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Journal of the American Heart Association

ORIGINAL RESEARCH

Association Between Uric Acid, Carotid Intima-Media Thickness, and Cardiovascular Events: Prospective Results From the IMPROVE Study

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BACKGROUND: The association between elevated serum uric acid (SUA), cardiovascular disease (CVD) risk, and carotid atherosclerosis has long been explored, and contrasting results have been reported. Therefore, the role of SUA as an independent risk factor for vascular events (VEs) and carotid atherosclerosis deserves further attention. We investigated the relationship between SUA, incident VEs, carotid intima-media thickness (cIMT), and cIMT progression in subjects at moderate-to-high CVD risk.

METHODS AND RESULTS: In the IMPROVE (IMT-Progression as Predictors of VEs) study, 3686 participants (median age 64 years; 48% men) with ≥ 3 vascular risk factors, free from VEs at baseline, were grouped according to SUA quartiles (division points: 244–284–328 μmol/L in women, 295–336–385 μmol/L in men). Carotid-IMT and its 15-month progression, along with incident VEs, were recorded. A U-shaped association between SUA and VEs was observed in men, with 2.4-fold (P = 0.004) and 2.5-fold (P = 0.002) increased CVD risk in the first and fourth SUA quartiles as compared with the second. Adjusted hazard ratios (HRs) for cerebro-VEs in men were the highest (first and fourth quartile versus second: HR, 5.3, P = 0.010 and HR, 4.4, P = 0.023, respectively). SUA level was independently associated with cIMT progression in men (β = 0.068, P = 0.014). No significant association between SUA levels, CVD end points, and cIMT progression were found in women.

CONCLUSIONS: Both low and high SUA levels are associated with an increased risk of VEs in men at moderate-to-high CVD risk but not in women. Only elevated SUA levels predict cIMT progression and at a lesser but not significant extent in women.

Key Words: atherosclerosis ■ cardiovascular ■ carotid ■ intima media thickness ■ prospective ■ uric acid

Hyperuricemia has long been a subject of investigation and debate as a potential marker of cardiovascular disease (CVD) risk. Although uric acid has been recognized to have an intrinsic antioxidative activity,[1] experimental and clinical data suggest that elevated serum uric acid (SUA) levels are associated with pro-oxidant effects, endothelial dysfunction, and increased CVD risk.[1–3]

Since the first descriptions of a possible link between hyperuricemia and hypertension, CVD, and kidney failure, a large number of epidemiological studies have variably documented an association between SUA levels and a wide variety of cardiometabolic complications (eg, arterial hypertension, obesity, dyslipidemia, metabolic syndrome, type 2 diabetes mellitus, ischemic heart

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†A complete list of the IMPROVE study group members can be found in Appendix at the end of the manuscript.

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For Sources of Funding and Disclosures, see page 12.

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CLINICAL PERSPECTIVE

What Is New?

- In patients at moderate-to-high cardiovascular disease (CVD) risk who were free from overt CVD at baseline, both low and high serum uric acid (SUA) levels were associated with an increased CVD risk in men, irrespective of many potential confounders.
- A faster 15-month carotid intima-media thickness progression was associated with elevation of SUA levels, mostly in men.

What Are the Clinical Implications?

- SUA level may be an independent risk factor for carotid atherosclerosis progression and vascular events.
- The biological mechanisms underlying sex- and organ-specific patterns of the association of SUA levels and CVD risk and the impact of modulating SUA levels on different CVD end points should be addressed in further studies.

Nonstandard Abbreviations and Acronyms

CC	common carotid
cIMT	carotid intima-media thickness
Fastest-cIMT$_{max\text{-}progr}$	fastest cIMT maximum progression
IMPROVE	IMT-Progression as Predictors of VEs
SUA	serum uric acid
VEs	vascular events

disease, vascular dementia, preeclampsia, chronic kidney disease).[2] Albeit the coexistence of elevated SUA levels and the previously reported comorbidities might highlight a central role for UA in the cardiometabolic scenario, this might also represent an important statistical confounder of the association between SUA levels and CVD end points. In this regard, some epidemiological studies and meta-analyses have reported a significant and independent association between SUA levels and cardio vascular events (VEs).[4–7] However, several other studies failed to confirm such an independent association.[8,9] Also, Mendelian randomization studies that investigated the possible causal relationship between SUA levels and CVD outcomes showed mixed results.[10,11] Hence, investigating the association between SUA levels and CVD-based outcomes, with simultaneous correction for multiple confounders, might be of added statistical and clinical value.

Carotid artery intima-media thickness (cIMT), measured by B-mode ultrasound, is a recognized marker of carotid and coronary atherosclerosis[12] and is considered a useful tool for CVD risk stratification.[13] Accordingly, a number of prospective studies,[12–15] including the IMPROVE (IMT-Progression as Predictors of Vascular Events) study,[12,13] have confirmed the ability of both cIMT and cIMT progression in predicting the risk of future VEs in different geographical areas and clinical settings. In addition, the fastest cIMT maximum progression (Fastest-cIMT$_{max\text{-}progr}$) in the whole carotid tree, a robust surrogate marker of carotid atherosclerosis progression, appeared to better predict incident VEs as compared with different measures of cIMT progression.[16]

The association between SUA levels and cIMT has been explored in several cross-sectional studies. Although mixed results have been reported in these studies, possibly in relation to nonhomogeneous accounting for confounders across different studies,[17–19] the prospective association between SUA levels and cIMT progression has never been explored so far. Meanwhile, the conflicting results emerging from clinical trials evaluating the effect of hypouricemic drugs on cIMT progression further confuse the understanding of the link between UA and atherosclerosis.[20–22] Thus, additional large studies analyzing the association between SUA levels, cIMT, and cIMT progression after correction for a consistent number of cardiometabolic confounders were awaited.

