs and their corresponding 95% CIs were obtained from Cox regression analysis. Bold indicates statistically significant outcomes, i.e., $p < 0.05$.

Abbreviations: SUA, serum uric acid; ALT, alanine transaminase; AST, aspartate transaminase; CVD, cardiovascular disease; CI, confidence interval; CRP, C-Reactive Protein; eGFR, estimated glomerular filtration rate; HR, Hazard ratio; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; LDL-C, low density lipoprotein cholesterol.

3. Results

The 10-year CVD incidence was 14.9% (n = 253) [19.0% (n = 157) in men and 11.1% (n = 96) in women, $p < 0.001$]. Baseline sociodemographic, clinical, anthropometric, biochemical and lifestyle characteristics of men and women from the ATTICA study across SUA tertiles are summarized in Table 1.

Results from unadjusted analysis regarding the association between SUA and CVD incidence rate within the 10-year follow-up, separately for men and women, are presented in Table 2. In particular, women in the highest SUA tertile had almost twice as high risk to develop a fatal/non-fatal CVD event within the decade compared with their counterparts in the lowest tertiles (157 vs. 79 CVD events/1000 participants, respectively; $p = 0.008$). A similar trend was observed for men (237 vs. 169 CVD events/1000 participants, respectively; $p = 0.04$). Ranking from the lowest to the highest SUA tertile, the man-to-woman CVD event rate ratio was 2.13, 1.69 and 1.50, respectively.

Results from nested Cox regression models evaluating the association between SUA tertiles and CVD incidence in the total sample are presented in Table 3. In the unadjusted models, participants in the 2nd and 3rd SUA tertile had about 29% (HR 1.29, 95% CI: 1.19–1.40) and 73% (HR 1.73, 95% CI: 1.23–2.42) higher risk to develop CVD within the decade compared with their 1st tertile counterparts, respectively. In the age- and sex- adjusted model, the aforementioned associations were attenuated but retained the level of significance (Model 2). After adjusting for anthropometric, lifestyle, clinical and biochemical factors, the association between SUA and CVD incidence remained only for participants in the 3rd SUA tertile (Model 5). However, after adjusting for metabolic health status, the level of significance was lost (Model 6).

The associations between SUA and 10-year CVD event rate examined by nested Cox-regression analysis are presented in Table 4. After adjusting for anthropometric, lifestyle, biochemical and clinical factors, 1 mg/dL (0.06 mmol/L) rise in SUA levels resulted in about 10% higher 10-year CVD risk. The level of significance was lost when the analysis was adjusted for obesity and metabolic health status (Model 5 and 6).

Significant interactions were observed in analyses stratified by gender, obesity and metabolic health status (all p values for interaction <0.05; Tables 5 and 6). In particular, in Table 5, multi-adjusted gender-based sensitivity analysis revealed that the direct association between SUA and CVD incidence was independent only in women (p for interaction = 0.003); women in the 3rd SUA tertile had about 79% higher risk to develop CVD compared with their 1st tertile counterparts (HR 1.79, 95% CI: 1.04–3.17). However, the level of significance was lost when metabolic health status was taken into account (Model 4).

As shown in Table 6, increased SUA levels (i.e., in the 3rd tertile) were related to almost twice as high CVD risk compared with the 1st tertile only in obese patients (HR 1.89, 95% CI: 1.10–3.20; p for interaction = 0.02) and not in non-obese

Table 5. Gender-based sensitivity analyses to evaluate the association of serum uric acid with 10-year cardiovascular disease incidence (n = 1687).

