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Serum uric acid and fatal myocardial infarction: detection of prognostic cut-off values: The URRAH (Uric Acid Right for Heart Health) study

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Objective: The Working Group on Uric Acid and Cardiovascular Risk of the Italian Society of Hypertension conceived and designed an ad-hoc study aimed at searching for prognostic cut-off values of serum uric acid (SUA) in predicting fatal myocardial infaction (MI) in women and men.

Methods: The URic acid Right for heArt Health study is a nationwide, multicentre, observational cohort study involving data on individuals aged 18–95 years recruited on a regional community basis from all the territory of Italy under the patronage of the Italian Society of Hypertension with a mean follow-up period of 122.3 ± 66.9 months.

Results: A total of 23 467 individuals were included in the analysis. Cut-off values of SUA able to discriminate MI status were identified by mean of receiver operating characteristic curves in the whole database (>5.70 mg/dl), in women (>5.26 mg/dl) and in men (>5.49 mg/dl). Multivariate Cox regression analyses adjusted for confounders (age, arterial hypertension, diabetes, chronic kidney disease, smoking habit, ethanol intake, BMI, haematocrit, LDL cholesterol and use of diuretics) identified an independent association between SUA and fatal MI in the whole database (hazard ratio 1.381, 95% confidence intervals, 1.096–1.758, $P = 0.006$) and in women (hazard ratio 1.514, confidence intervals 1.105–2.075, $P < 0.01$), but not in men.

Conclusion: The results of the current study confirm that SUA is an independent risk factor for fatal MI after adjusting for potential confounding variables, and demonstrate that a prognostic cut-off value associated to fatal MI can be identified at least in women.

Keywords: cut-off value, mortality, myocardial infarction, sex, uric acid

Abbreviations: CAD, coronary artery disease; CI, confidence interval(s); LDLC, LDL cholesteol; MI, myocardial infarction; ROC, receiver operating characteristic; SUA, serum uric acid; URRAH, URic acid Right for heArt Health

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INTRODUCTION

About serum uric acid as a risk factor

During the last few decades, a large number of epidemiological studies have reported an association between serum uric acid (SUA) and cardiovascular disease, especially coronary artery disease (CAD) [1–9], and literature shows an increasing interest for the direct deleterious impact of the synergistic effect of SUA on other cardiovascular risk factors [10]. Uric acid is the final product of nucleic acid metabolism, and its production is controlled by a multitude of different factors, including dietary intake of various foods, renal excretion, and rate of uric acid cell turnover [11].

The problem of cut-off values

SUA is often taken into consideration by researchers and clinicians as a continuous variable, but they would strongly prefer to use cut-off values, that are more useful in clinical setting. Different SUA values have been proposed as 'normal' in many countries based on cross-sectional studies [3] or even on the reports of public and private laboratories [12,13]. Different levels above 6 mg/dl are usually considered as pathologic. However, observational cut-off does not have necessarily a prognostic value, and a growing body of evidences suggests that SUA might exert a detrimental influence on the cardiovascular system, brain and kidney and also negatively influence glucose metabolism for circulating levels below the saturation limit [2,3], indicating its effects is in part independent of precipitation of urate monosodium crystals. Indeed, some studies demonstrated that the relation between SUA and cardiovascular disease is evident not only in the presence of the so-called overt hyperuricemia or gout, but also with SUA levels usually considered in the normal-to-high range [5,14,15].

Serum uric acid and cardiovascular events in men and women

Furthermore, several studies have shown that the association between SUA levels and cardiovascular disease appears for lower SUA values in women than in men [6,16,17]. For instance, among the 5926 North-American participants in the National Health and Nutrition Survey observed for 16.4 years, for each mg/dl increase in SUA cardiovascular mortality increased by 9% in men (hazard ratio 1.09, 95% confidence intervals, CI, 1.02–1.18) and by 26% in women (hazard ratio 1.26, 95% CI 1.16–1.36) [18]. Furthermore, a meta-analysis on the link between hyperuricemia and CAD, taking into account the traditional cardiovascular risk factors and including subgroup analyses, showed a strong association between hyperuricemia and increased risk of CAD mortality in women, while no significant association was found in men [6]. This suggests a sex-specific action of SUA with different prognostic cut-off values in women and men [10].