Based on these premises and expectations, the high prevalence of hyperuricemia in the general population[23] and the availability of drugs capable of modifying SUA levels,[24] clarifying the role of SUA levels as an independent predictor of multiple cross-sectional (eg, baseline cIMT) and longitudinal (eg, Fastest-cIMT$_{max\text{-}progr}$, incident VEs) measures of CVD risk would be impactful. In this regard, the IMPROVE study lends itself to give an answer to this need. Hence, the aim of our study was to investigate the prospective relationship between SUA levels, baseline cIMT, cIMT progression, and incident VEs accounting for the potential interference exerted by a significant number of cardiometabolic confounders.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Subjects

Design, objectives, sampling strategy, and methods of the IMPROVE study have been reported elsewhere.[13] In brief, 3703 individuals (age 54–79 years) were

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recruited, with at least 3 CVD risk factors, but free of any cardio- or cerebrovascular event at baseline. The participants were enrolled at 7 centers in 5 European countries: Finland (Kuopio, 2 centers), France (Paris), Italy (Milan and Perugia), The Netherlands (Groningen), and Sweden (Stockholm).

Medical history was obtained and clinical examination was carried out. Blood sampling for laboratory tests was performed after an overnight fast. Methods for laboratory analyses have been previously reported.[16] Glomerular filtration rate was estimated by Cockroft–Gault formula.

The occurrence of combined VEs, including coronary VEs (myocardial infarction, sudden cardiac death, angina pectoris, any revascularization or surgical intervention of the coronary arteries), cerebro-VEs (ischemic stroke, transient ischemic attack, any revascularization or surgical intervention of the carotid arteries), and lower extremity artery disease events (new diagnosis of intermittent claudication, any revascularization or surgical intervention of lower limb arteries) were recorded at months 15 and 30 by regular visits and at the end of follow-up (average 36.2 months) by phone interview. The occurrence of VEs and death of all participants were validated by local specialists, and copies of medical documents and death certificates were sent to a designated specialist, who was unaware of the relevant clinical history and C-IMT data, for adjudication. The sample size considered for this report is 3686, because SUA measurement was not available in 17 subjects.

Ultrasonographic Assessment

The ultrasonographic assessment of carotid arteries of the IMPROVE study was performed as extensively described previously.[13,16] The ultrasonographic variables were measured centrally by trained readers at the ultrasound reading center in Milan (Italy). Baseline ultrasound scans were performed from January 2004 to December 2005. For each participant, the 15-month follow-up scans were performed 15 months later. All scans were recorded on VHS videotapes. Ultrasound scans were all performed with 7 identical scanners equipped with 5 to 10 MHz array probes at baseline and follow-up in all 7 research sites. Calibration of all devices was checked with a phantom at baseline and after 12 months. Similarly, image storage and analysis were the same across research sites and over time. cIMT was assessed in the first cm of common carotid artery proximal to the bifurcation, in the remaining part of the common carotid (CC), in the carotid artery bifurcation, and in the internal carotid artery, 1 cm immediately distal to the flow divider, of both left and right carotids, as previously described.[16] In each carotid segment (1 cm length), both mean ($_{mean}$) and maximal ($_{max}$) IMT were evaluated. Composite variables IMT_{mean}, IMT_{max} and $IMT_{mean\text{-}max}$ refer to the whole carotid tree. IMT_{mean} is the average of first CC-IMT_{mean}, CC-IMT_{mean}, carotid artery bifurcation-IMT_{mean}, and internal carotid artery-IMT_{mean}. IMT_{max} is the greatest value among first CC-IMT_{max}, CC-IMT_{max}, carotid artery bifurcation-IMT_{max} and internal carotid artery-IMT_{max}. $IMT_{mean\text{-}max}$ is the average of first CC-IMT_{max}, CC-IMT_{max}, carotid artery bifurcation-IMT_{max}, and internal carotid artery-IMT_{max}. The common carotid IMT in plaque-free $areas_{mean}$ was also measured.

To evaluate changes of cIMT over time, ultrasonographic measurements were repeated at 15 months using the same ultrasonographic protocol (positions and angles of ultrasound transducer with respect to the neck) used at baseline. Carotid IMT change for each ultrasonographic variable, expressed in mm/year, was calculated as the difference between the 15-month measurement and the corresponding baseline value divided by the length of the intervening time period. The Fastest-$cIMT_{max\text{-}progr}$, that is, the greatest value chosen among the progressions of IMT_{max}, was also assessed, as a measure of the maximal focal progression of cIMT.