N, cases	Men	Women	Models adjusted for
	825/157	862/96	
	HR (95% CI)	HR (95% CI)	
Model with SUA as continuous variable			Crude model
per 1 mg/dL	1.11 (0.97, 1.27)	1.34 (1.13, 1.58)	
Model with SUA tertiles			
1st	Ref	Ref	
2nd	0.94 (0.59, 1.48)	1.21 (0.67, 2.19)	
3rd	1.52 (1.10, 2.33)	2.16 (1.24, 3.76)	
Model with SUA as continuous variable			Model 1: Age, years of school, MedDietScore, alcohol consumption physical activity, current smoking
per 1 mg/dL	0.99 (0.87, 1.14)	1.20 (1.02, 1.77)	
Model with SUA tertiles			
1st	Ref	Ref	
2nd	0.85 (0.52, 1.31)	1.09 (0.60, 1.97)	
3rd	1.35 (0.98, 2.09)	1.94 (1.11, 3.38)	
Model with SUA as continuous variable			Model 2: Model 1 plus LDL-C, family history of CVD, ALT, AST, waist circumference, HOMA-IR, CRP, eGFR, menopause status (only in women)
per 1 mg/dL	0.95 (0.48, 1.24)	1.01 (0.55, 1.85)	
Model with SUA tertiles			
1st	Ref	Ref	
2nd	0.82 (0.51, 1.30)	1.04 (0.57, 1.94)	
3rd	1.27 (0.97, 2.05)	**1.85 (1.05, 3.29)**	
Model with SUA as continuous variable			Model 3: Model 2 plus obesity
per 1 mg/dL	0.93 (0.47, 1.21)	0.98 (0.53, 1.81)	
Model with SUA tertiles			
1st	Ref	Ref	
2nd	0.78 (0.48, 1.24)	1.01 (0.55, 1.85)	
3rd	1.21 (0.93, 1.96)	**1.79 (1.04, 3.17)**	
Model with SUA as continuous variable			Model 4: Model 3 plus metabolic health status
per 1 mg/dL	0.89 (0.45, 1.16)	0.94 (0.50, 1.73)	
Model with SUA tertiles			
1st	Ref	Ref	
2nd	0.76 (0.47, 1.21)	0.98 (0.53, 1.81)	
3rd	1.18 (0.91, 1.92)	1.75 (0.97, 3.01)	

HRs and their corresponding 95% CIs were obtained from Cox regression analysis. Bold indicates statistically significant outcomes, i.e., $p < 0.05$.
Abbreviations: SUA, serum uric acid; ALT, alanine transaminase; AST, aspartate transaminase; CVD, cardiovascular disease; CI, confidence interval; CRP, C-Reactive Protein; eGFR, estimated glomerular filtration rate; HR, Hazard ratio; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; LDL-C, low density lipoprotein cholesterol.

individuals. Similar results were observed for metabolically healthy (HR 2.10, 95% CI: 1.15–3.23; *p* for interaction = 0.04) and not for metabolically unhealthy participants, as well as for MHO patients (HR 1.99, 95% CI: 1.13–3.21; *p* for interaction = 0.02) and not for MHN, MUN and MUO.

The ROC analysis is presented in Fig. 1. Based on the generated AUC, SUA seemed to better detect 10-year CVD events in women, but this was not significant. Further analysis showed that the cut-off points of SUA levels with the highest predictive capacity for CVD events were 5.05 mg/dL (0.29 mmol/L) for men and 4.15 mg/dL (0.24 mmol/L) for women.

4. Discussion

The aim of the present study was to evaluate the association between SUA levels and 10-year CVD incidence. Participants in the 2nd and 3rd SUA tertile had a 29% and 73% higher 10-year CVD incidence compared with those in the 1st tertile, irrespective of age and sex of the participants. However, after further adjustment for anthropometric, lifestyle, clinical and biochemical factors, the link between SUA and CVD incidence persisted only in participants in the 3rd SUA tertile; however, the later association was masked after adjusting for metabolic health status of the participants. Despite the potential limitations of the present, observational study, the results presented here deserves further attention from a clinical point of view. In particular, physicians should

Table 6. Multi-adjusted sensitivity analysis to evaluate the association between serum uric acid and 10-year cardiovascular disease incidence according to A. obesity, B. metabolic health and C. combined obesity- and metabolic health-status in men and women participants of the ATTICA study (n = 1687).

	1st tertile of SUA	2nd tertile of SUA	3rd tertile of SUA
Stratified by	HR (95% CI)	HR (95% CI)	HR (95% CI)
A. Obesity status			
Non obese	Ref	0.95 (0.57, 2.10)	1.47 (0.86, 2.90)
Obese	Ref	1.06 (0.67, 1.91)	1.89 (1.10, 3.20)
Obesity status * SUA: *p* for interaction = 0.02			
B. Metabolic health status			
Metabolically Healthy	Ref	1.12 (0.97, 1.87)	2.10 (1.15, 3.23)
Metabolically unhealthy	Ref	0.91 (0.62, 2.02)	1.36 (0.81, 2.79)
Metabolic status * SUA: *p* for interaction = 0.04			
C. Combined obesity- and metabolic health- status			
MHN	Ref	1.09 (0.91, 1.69)	1.95 (1.12, 3.10)
MHO	Ref	1.09 (0.82, 1.89)	1.99 (1.13, 3.21)
MUN	Ref	0.93 (0.59, 2.06)	1.41 (0.83, 2.82)
MUO	Ref	1.10 (0.63, 1.95)	1.59 (0.95, 3.01)
Combined obesity and metabolic status * SUA: *p* for interaction = 0.02			