An Italian network of excellence

The Working Group on Uric Acid and Cardiovascular Risk of the Italian Society of Hypertension conceived and designed a nationwide ad-hoc protocol involving a great number of Italian people, aimed at finding, if any, the cut-off value of SUA able to stratify men and women into having or having not an increased risk of cardiovascular events. The URRAH (URic acid Right for heArt Health) intends to clarify if SUA is associated with CAD and with other cardiovascular and renal diseases, if univariate cut-off levels of SUA exist, if they are able to separate clearly the cohort in two subcohorts as regards of incident events, and if those cut-off values can be confirmed being accepted in multivariate Cox regression models adjusted for confounders and being used in population-based control cohorts.

For the specific purpose of the analysis shown herein, the possible cut-off of SUA in relation to incident fatal myocardial infarction (MI) was considered.

METHODS

Database and study protocol

The database called URRAH is a multicenter observational cohort study which involves data on individuals aged 18–95 years collected on a regional community basis from all the territory of Italy under the patronage of the Italian Society of Hypertension with a mean follow-up period of 122.3 ± 66.9 months (CI 121.5–123.2) up to 31 July 2017 [19].

The study protocol has been previously extensively described [19]. In brief, a nationwide Italian database was built on a regional basis by collecting data on individuals from representative cohorts having SUA measurement and complete information about several variables. For all individuals, a standardized set of items was recorded, including demographics, metabolic parameters, smoking habit, systolic and diastolic arterial blood pressure, renal function, target organ damage (intima–media thickness, left ventricular hypertrophy, urinary and albumin excretion), history of cardiovascular, renal and brain disease, concomitant treatments and outcome.

Ethics

The study data were collected routinely or *ad hoc* in authorized studies. Individuals underwent no extra tests or interventions, and there was no impact on individuals' care or outcome. The URRAH was performed according to the Declaration of Helsinki for Human Research (41st World Medical Assembly, 1990). The processing of the patients' personal data collected in this study comply with the European Directive on the Privacy of Data. All data to be collected, stored and processed are anonymized, and all study-related documents are retained in a secure location. No personal information is stored on local personal computers. Approval was sought from the Ethical Committee of the coordinating center at the Division of Internal Medicine of the University of Bologna (no. 77/2018/Oss/AOUBo). Informed consent was obtained from all individuals at recruitment.

Outcome

Incidence of fatal MI was evaluated at the end of the follow-up, based on the International Classification of Diseases Tenth Revision codes I21, I22 and I23. Information about death was obtained from hospital records or death certificates.

Statistics

General description

The SAS package version 9.4 (SAS Institute, Cary, North Carolina, USA) was used for statistical analysis.

A preliminary power analysis based on differences from stratified values of uric acid for $\alpha = 0.05$ and power $(1 - \beta) = 0.80$ was performed. To our knowledge, no study exists about possible cut-off values of SUA discriminating individuals into doomed to and not doomed to develop fatal MI, much less after sex stratification. Consequently, based on previous work of our research staff [20,21], we considered 1 mg/dl SUA as a possible difference able to stratify individuals according to the above-mentioned outcome. Power analysis showed that the number of individuals in the database ($n = 23\,467$) represented a sample largely sufficient to avoid β error also after stratification by sex and by fatal MI. The Kolmogorov–Smirnov normality test was performed. Continuous variables were expressed as mean ± SD and compared among classes or categories by the analysis of covariance adjusted time to time for proper confounders and followed by the Bonferroni's post-hoc test. Categorical variables were compared by means of the Pearson χ^2 test. In multivariate analyses, the covariables that were not independent from each other were previously log-transformed. The null hypothesis was rejected for values of P less than 0.05.

Preliminary cox analysis

SUA as a continuous item (in mg/dl) was used as independent variable in Cox analyses having fatal MI both in the whole database and separately in men and women as dichotomic dependent variable, and sex, age, arterial hypertension (AH), diabetes, chronic kidney disease, smoking habit, ethanol intake, BMI, haematocrit, LDL cholesterol (LDLC) and use of diuretics as possible confounders. Hazard ratios with 95% CI were produced. The null hypothesis was rejected for values of P less than 0.05.