Ethical Considerations

The Ethics Committees of all participating institutions approved the IMPROVE study, which complied with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Statistical Analysis

Participants have been grouped according to SUA sex-specific quartiles (division points: 295, 366, and 385 μmol/L [5.0, 5.7, and 6.5 mg/dL] in men; 244, 284, and 328 μmol/L [4.1, 4.8 and 5.5 mg/dL] in women). Standard descriptive and comparative statistical analyses have been performed. In 2-tailed tests, probability values <0.05 have been considered statistically significant. Bivariate correlations between SUA levels and baseline carotid ultrasonographic measures have been assessed and Spearman's correlation coefficients were reported. Multiple linear regression analyses have been performed with each ultrasonographic measure as the dependent variable, in the entire population and separately by sex. Covariates were age; sex; systolic blood pressure; diastolic blood pressure; body mass index; waist-to-hip ratio; smoking status; low-density lipoprotein cholesterol (LDL-C); high-density lipoprotein cholesterol; triglyceride; glucose; glomerular filtration rate; alcohol intake; meat consumption; treatment with diuretics, lipid-lowering, antihypertensive, antidiabetic, anti-platelet drugs, allopurinol, or colchicine; and site of subjects' enrollment. The interaction between sex and SUA was also explored.

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Cox regression analyses have been used to estimate crude and adjusted hazard ratios (HRs). In model 1, unadjusted HRs for combined VEs, coronary VEs, peripheral VEs (ie, lower extremity artery disease plus cerebrovascular events), and cerebro-VEs have been calculated for each SUA quartile. In model 2, age, sex, body mass index, and waist-to-hip ratio have been added as covariates. Model 3 was as model 2 plus systolic blood pressure, diastolic blood pressure, LDL-C, high-density lipoprotein cholesterol, triglyceride, diabetes mellitus presence, smoking status, and glomerular filtration rate. In model 4, alcohol intake; meat consumption; treatment with diuretics, lipid-lowering, antihypertensive, antidiabetic, antiplatelet drugs, allopurinol, or colchicine; and site of subjects' enrollment have been further added along with the aforementioned covariates. Diabetes mellitus presence was also replaced in model 3 and 4 with fasting plasma glucose levels; the corresponding results were presented only if the replacement materially changed the results. Interaction between SUA quartiles and sex in the prediction of each separate CVD end point was also tested. Cox regression models have been performed separately in men and women to calculate HRs and 95% CI. Adjusted survival functions, over a 36.2 month follow-up, have been generated to compare event-free survival between SUA quartiles. Logarithmic transformation was applied to skewed variables. All the analyses have been performed using the SPSS statistical package v. 22.0 (IBM Statistics, Armonk, NY).

RESULTS

The demographic and clinical characteristics of the study participants grouped into SUA quartiles are presented in Table 1. Characteristics of the study participants by sex are reported in Tables S1 and S2. Higher systolic blood pressure, body mass index, waist-to-hip ratio, triglyceride, and lower high-density lipoprotein cholesterol levels were observed with increasing SUA quartiles. Lower total and LDL-C levels were observed in the first SUA quartile as compared with the remaining quartiles. Participants in the highest SUA quartile had significantly higher glucose levels as compared with those in the other quartiles.

SUA Levels, Baseline cIMT Measures, and Fastest-cIMT$_{max\text{-}progr}$

No significant differences across SUA quartiles have been found for the cross-sectional cIMT measures, whereas higher Fastest-cIMT$_{max\text{-}progr}$ values were found with increasing SUA quartiles (Table 1). Linear regression analysis including SUA levels as an independent variable along with covariates (ie, age; sex; systolic blood pressure; diastolic blood pressure; body mass index; waist-to-hip ratio; smoking status; LDL-C; high-density lipoprotein cholesterol; triglyceride; glucose; glomerular filtration rate; alcohol intake; meat consumption; treatment with diuretics, lipid-lowering, antihypertensive, antidiabetic, antiplatelet drugs, allopurinol, or colchicine; and site of subjects enrollment) did not reveal an independent association of SUA levels with any cross-sectional cIMT measure (P>0.05 for all analyses). By contrast, linear regression analysis showed an independent association between SUA levels and Fastest-cIMT$_{max\text{-}progr}$ (β=0.056; P=0.008). When linear regression was performed separately by sex, the independent association between SUA and Fastest-cIMT$_{max\text{-}progr}$ was significant in men (standardized β 0.068; P=0.014) but not in women (standardized β 0.045; P=0.117). The interaction between SUA and sex in the prediction of Fastest-cIMT$_{max\text{-}progr}$ did not reach statistical significance (P=0.073).

SUA Levels and VEs

A total of 215 combined VEs were recorded during the median 36.2-month follow-up period, including 125 coronary VEs, 73 cerebro-VEs, and 17 lower extremity artery disease events. Total and sex-stratified rates of CVD end points across SUA quartiles are reported in Table 2. As 1 coronary VE occurred in a patient for whom SUA determination was not available, in all the analyses, the number of combined VEs was 214 and that of coronary VEs was 124.