HRs and their corresponding 95% CIs were obtained from Cox regression analysis adjusted for age, (gender), body mass index, physical activity, current smoking, MedDietScore, (history of hypertension, diabetes and hypercholesterolemia, in case A) and family history of cardiovascular disease. Metabolically healthy status was defined as the absence of hypertension, dyslipidemia and diabetes at baseline. Bold indicates statistically significant outcomes, i.e., $p < 0.05$.

Abbreviations: SUA, serum uric acid; MHN, metabolically healthy non-obese; MHO, metabolically healthy obese; MUN, metabolically unhealthy non-obese; MUO, metabolically unhealthy obese.

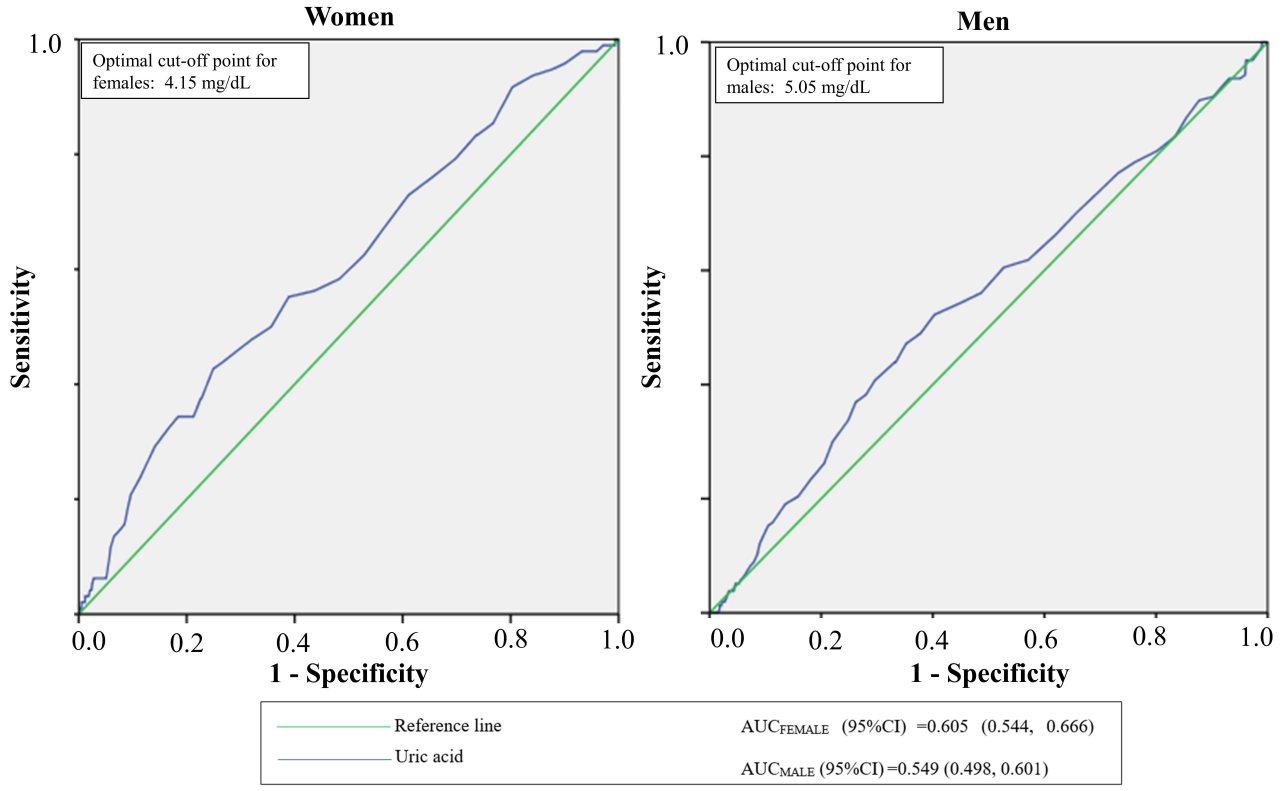

Fig. 1. Receiver operating characteristic curve to evaluate the predictive capacity of serum uric acid on 10-year cardiovascular disease incidence through the area under the curve (AUC) and the corresponding 95% confidence intervals (95% CI) in male and female participants of the ATTICA study (n = 1687).

be aware of the increased CVD risk in individuals with higher SUA levels; obesity and other CVD risk factors should be early and aggressively treated in such patients. Nevertheless, further evidence is needed to establish SUA thresholds predicting CVD incidence in different populations.