Univariate prognostic cut-off values

The receiver operating characteristic (ROC) curves method was used to search for prognostic cut-off of SUA for fatal MI in the whole database and by sex. SUA was used as basic variable and fatal MI as dichotomic classification variables. The methodology by DeLong *et al.* [22] was used. Ratio of cases in the positive group (prevalence), sensitivity and specificity were calculated. ROC curves were generated in the whole database and in women and men, and the prognostic cut-off values were identified as the curve point nearest to the 100% of axis of the ordinates [23]. In practical terms, this was made by identifying the SUA value associated to the highest values of the sum *sensitivity* + *specificity*. Youden's index [24] defined for all points of ROC curves were used as a criterion for selecting the optimum cut-off. The area under the curve was also shown for each ROC analysis [25].

Validation of the prognostic cut-off values

The cut-off values of SUA identified by mean of the ROC were tested in two ways: first, they were used separately as independent variables in multivariate Cox analyses adjusted for the confounders already identified, having fatal MI as dichotomic dependent variable. The analysis was performed in the whole database as well as in men and women. A cut-off value identified *via* the ROC method was considered as valid if accepted in the model being the null hypothesis rejected, otherwise it was considered a false cut-off. The corresponding hazard ratio with 95% CI were obtained. Second, the validity of the cut-off values of SUA was then confirmed using internal validation, that is retesting each cut-off point using a subsample of 9385 individuals from structured population-based cohorts (refer to Table 1s and Supplemental materials, http://links.lww.com/HJH/B164). The aim of this procedure was to clarify whether in the control cohort from general population the three cut-off values of SUA concerning fatal MI in the whole cohort and in men and women significantly separated those developing the event from those who did not during the follow-up.

Myocardial infaction in relation to cut-off values

In the whole database and separately in women and in men, the validated cut-off values were used to stratify MI in descriptive analysis and for generating outcome curves according to the Kaplan–Meier nonparametric estimator of limit product.

RESULTS

Whole cohort

Descriptive statistics

The general characteristics of the 23 467 individuals are shown and also stratified by sex in Table 1.

In the overall study population, median follow-up was 11.0 years (5th to 95th percentile interval: 0.7–19.4 years). During 203 274 person-years of follow-up, 445 participants experienced fatal MI: 231 events occurred in women during 103 575 person-years of follow-up (2.23 per 1000 age-adjusted person-years), and 214 events occurred in men during 99 699 person-years of follow-up (2.15 per 1000 age-adjusted person-years).

Multivariate analysis

Preliminary Cox models having fatal MI as dependent variable showed that, in the whole cohort, SUA as a continuous variable was associated to fatal MI (hazard ratio 1.146, 95% CI 1.060–1.239, $P = 0.0007$), being sex a significant confounder (Table 2).

Search for cut-off values

ROC curve furnished plausible univariate cut-off value of SUA for fatal MI (>5.70 mg/dl). The ROC curve for whole cohort is shown in Fig. 1, and ROC curve parameters are summarized in Table 3.

Furthermore, in multivariate Cox analyses performed in all participants and adjusted for sex, age, AH, diabetes, chronic kidney disease, smoking habit, ethanol intake, BMI, haematocrit, LDLC and use of diuretics, the cut-off value of SUA for fatal MI was accepted in the model (hazard ratio