Table 3 shows the crude and adjusted HRs and 95% CIs for combined VEs across SUA quartiles. The crude HR for combined VEs was the lowest in the second quartile of SUA levels as compared with the other SUA quartiles, configuring a U-shaped distribution of HRs across SUA quartiles (Table 3, Model 1, Whole Group); thus, the second SUA quartile was treated as the reference risk group. In the minimally adjusted Cox regression model (Table 3, Model 2, Whole Group), HRs for combined VEs were 1.51, 1.66, and 1.73 for the first, third, and fourth quartiles, respectively (P=0.065, 0.019, and 0.011). Further adjustment of the Cox regression models for additional potential confounders (Table 3, Model 3 and 4, Whole Group) left the same U-shaped relationship between SUA quartiles and the risk of combined-VEs, with the significance of the association between the fourth SUA quartile and combined VEs not reaching statistical significance both in Model 3 and 4 (HRs, 1.53 and 1.55, P=0.055 and 0.066, respectively). A significant interaction emerged between SUA quartiles and sex in the prediction of total combined VEs (P=0.009); thus, we repeated the Cox regression analysis separately in men and women. In men, the U-shaped fully adjusted distribution of risk of combined VEs across

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Table 1. Characteristics of IMPROVE Study Participants According to SUA Quartiles

	SUA Quartiles				*P* Value for Trend	Between Groups Difference *P* Value
	1st	2nd	3rd	4th		
SUA range, μmol/L (mg/dL)	<244 (<4.1) F <295 (<5.0) M	244, 284 (4.1–4.8) F 295, 336 (5.0–5.7) M	284, 328 (4.8–5.5) F 337, 385 (5.7–6.5) M	>328 (>5.5) F >385 (>6.5) M	NA	NA
Number of patients	921	921	923	921	NA	NA
Age, y	64.7 (59.7–67.2)	64.2 (59.4–67.2)	64.5 (59.9–67.2)	64.3 (59.6–67.4)	0.95	0.72
Sex, male, %	48	48	48	48	NA	NA
Current smoke, %	31.5	35.5	37.7	43.3	<0.001	<0.001
Diabetes mellitus, %	20.7	22.6	23.2	32.1	<0.001	<0.001
Hypertension, %	63.9	70.4	73.0	82.0	<0.001	<0.001
Obesity, %	13.8	21.9	26.5	28.9	<0.001	<0.001
Gout, %	2.8	3.3	4.7	9.0	<0.001	<0.001
Cardiac diseases, %	4.6	5.8	6.1	6.7	<0.001	<0.001
Diuretics, %	12.1	20.1	21.3	39.1	<0.001	<0.001
Allopurinol/colchicine, %	2.0	1.8	2.5	2.8	0.14	0.45
Lipid-lowering, %	53.0	48.1	48.0	45.0	<0.001	<0.001
Statins, %	41.0	39.8	41.5	37.6	0.22	0.31
Fibrate, %	11.6	7.7	6.0	5.3	<0.001	<0.001
Antiplatelet, %	15.5	16.9	16.5	17.8	0.25	0.62
Angiotensin-converting enzyme inhibitors, %	16.3	18.1	20.2	23.6	<0.001	<0.001
Angiotensin receptor blockers, %	11.8	13.5	16.0	19.4	<0.001	<0.001
Beta blockers, %	18.1	21.1	23.2	32.5	<0.001	<0.001
Calcium-antagonists, %	15.2	14.4	16.9	18.2	0.039	0.16
Anti-inflammatory, %	17.5	19.1	18.6	22.5	0.013	0.043
Meat consumption, portions/wk	3 (2–5)	3 (2–5)	4 (2–5)	4 (3–5)	<0.001	0.002
Alcohol consumption, g/d	5 (0–20)	5 (0–20)	5 (0–20)	10 (0–30)	0.011	0.042
Systolic blood pressure, mm Hg	140 (128–152)	141 (130–153)	140 (130–152)	141 (130–154)	0.013	0.036
Diastolic blood pressure, mm Hg	81 (75–88)	82 (75–89)	82 (76–89)	82 (76–89)	0.007	0.020
Body mass index, kg/m^2	25.5 (23.9–28.9)	26.3 (23.9–28.9)	27.1 (24.6–29.8)	28.4 (26.0–31.5)	<0.001	<0.001
Waist-to-hip ratio	0.90 (0.84–0.95)	0.91 (0.85–0.96)	0.91 (0.86–0.97)	0.93 (0.87–0.99)	<0.001	<0.001
Blood glucose, mmol/L	5.50 (5.00–6.20)	5.50 (5.17–6.78)	5.50 (5.00–6.20)	5.70 (5.17–6.78)	<0.001	<0.001
Total cholesterol, mg/dL	205 (178–234)	214 (183–244)	207 (183–238)	214 (183–245)	<0.001	<0.001
Triglyceride, mg/dL	98 (70–140)	107 (80–152)	119 (85–171)	141 (97–199)	<0.001	<0.001
High-density lipoprotein cholesterol, mg/dL	46 (39–56)	45 (38–54)	46 (39–56)	45 (38–54)	<0.001	<0.001
Low-density lipoprotein cholesterol, mg/dL	132 (106–159)	138 (110–166)	134 (110–162)	136 (108–164)	0.19	0.058
Glomerular filtration rate, mL/min	82 (68–96)	82 (68–96)	81 (67–97)	80 (67–95)	0.11	0.40
IMT_{mean}, mm	0.848 (0.746–0.988)	0.851 (0.736–1.000)	0.845 (0.741–0.993)	0.851 (0.739–1.016)	0.77	0.97
IMT_{max}, mm	1.85 (1.45–2.50)	1.85 (1.39–2.50)	1.85 (1.39–2.42)	1.85 (1.45–2.51)	0.84	0.81
$IMT_{mean-max}$, mm	1.34 (1.13–1.64)	1.33 (1.11–1.65)	1.34 (1.13–1.64)	1.35 (1.12–1.68)	0.48	0.79
Common carotid IMT in plaque-free $areas_{mean}$, mm	0.705 (0.648–0.762)	0.699 (0.645–0.763)	0.698 (0.645–0.754)	0.704 (0.644–0.761)	0.67	0.79