In multi-adjusted gender-based analysis, SUA was independently associated with CVD incidence only in women; the 3rd SUA tertile had 79% greater 10-year CVD event risk compared with the 1st tertile. However, after adjustment for metabolic health status, this association lost significance. Obese patients in the 3rd SUA tertile had almost twice as high CVD incidence compared with those in the 1st tertile; this link was not observed in non-obese individuals. Similar findings were observed in metabolically healthy participants (and not for metabolically unhealthy ones) and in MHO patients (and not in MHN, MUN and MUO). Finally, the best SUA cut-off value to detect 10-year CVD incidence rate was 5.05 mg/dL (0.29 mmol/L) in men and 4.15 mg/dL (0.24 mmol/L) in women.

Overall, the present analysis showed that higher SUA levels were significantly related to a greater 10-year CVD incidence, especially in women. Such a gender-specific association has also been reported in a few studies [33–36]. In particular, a subanalysis of the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study showed that a significant positive association was found between SUA levels and CVD morbidity only in women (n = 4963) and not in men (n = 4230) [35]. In a retrospective study, including 9139 apparently healthy individuals (i.e., without diabetes or CVD) followed-up for a mean of 4.8 years, the multivariate-adjusted HR for CVD incidence for each 1 mg/dL (0.06 mmol/L) increase in SUA levels was 1.24 (95% CI: 1.08–1.41) for women (n = 2559) and 1.06 (95% CI: 1.00–1.13) for men (n = 6580) [33]. In the Circulatory Risk in Communities Study (CIRCS) (n = 5235 men and 8185 women free from CVD, median follow-up: 23.1 years), the multivariable HR in the highest vs. lowest quintile of SUA levels for ischemic stroke was 1.61 (95% CI: 1.07–2.41) in women and 1.00 (95% CI: 0.70–1.41) in men [55].

The Research on Obesity and Diabetes among African Migrants (RODAM) cross-sectional study (n = 3864) reported that hyperuricemia correlated with 10-year CVD risk [assessed by the American College of Cardiology (ACC)/American Heart Association (AHA) risk score [56]] in migrants, rural and urban residents; the risk was greater in women than in men in migrants [adjusted odds ratio (OR) 4.61 (95% CI: 3.05–6.97) vs. 1.73 (95% CI: 1.01–2.96), respectively], rural residents [adjusted OR 6.36 (95% CI: 2.98–13.56) vs. 3.28 (95% CI: 1.21–8.96), respectively] and urban residents [adjusted OR 2.11 (95% CI: 1.26–3.52) vs. 1.12 (95% CI: 0.45–2.81), respectively] [34]. In a population-based study (n = 1346 individuals), elevated SUA levels were related to MetS features in both genders; the association was greater in women than in men i.e., women in the 4th SUA tertile had a 4.18-fold increase of MetS risk compared with those in the 1st tertile, whereas the corresponding value for men was 3.29-fold increase [36].

In the subgroup analyses of the present study, a direct association between SUA levels and 10-year CVD incidence was observed in obese, metabolically healthy and MHO patients. These findings suggest that SUA could be used to further identify individual CVD risk in obese patients, especially those without other metabolic disorders (i.e., dyslipidemia, hypertension and hyperglycemia). There is a paucity of data in this field and more studies should be conducted to draw definitive conclusions.

In the present study, the optimal SUA threshold to detect 10-year CVD incidence rate was 5.05 mg/dL (0.29 mmol/L) in men and 4.15 mg/dL (0.24 mmol/L) in women. A few trials investigated such SUA cut-off points. In brief, the URRAH study found that SUA cut-off values that predicted fatal myocardial infarction were 5.49 mg/dL (0.33 mmol/L) in men and 5.26 mg/dL (0.31 mmol/L) in women [37]. In the RODAM study, SUA thresholds for the detection of 10-year CVD risk (defined by the ACC/AHA risk score) were 6.77 mg/dL (0.40 mmol/L) in men and 5.15 mg/dL (0.31 mmol/L) in women [34]. Finally, the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) study, involving 1720 untreated hypertensive patients followed-up a mean of 12 years, reported that the lowest risk for CVD events was observed at SUA levels 4.5–5.2 mg/dL (0.27–0.31 mmol/L) in men and 3.2–3.9 mg/dL (0.19–0.23 mmol/L) in women [57]; the highest CVD incidence was observed at SUA $\geq$6.2 mg/dL (0.37 mmol/L) in men and $\geq$4.6 mg/dL (0.27 mmol/L) in women [57]. These findings highlight the need for further research to identify SUA cut-off values predicting CVD incidence in the general population, as well as in certain patient populations.