TABLE 1. General characteristics of the study database

Variables	Whole database, $n = 23\,467$	Females, $n = 11\,913$	Males, $n = 11\,554$	P values between sexes
Age (years)	57.2 ± 15.1	57.7 ± 15.5	56.7 ± 14.6	<0.0001
Serum uric acid (mg/dl)	5.03 ± 1.47	4.82 ± 1.40	5.24 ± 1.45	<0.0001
Waist circumference (cm)	90.5 ± 12.7	87.6 ± 13.4	93.5 ± 11.4	<0.0001
Heart rate (bpm)	71.9 ± 12.5	72.9 ± 12.2	70.9 ± 12.7	<0.0001
SBP (mmHg)	143.5 ± 23.6	144.0 ± 24.6	143.1 ± 22.5	0.003
DBP (mmHg)	83.4 ± 12.7	85.2 ± 13.0	85.5 ± 12.4	0.07
BMI (kg/m^2)	26.3 ± 4.1	26.6 ± 4.5	26.6 ± 4.0	0.9
Azotaemia (mg/dl)	34.1 ± 11.1	34.2 ± 11.1	34.0 ± 11.0	0.2
Serum creatinine (mg/dl)	0.93 ± 0.26	0.91 ± 0.29	0.96 ± 0.22	<0.0001
Serum glucose (mg/dl)	98.7 ± 24.9	98.8 ± 26.1	98.6 ± 22.6	0.5
LDL serum cholesterol (mg/dl)	132.9 ± 37.8	132.5 ± 37.9	133.4 ± 37.6	0.07
Haematocrit (%)	42.6 ± 4.9	41.5 ± 3.8	43.6 ± 4.1	<0.0001
Smoking habit (yes %)	24.8	21.1	24.5	<0.0001
Ethanol intake (yes %)	62.4	60.8	64.1	<0.0001
Diabetes (yes %)	10.6	10.4	10.8	0.3
Hypertension (yes %)	63.8	64.1	63.4	0.2
CKD (yes %)	16.2	16.9	15.5	0.004
Gout (yes %)	1.1	0.5	1.8	<0.0001
Heart failure (yes %)	12.6	15.0	9.9	<0.0001
Diuretics use (yes %)	16.8	17.7	15.8	<0.0001
Statin use (yes %)	5.1	5.1	5.1	0.9

Continuous variables are expressed as mean ± SD. Categorical variables are in %. BP, blood pressure; CKD, chronic kidney disease; yes = 1, no = 0.

TABLE 2. Cox models for fatal myocardial infarction using serum uric acid as a continuous independent variable in the whole cohort

Independent variables	HR	95% CI	Z	P value
Serum uric acid (mg/dl)	1.146	1.060–1.239	3.409	<0.001
Sex (1 = men, 0 = women)	1.289	1.001–1.659	1.968	<0.05
Age (years)	1.123	1.105–1.141	14.226	<0.0001
Diabetes (1 = yes, 0 = no)	2.038	1.586–2.620	5.559	<0.0001
Smoking (1 = yes, 0=no)	1.387	1.014–1.897	2.046	<0.05
LDLC (mg/dl)	1.002	0.998–1.005	0.922	0.36
Ethanol (1 = yes, 0 = no)	1.311	0.879–1.955	1.330	0.18
Hypertension (1 = yes, 0 = no)	1.210	0.890–1.645	1.217	0.22
CKD (1 = yes, 0 = no)	1.285	0.986–1.676	1.855	0.07
BMI (kg/m^2)	0.981	0.953–1.009	-1.342	0.18
Haematocrit (%)	0.980	0.947–1.014	-1.177	0.24
Use of diuretics (1 = yes, 0 = no)	0.710	0.476–1.059	-1.678	0.09

CI, confidence intervals; CKD, chronic kidney disease; HR, hazard ratio; LDLC, LDL cholesterol.

1.381, CI 1.096–1.758, $P = 0.006$) (Table 4). Male sex, age, diabetes, smoking and chronic kidney disease directly contributed to incident fatal MI.

When the above-mentioned cut-off value was tested in the population-based control subsample of 9385 individuals, it significantly divided those who developed fatal MI