(*Continued*)

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Table 1. Continued

	SUA Quartiles				*P* Value for Trend	Between Groups Difference *P* Value
	1st	2nd	3rd	4th		
Fastest-carotid $IMT_{max\text{-}progr}$, mm/y	0.184 (0.103–0.311)	0.172 (0.093–0.320)	0.215 (0.114–0.375)	0.215 (0.106–0.359)	0.008	0.004

Values are median (25th, 75th percentile) or percentage. *P* values were calculated by Jonckheere-Terpstra and Kruskal Wallis tests. F indicates female; IMPROVE, IMT-Progression as Predictors of Vascular Eventss; IMT, intima media thickness; max-progr, maximum progression; M, male; NA, not applicable, and SUA, serum uric acid.

SUA quartiles was evident, with the highest risk of combined VEs in the first and fourth SUA quartiles as compared with the second SUA quartile (HR, 2.41, *P*=0.004 and HR, 2.55, *P*=0.002, respectively). No significant differences in the risk of combined VEs across SUA quartiles emerged among women (Table 3).

HRs for coronary VEs and peripheral VEs across SUA quartiles are presented in Tables 4 and 5, respectively. Increased unadjusted rates of coronary VEs in men were observed in the third and fourth SUA quartiles, respectively (Table 4, Model 1); in the minimally and fully adjusted Cox regression models restricted to male sex, SUA levels in the fourth quartile were significantly associated with coronary VEs (Table 4, Models 2 and 4). No significant association emerged between SUA quartiles and coronary heart disease (CHD) risk in women. A significant U-shaped association was observed in men, but not in women, between SUA levels and the risk of peripheral VEs (Table 5). Men in the first and fourth SUA quartiles had the greatest fully adjusted HRs for peripheral VEs (HR, 3.69, *P*=0.013 and HR, 3.37, *P*=0.020, respectively) as compared with those in the second SUA quartile (Table 5). An additional Cox regression analysis was performed by excluding lower extremity artery disease events from the peripheral VEs end point. In this analysis, the U-shaped association between SUA quartiles and cerebro-VEs was even more evident in the total cohort and in men, but not in women (Table 6).

Combined, coronary and cerebrovascular event-free survival curves across SUA quartiles are presented in Figure.

DISCUSSION

In this study of subjects at moderate-to-high CVD risk at baseline, 3 main results have been observed: (1) a positive linear association between SUA levels and Fastest-$cIMT_{max\text{-}progr}$, (2) a U-shaped association between SUA levels and CVD risk, and (3) a significant impact of sex on the association between SUA levels and both CVD and carotid atherosclerotic progression.

We found an independent association between SUA levels and 15-month Fastest-$cIMT_{max\text{-}progr}$, a reliable measure of cIMT progression and a stronger predictor of CVD events as compared with other measures of cIMT progression.[16] From a pathophysiological perspective, UA may play a key role in promoting atherosclerosis and CVD by inducing oxidative stress, LDL peroxidation, the expression of proinflammatory cytokines,[25,26] endothelial dysfunction,[27]

Table 2. Rates of Combined, Coronary, Peripheral, and Cerebrovascular Events in Serum Uric Acid Quartiles

	Sex	Serum Uric Acid Quartiles			
		First	Second	Third	Fourth
Combined vascular events, n (%) (coronary and peripheral vascular events)	Women	15 (3.13)	18 (3.75)	26 (5.41)	22 (4.58)
	Men	35 (7.94)	16 (3.63)	33 (7.47)	49 (11.11)
	Total	50 (5.43)	34 (3.69)	59 (6.39)	71 (7.71)
Coronary vascular events, n (%)	Women	9 (1.88)	10 (2.08)	13 (5.41)	12 (2.50)
	Men	19 (4.31)	11 (2.49)	23 (5.20)	27 (6.12)
	Total	28 (3.04)	21 (2.28)	36 (3.87)	39 (4.23)
Peripheral vascular events, n (%) (lower extremity artery disease events and cerebrovascular events)	Women	6 (1.25)	8 (1.67)	13 (2.70)	10 (2.08)
	Men	16 (3.63)	5 (1.13)	10 (2.26)	22 (4.99)
	Total	22 (2.39)	13 (1.41)	23 (2.49)	32 (3.47)
Cerebrovascular events, n (%)	Women	5 (1.04)	5 (1.04)	13 (2.70)	10 (2.08)
	Men	14 (3.17)	3 (0.68)	8 (1.81)	15 (3.40)
	Total	19 (2.06)	8 (0.87)	21 (2.28)	25 (2.71)

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Table 3. HRs of Combined Vascular Events Across SUA Quartiles