Overall, there are certain key results in relation to the present study. First of all, SUA, at much lower concentrations than those defining hyperuricemia, may predict 10-year CVD risk in both genders. However, this association seems greater in women since it persisted after multi-adjustments. Secondly, there are gender-specific SUA thresholds for CVD risk assessment, being lower in women [i.e., 5.05 mg/dL (0.29 mmol/L) in men and 4.15 mg/dL (0.24 mmol/L) in women]. Third, the observed link between SUA and 10-year CVD incidence depended on the presence of obesity and metabolically healthy status. Indeed, SUA levels correlated with CVD morbidity in obese patients (and not in non-obese) and in MHO. A positive relationship has been reported between SUA concentrations (at levels of $<$7 mg/dL) and the expression of hepatic inflammatory molecules [58]. This pro-inflammatory effect of SUA may further enhance chronic inflammation observed in obese patients, thus promoting CVD development. On the other hand, SUA was predictive of CVD incidence only in metabolically healthy individuals (and not in metabolically unhealthy). Taking into consideration that metabolically healthy status was defined as absence of dyslipidemia, dysglycemia and hypertension, it

follows that in the presence of these strong and independent CVD risk factors, SUA loses its predictive "ability". However, it should be noted that more data are needed before we reach safe conclusions.

The present study has some limitations. Only baseline measurements were taken into account; hence misclassifications of transitions or modifications cannot be precluded due to the extended interim periods between follow-up assessments. Furthermore, although there is a close relationship between renal function and SUA [59], adjusting for eGFR did not alter the association between SUA and CVD in our study. This could be attributed to the fact that renal function was normal for the vast majority of our participants as implied by the high eGFR values (in line with the generally low SUA levels recorded). Finally, information on uric acid treatments and other medications within the decade were not available. However, this study also has several strengths. First, we evaluated the gender-based effect of SUA levels on 10-year CVD incidence after adjusting for various conventional and novel risk factors. Secondly, sensitivity analyses were performed according to combined obesity- and metabolic- related status. Third, SUA cut-off points predicting 10-year CVD onset were estimated.

5. Conclusions

In conclusion, in the present analysis of the ATTICA cohort study, elevated SUA levels were associated with increased risk to develop CVD within a decade. This association was independent of other confounders, after multivariable analysis, in women. SUA was also independently associated with 10-year CVD event in obese and metabolically healthy individuals. SUA thresholds detecting 10-year CVD event rate was 4.15 mg/dL (0.24 mmol/L) in women and 5.05 mg/dL (0.29 mmol/L) in men, i.e., much lower than those defining hyperuricemia [>6 mg/dL (0.36 mmol/L) in women and >7 mg/dL (0.42 mmol/L) in men]. Further studies are warranted to identify CVD SUA cut-off values that may improve the classification of individual CVD risk.

Author contributions

NK and MK interpreted the outcomes, wrote the manuscript and analyzed the data. DBP and CP designed the research study and critically reviewed the manuscript. CB, CC and DBM critically reviewed the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The ATTICA study was carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association. The study was approved by the Institutional Ethics committee of Athens Medical School (#017/1.5.2001) and all participants were informed about the aims and procedures and agreed to participate providing written consent.

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Conflict of interest

NK has given talks, attended conferences and participated in trials sponsored by Angelini, Astra Zeneca, Bausch Health, Boehringer Ingelheim, Elpen, Mylan, Novo Nordisk, Sanofi and Servier. DPM has given talks and attended conferences sponsored by Amgen, Novo Nordisk and Libytec. CC has given talks sponsored by Astra Zeneca, Boehringer Ingelheim, Elpen, Sanofi and Roche Diagnostics. MK, DBP, CP declare no conflict of interest. MK and DBP are the Guest Editors of this journal, given their roles as Guest Editors, had no involvement in the peer-review of this article and had no access to information regarding its peer-review.

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