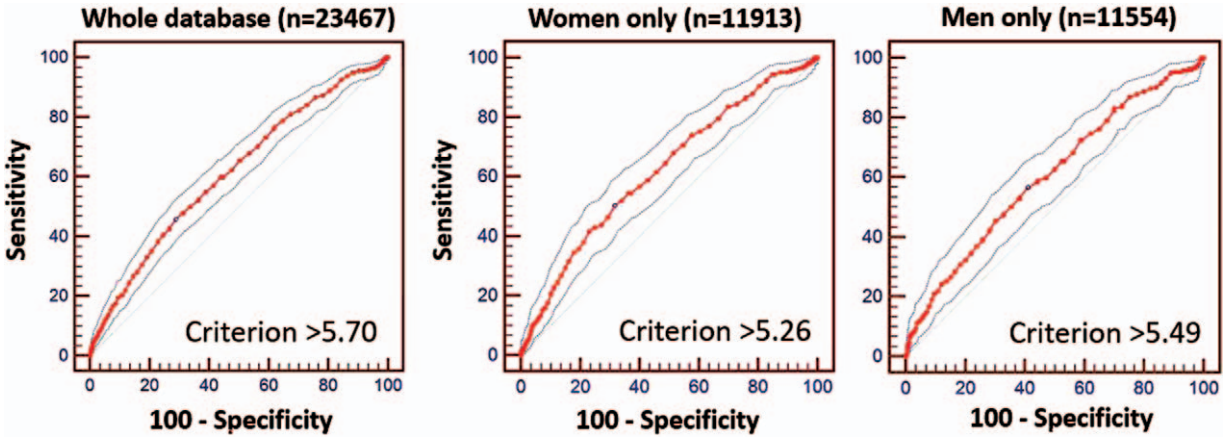

FIGURE 1 Receiver operating characteristic curves of fatal myocardial infarction. 95% confidence intervals are shown (thin lines).

TABLE 3. Receiver operating characteristic curves parameters of the cut-off values for fatal myocardial infarction in a regional-based community cohort of 23 467 men and women

	All, $n = 23\,467$	Women, $n = 11\,913$	Men, $n = 11\,554$
Cut-off (CI*)	>5.70 mg/dl (5.10–6.42)	>5.26 mg/dl (4.37–5.90)	>5.49 mg/dl (4.25–6.10)
AUC (SE, CI)	0.614 (0.013, 0.607–0.620)	0.623 (0.019, 0.614–0.632)	0.606 (0.020, 0.596–0.615)
Youden index (CI)	0.1687 (0.1218–0.2043)	0.187 (0.114–0.234)	0.158 (0.086–0.198)
Sensitivity% (CI)	45.6 (40.9–50.4)	50.2 (43.6–56.8)	56.7 (49.8–63.5)
Specificity% (SE, CI)	71.2 (70.6–71.9)	68.4 (67.6–69.3)	59,0 (58.0–60.0)
Z statistics, *P*	8.336, <0.00001	6.548, <0.0001	5.311, <0.0001

AUC, area under the curve; CI, 95% confidence intervals; SE, standard error.
*Bootstrap confidence intervals (1000 iterations).

TABLE 4. Hazard ratios of the cut-off values of serum uric acid for fatal myocardial infarction in the whole database

Independent variables	HR	95% CI	Z	*P* value
Specific cutoff of SUA (mg/dl)	1.381	1.096–1.758	2.728	0.006
Sex (1 = men, 0 = women)	1.321	1.026–1.700	2.157	0.03
Age (years)	1.123	1.105–1.141	14.434	<0.0001
Diabetes (1 = yes, 0 = no)	2.048	1.592–2.636	5.605	<0.0001
Smoking (1 = yes, 0 = no)	1.470	1.076–2.006	2.432	0.015
LDLC (mg/dl)	1.001	0.997–1.005	0.687	0.5
Ethanol (1 = yes, 0 = no)	1.354	0.906–2.024	1.488	0.1
Hypertension (1 = yes, 0 = no)	1.208	0.887–1.656	1.206	0.2
CKD (1 = yes, 0 = no)	1.339	1.026–1.747	2.165	0.03
BMI (kg/m^2)	0.981	0.954–1.009	1.348	0.2
Haematocrit (%)	0.995	0.964–1.027	0.322	0.7
Use of diuretics (1 = yes, 0 = no)	0.702	0.470–1.047	1.749	0.08

CI, confidence intervals; CKD, chronic kidney disease; HR, hazard ratios; LDLC, LDL cholesterol; SUA, serum uric acid; *Z*, *Z* statistics.

from those who resulted to be free from this event. In this control cohort, incidence of fatal MI was 2.6% among the individuals who did not exceed 5.70 mg/dl, and 4.8% among those over this value ($\chi^2 = 33.36$, $P < 0.0001$).

Application of the confirmed cut-off to the study database

Kaplan-Meier curves in the whole database are shown in Fig. 2, left panel. The curves of individuals having SUA cut-off or less and SUA more than cut-off were clearly separate.

Women

Multivariate analysis

In women, preliminary Cox model showed that SUA as a continuous variable was a predictor of fatal MI (hazard ratio 0.136, 95% CI 0.058–0.215, $P < 0.001$).