	SUA Quartiles	Number of Subjects With/Without Events	HR of Combined Vascular Events (95% CI) Second vs First, Third, and Fourth SUA Quartiles			
			Model 1	Model 2	Model 3	Model 4
Whole group	First	50/871	1.46 (0.94–2.26)	1.51 (0.98–2.34)	1.59 (1.02–2.47)*	1.68 (1.08–2.62)*
	Second	34/887	1.00	1.00	1.00	1.00
	Third	59/864	1.72 (1.13–2.62)*	1.66 (1.09–2.54)*	1.58 (1.03–2.42)*	1.58 (1.03–2.42)*
	Fourth	71/850	1.90 (1.25–2.88)†	1.73 (1.13–2.65)*	1.53 (0.99–2.36)	1.51 (0.97–2.35)
Women	First	15/465	0.82 (0.41–1.62)	0.86 (0.43–1.71)	0.89 (0.44–1.79)	1.10 (0.54–2.24)
	Second	18/462	1.00	1.00	1.00	1.00
	Third	26/455	1.39 (0.76–2.54)	1.31 (0.71–2.39)	1.19 (0.65–2.19)	1.30 (0.70–2.41)
	Fourth	22/458	1.05 (0.55–2.01)	0.90 (0.46–1.74)	0.76 (0.38–1.51)	0.67 (0.33–1.36)
Men	First	35/406	2.19 (1.21– 3.96)†	2.22 (1.23–4.01)†	2.42 (1.33–4.40)†	2.41 (1.32–4.42)†
	Second	16/425	1.00	1.00	1.00	1.00
	Third	33/409	2.07 (1.14–3.75)*	2.03 (1.11–3.69)*	2.02 (1.11–3.70)*	1.95 (1.06–3.58)*
	Fourth	49/392	2.86 (1.61–5.07)‡	2.70 (1.51–4.81)†	2.46 (1.37–4.43)†	2.55 (1.41–4.62)†

Model 1: unadjusted. Model 2: adjusted for age, sex, body mass index, waist-to-hip ratio. Model 3: as model 2 plus, systolic blood pressure, diastolic blood pressure, diabetes mellitus presence, smoking status, triglyceride, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, glomerular filtration rate. Model 4: as model 3 plus alcohol intake; meat consumption; treatment with diuretics, antiplatelet, antidiabetic, lipid-lowering, antihypertensive drugs, allopurinol, or colchicine; site of enrolment. HR indicates hazard ratio; and SUA, serum uric acid.

Replacement of diabetes mellitus presence with fasting plasma glucose did not materially affect the results *P<0.05, †P<0.01, ‡P<0.001.

and by activating the renin-angiotensin-aldosterone system.[28,29] Furthermore, inhibition of xanthine oxidase, which is responsible for the reduction in UA production and its serum levels, was found to improve endothelial function[19] and CVD outcomes.[30] Therefore, our results of an independent prospective association between elevated SUA levels and IMT progression, may support the detrimental role of elevated SUA levels on the development of atherosclerosis and related CVD prognosis.

A U-shaped prospective association between SUA levels and the risk of incident cardiovascular events was found after correction for multiple confounders. In particular, subjects with SUA levels above or below the SUA reference range of values (295–336 µmol/L [5.0–5.7 mg/dL] for men and 244–284 µmol/L [4.1–4.8 mg/dL] for women) had a 1.5- to 1.6-fold increased risk of cardiovascular events as compared with those having their SUA levels within the aforementioned ranges of values.

The association between elevated SUA levels and CVD risk has long been known. An increase in SUA levels has been commonly observed in subjects with traditional cardiometabolic risk factors, including

Table 4. HRs of Coronary Vascular Events Across SUA Quartiles

	SUA Quartiles	Number of Subjects With/Without Events	HR of Coronary Vascular Events (95% CI) Second vs First, Third, and Fourth SUA Quartiles			
			Model 1	Model 2	Model 3	Model 4
Whole group	First	28/893	1.33 (0.75–2.34)	1.43 (0.81–2.53)	1.50 (0.85–2.66)	1.61 (0.90–2.87)
	Second	21/900	1.00	1.00	1.00	1.00
	Third	36/887	1.69 (0.98–2.89)	1.57 (0.91–2.69)	1.51 (0.87–2.61)	1.54 (0.90–2.67)
	Fourth	39/882	1.70 (0.99–2.92)	1.42 (0.82–2.46)	1.26 (0.72–2.22)	1.31 (0.74–2.32)
Women	First	9/471	0.88 (0.36–2.17)	1.01 (0.41–2.50)	1.02 (0.41–2.55)	1.55 (0.59–4.04)
	Second	10/470	1.00	1.00	1.00	1.00
	Third	13/468	1.21 (0.53–.77)	1.04 (0.45–2.39)	0.93 (0.40–2.17)	1.19 (0.50–2.81)
	Fourth	12/468	0.98 (0.41–2.35)	0.68 (0.28–1.68)	0.55 (0.21–1.41)	0.51 (0.19–1.33)
Men	First	19/422	1.72 (0.82–3.62)	1.78 (0.85–3.76)	1.89 (0.89–4.00)	1.84 (0.86–3.94)
	Second	11/430	1.00	1.00	1.00	1.00
	Third	23/419	2.10 (1.02–4.31)*	2.03 (0.99–4.17)	1.98 (0.96–4.12)	1.96 (0.94–4.08)
	Fourth	27/414	2.37 (1.17–4.82)*	2.16 (1.06–4.44)*	1.96 (0.94–4.08)	2.10 (1.00–4.41)*

Models as in Table 3. HR indicates hazard ratio; and SUA, serum uric acid.

*P<0.05.

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Table 5. HRs of Peripheral VEs Across SUA Quartiles (Peripheral VEs Include Both LEAD and Cerebro-VEs)

	SUA Quartiles	Number of Subjects With/Without Events	HR of Peripheral VEs (95% CI) Second vs First, Third, and Fourth SUA Quartiles			
			Model 1	Model 2	Model 3	Model 4
Whole group	First	22/899	1.68 (0.85–3.33)	1.63 (0.82–3.24)	1.75 (0.88–3.51)	1.80 (0.90–3.63)
	Second	13/908	1.00	1.00	1.00	1.00
	Third	23/900	1.76 (0.89–3.48)	1.80 (0.91–3.56)	1.67 (0.84–3.31)	1.63 (0.82–3.23)
	Fourth	32/889	2.22 (1.15–4.28)*	2.30 (1.18–4.49)*	2.00 (1.02–3.96)*	1.81 (0.90–3.62)
Women	First	6/474	0.73 (0.25–2.1)	0.70 (0.24–2.02)	0.74 (0.25–2.15)	0.80 (0.27–2.40)
	Second	8/472	1.00	1.00	1.00	1.00
	Third	13/468	1.62 (0.67–3.91)	1.65 (0.68–4.00)	1.56 (0.64–3.79)	1.48 (0.60–3.63)
	Fourth	10/470	1.15 (0.44–2.98)	1.24 (0.47–3.31)	1.08 (0.39–2.98)	0.90 (0.31–2.56)
Men	First	16/425	3.22 (1.18–8.80)*	3.15 (1.15–8.63)*	3.73 (1.35–10.29)*	3.69 (1.32– 10.31)*
	Second	5/436	1.00	1.00	1.00	1.00
	Third	10/432	2.00 (0.68–5.84)	2.02 (0.69–5.92)	1.97 (0.66–5.84)	1.91 (0.64–5.71)
	Fourth	22/419	3.93 (1.47–10.51)†	3.91 (1.45–10.58)*	3.49 (1.28–9.54)*	3.37 (1.22–9.33)†

Models as in Table 3. HR indicates hazard ratio; LEAD, lower extremity artery disease; SUA, serum uric acid; and VE, vascular event.
*$P<0.05$.
†$P<0.01$.

obesity, hypertension, dyslipidemia, diabetes mellitus, and chronic kidney disease.[31] In particular, the association between elevated SUA levels and development of hypertension is supported by numerous epidemiological and pathophysiological evidences. Genetic polymorphysms of the xanthine oxidoreductase are associated with hypertension.[32,33] Also, clinical studies suggest that lowering SUA may reduce blood pressure in hypertensive patients.[34,35] Possible mechanisms linking SUA levels and hypertension involve the activation of renin-angiotensine-aldosterone system, the promotion of a pro-oxidant and proinflammatory state, a direct damage of the kidney afferent arteriola and the development of endothelial dysfunction.[36]

Several observational studies, many of whom included in some meta-analyses, have found a direct association between SUA levels and cardiovascular events in the general population[4–7] and in patients with hypertension[37,38] or diabetes mellitus.[39]

An intriguing aspect emerging from our research was the evidence of an increased CVD risk among subjects with extremely low SUA levels, thus configuring a U-shaped association between SUA levels and incident cardiovascular events. A similar U-shaped distribution of CVD risk across different SUA levels has

Table 6. HRs of Cerebro-VEs Across SUA Quartiles

	SUA Quartiles	Number of Subjects With/Without Events	HR of Cerebro-VEs (95% CI) Second vs First, Third, and Fourth SUA Quartiles			
			Model 1	Model 2	Model 3	Model 4
Whole group	First	19/902	2.34 (1.03–5.35)*	2.28 (1.00–5.23)	2.44 (1.06–5.61)*	2.51 (1.08–5.79)*
	Second	21/900	1.00	1.00	1.00	1.00
	Third	36/887	2.63 (1.17–5.95)*	2.66 (1.18–6.01)*	2.50 (1.10–5.66)*	2.46 (1.08–5.60)*
	Fourth	39/882	3.12 (1.40–6.93)†	3.15 (1.40–7.09)†	2.71 (1.19–6.19)*	2.48 (1.07–5.74)*
Women	First	5/475	0.97 (0.28–3.35)	0.93 (0.27–3.23)	0.98 (0.28–3.43)	1.03 (0.29–3.67)
	Second	5/475	1.00	1.00	1.00	1.00
	Third	13/468	2.62 (0.93–7.34)	2.65 (0.94–7.46)	2.49 (0.88–7.05)	2.42 (0.85–6.92)
	Fourth	10/470	1.86 (0.63–5.56)	1.98 (0.64–6.07)	1.76 (0.56–5.59)	1.50 (0.46–4.93)
Men	First	14/427	4.67 (1.34–16.26)*	4.59 (1.32–16.02)*	5.43 (1.54–19.17)†	5.34 (1.49–19.13)*
	Second	3/438	1.00	1.00	1.00	1.00
	Third	8/434	2.67 (0.71–10.05)	2.67 (0.71–10.11)	2.74 (0.72–10.48)	2.48 (0.64–9.57)
	Fourth	15/426	5.19 (1.50–17.93)†	5.01 (1.44–17.48)*	4.50 (1.27–15.91)*	4.39 (1.22–15.80)*

Models as in Table 3. HR indicates hazard ratio; SUA, serum uric acid; and VE, vascular event.
*$P<0.05$.
†$P<0.01$.