Search for a cut-off value

The ROC curve furnished a plausible univariate cut-off value of SUA for fatal MI (>5.26 mg/dl); ROC curve is shown in Fig. 1, middle panel, and ROC curve parameters are summarized in Table 3.

Confirmation of the cut-off value

In multivariate Cox analysis adjusted for confounders (age, AH, diabetes, chronic kidney disease, smoking habit, ethanol intake, BMI, haematocrit, LDLC and use of diuretics), the cut-off value of SUA for fatal MI was accepted in the model identifying a hazard ratio of 1.514 (CI 1.105–2.075, P <<< 0.01) (Table 5, upper panel). Age, diabetes and smoking directly contributed to fatal MI, while use of diuretics was protective.

When the above-mentioned cut-off value, confirmed in multivariate analysis, was tested in the control cohort of 5276 women from general population, it significantly divided those who developed fatal MI (6.88%, $P < 0.0001$) from those who resulted to be free from these events (2.62%, $\chi^2 = 53.14$, $P < 0.0001$). In this control cohort, the hazard ratio of having SUA greater than the cut-off was 1.43 (CI 1.05–1.96, $P = 0.026$).

Application of the confirmed cut-off to the study database

Kaplan-Meier curves in women are shown in Fig. 2, middle panel. The curves of individuals having SUA cut-off or less and SUA more than cut-off were clearly separate.

Men

Multivariate analysis

In men, preliminary Cox models having fatal MI as dependent variable showed that SUA as a continuous item was rejected from the model (hazard ratio 0.088, $P = 0.2$).

Search for a cut-off value

Univariate search for a cut-off value for fatal MI was anyway performed, leading to apparent identification of more than 5.49 mg/dl. In univariate cut-off analysis, this cut-off apparently stratified men into those having a fatal MI (3.03 vs. 1.64%, χ^2 20.92, $P < 0.0001$). ROC curve is shown in Fig. 1, right panel, and ROC curve parameters are summarized in Table 3.

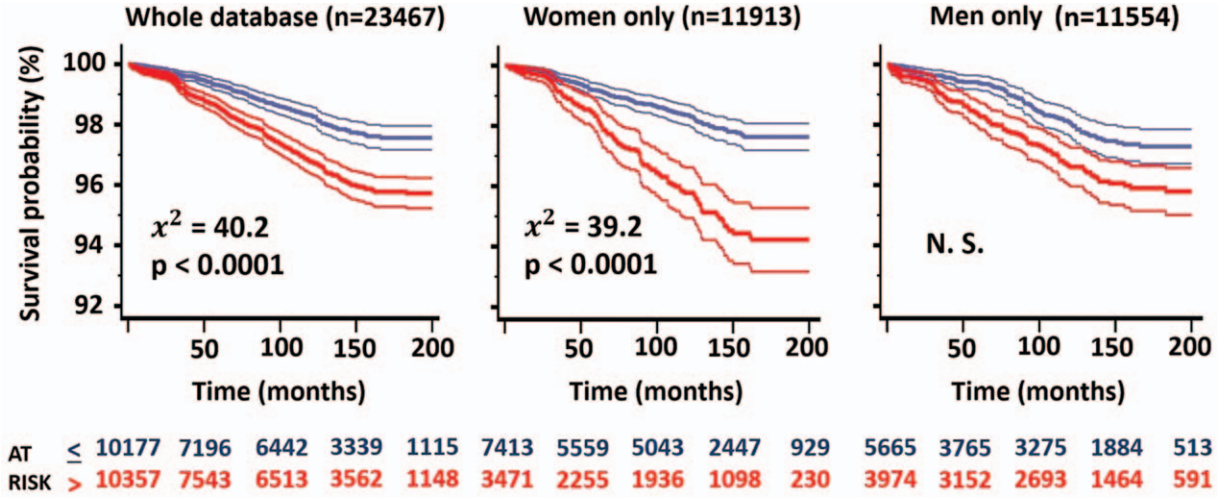

FIGURE 2 Kaplan–Meier curves of survival probability for fatal myocardial. Trends of individuals having serum uric acid more than cut-off (red line) and cut-off (blue line) or less are shown: 95% confidence intervals (thin lines in the same colors) are clearly separate in the while database and in women while partially overlapping in men, reflecting significant difference in the former and lack of statistical significance in the latter. Numbers of individuals at risk are shown in the two footnotes.

Nevertheless, when tested in multivariate Cox model adjusted for the confounders including all men, this cut-off was not accepted in the equation (Table 5, lower panel). Accordingly, this apparent cut-off was also rejected from the Cox analysis performed in the population-based control cohort of 4109 men (hazard ratio 1.39, CI 0.96–2.02, $P = 0.1$).

Application of the confirmed cut-off to the study database

As obvious, when used in Kaplan–Meier analysis, the false cut-off produced curves whose CI were partially overlapping, indicating lack of statistically significant difference between individuals having SUA false cut-off or less and SUA more than false cut-off.

DISCUSSION

The results of the current study confirm that SUA is an independent risk factor for fatal MI after adjusting for potential confounding variables, and demonstrate that a prognostic cut-off value able to separate the individuals at risk of developing the event from those free from this event can be identified (>5.70 mg/dl).

Concerning sex, the literature suggests that a difference exists between men and women as regards SUA [26]. In

TABLE 5. Hazard ratios of the cut-off values of serum uric acid for fatal myocardial infarction in women and men

Independent variables	HR	95% CI	Z	*P* value
Women, $n = 1913$				
Specific cutoff of SUA (mg/dl)	1.514	1.105–2.075	2.600	<0.01
Age (years)	1.131	1.197–1.556	10.991	<0.0001
Diabetes (1 = yes, 0 = no)	2.455	1.773–3.397	5.434	<0.0001
Smoking (1 = yes, 0 = no)	2.044	1.222–3.419	2.740	0.006
LDLC (mg/dl)	1.001	0.996–1.004	−0.180	0.9
Ethanol (1 = yes, 0 = no)	1.475	0.835–2.607	1.347	0.2
Hypertension (1 = yes, 0 = no)	1.069	0.685–1.669	0.296	0.8
CKD (1 = yes, 0 = no)	1.171	0.776–1.768	0.753	0.4
BMI (kg/m^2)	0.981	0.947–1.017	−1.073	0.3
Haematocrit (%)	0.973	0.928–1.020	−1.106	0.3
Use of diuretics (1 = yes, 0 = no)	0.506	0.279–0.917	−2.255	0.02
Men, $n = 11\,154$				
Specific cutoff of SUA (mg/dl)	1.294	0.924–1.813	1.507	0.1
Age (years)	1.114	1.088–1.141	9.166	<0.0001
Diabetes (1 = yes, 0 = no)	1.617	1.067–2.451	2.279	0.023
Smoking (1 = yes, 0 = no)	1.195	0.806–1.772	0.890	0.4
LDLC (mg/dl)	1.003	0.999–1.007	1.395	0.2
Ethanol (1 = yes, 0 = no)	0.988	0.562–1.734	−0.045	0.9
Hypertension (1 = yes, 0 = no)	1.401	0.910–2.156	1.541	0.1
CKD (1 = yes, 0 = no)	1.465	1.028–2.089	2.115	0.034
BMI (kg/m^2)	0.983	0.943–1.037	−0.692	0.5
Haematocrit (%)	0.989	0.944–1.037	−0.450	0.6
Use of diuretics (1 = yes, 0 = no)	1.122	0.654–1.925	0.419	0.7

CI, confidence intervals; CKD, chronic kidney disease; HR, hazard ratios; LDLC, LDL cholesterol; SUA, serum uric acid; *Z*, *Z* statistics.

agreement with this evidence, we divided the database according to sex, and actually SUA was 4.3% lower in women than in men.

Several studies have also reported a stronger association between SUA and cardiovascular events in women than in men [6,17,18,27] or the existence of such an association in women only [28–30]. This is why we felt the need for a separate search of cut-off values in men and women. On the other hand, cut-off values generically derived from a population including both genders would be of no help in clinical practice, where a patient can only be male or female.

After sex stratification, we observed that predictive values of SUA for fatal MI could be identified in women but not in men, probably due to the nonlinear relationship between SUA and MI in this sex.

In women, the cut-off value of SUA identifying those at higher risk of developing fatal MI during the follow-up was more than 5.26 mg/dl, that is lower than that conventionally accepted as a cut-off based on cross-sectional evidence and also much lower than the SUA values commonly associated with gout [31].

In men, a theoretical univariate cut-off of SUA could be identified by the ROC method, but it was without any independent value when played in multivariate Cox models adjusted for confounders. It must therefore be rejected as devoid of prognostic value.

The cut-off values identified in the whole database are therefore due to women only. These results are consistent with a series of studies showing a stronger effect of SUA levels in women than in men. A metanalysis of prospective cohort studies showed a significant association between hyperuricemia and CAD events in women only (+17% for each increase of 1 mg/dl of SUA, independent of traditional risk factors), although its results are quite questionable because the definitions of hyperuricemia were different across the studies [6]. The AMORIS study, a large population-based prospective study involving 417 734 men and women from the Stockholm area, demonstrated that in women, but not in men, the risk of fatal MI increased by 19% for each increase of 1 mg/dl of SUA [27]. In another study, in which the associations between SUA and MI followed a J-shaped pattern, the association between increased SUA and risk of cardiac mortality stronger in women than in men [7]. In the study performed by Culleton *et al.* [26] in 6763 individuals from the Framingham Heart Study, an increased risk for adverse outcome associated to higher SUA was found for women only after age adjustment. Also in the First National Health and Nutrition Examination Survey [18], were coronary mortality was 17% in women and 30% in men, there was no association between hyperuricemia and CAD in men, although an association was detected in women. In a study on a Belgian population SUA level was associated with cardiovascular and coronary mortality in women only [32]. In countertrend, Reboldi *et al.* [10], in the frame of the Ambulatory Blood Pressure International Study, recently found in a medium-term follow-up a positive association between SUA and composite fatal and morbid events including stroke in men only after adjustment.

Currently available models used for the study of pathophysiological mechanisms of the effects of SUA on coronary disease do not adequately explain this relationship. Soluble uric acid has been shown to act as a pro-oxidant as well as facilitator of free radical production [33]. Uric acid can crystallize, resulting in the formation of monosodium urate crystals which tend to precipitate in various tissues, triggering local inflammatory responses. The mechanistic actions involving the crystals have been shown to be intimately involved in the individuals of CAD [33]. It has been demonstrated that human atherosclerotic plaque contains a considerable amount of uric acid, and high SUA – via purine metabolism – may promote thrombus formation [34,35]. Moreover, SUA can stimulate oxidative stress and induce endothelial dysfunction, inflammation, and vasoconstriction [36]. SUA concentrations were also found to promote oxygenation of LDLC and to facilitate lipid peroxidation [37]. Each of these factors is known to play a crucial role in the progression of atherosclerosis and may potentially contribute to the development of CAD observed in patients with hyperuricemia. The reason why plausible multivariate cut-off values could be found in women only, although perfectly in line with current literature, has no explanation up to date in our experience. Clinical and biochemical studies are mandatory in this respect.

Of course, SUA levels as predictors of cardiovascular disease in patients without gout would not change the criteria for therapeutic intervention since there is a lack of clear evidence of its benefit.

The strength of the study shown herein is that, to our knowledge, it is the first aimed at finding prognostic cut-off values of SUA for the development of MI in a large nationwide database analysed longitudinally with a long-lasting follow-up. The limitations are represented by the fact that this was a retrospective evaluation, that the analysis was based on a single SUA measurement without taking into consideration the dilution bias, and that the design was fit to demonstrate an association but not a causality in the relationship between SUA and fatal MI. Furthermore, the determination of cut-off points resulted in a marginal area under the curve even in women, which would classify it on some scales as a test of poor discriminatory ability. Although the fatal infarction is a hard outcome, there may have been a bias in the diagnosis of infarction as the cause of each death in particular. Finally, the echogenetic context of the interaction between SUA and MI will be considered in further analysis [38].

In conclusion, measurement of the SUA level might provide significant prognostic information about incident MI in women, in addition to the evaluation of conventional risk factors in daily clinical practice; further, high levels of SUA may become surrogate markers of CAD severity in women.

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Conflicts of interest

There are no conflicts of interest.

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