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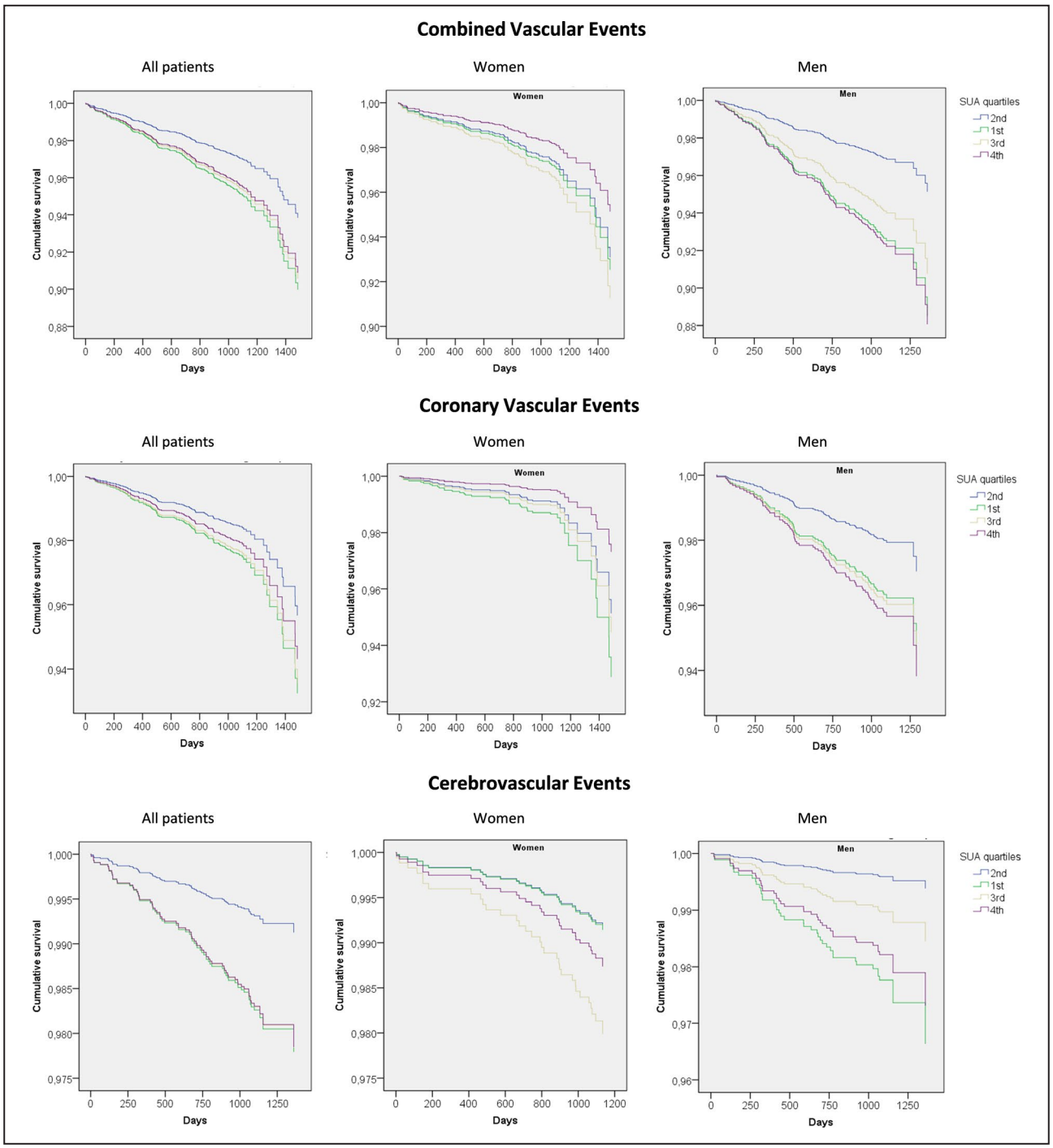

Figure. Combined, coronary, and cerebrovascular event-free survival in all patients and among men and women, across SUA quartiles.
SUA indicates serum uric acid.

been observed in previous studies.[6,37] The ambivalent role of UA with respect to oxidative stress should be considered in the interpretation of this result. Indeed, along with its pro-oxidative effects, UA has also the ability to scavenge oxygen free radicals and protect the erythrocyte membrane from lipid oxidation.[1] Furthermore, UA has the ability of chelating metal ions, like iron and copper, converting them to poorly reactive forms.[40] This latter evidence suggests that UA may also function as an antioxidant.[1] In agreement with a possible protective role of UA, a randomized, placebo-controlled trial showed that severe drug-induced hypouricemia impaired endothelium-dependent microvascular vasodilation and increased lipid peroxidation

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through loss of whole plasma antioxidant capacity.[41] In addition, both intraperitoneal and intravenous administration of UA attenuated brain injury in a rat model of acute cerebral ischemia induced by middle cerebral artery occlusion.[42] Based on these observations, it can be argued that both low and high UA levels could be associated with oxidative effects, leading to a higher risk of CVD events.

It should be noted that we found an excess CVD risk in men at SUA levels of <295 μmol/L (<5.0 mg/dL), the latter value representing the 25th percentile of SUA levels in this sex category within the IMPROVE study. In the study by Verdecchia et al[37] an increased CVD risk was found in patients with high SUA levels (>4.6 and >6.2 mg/dL, fourth quartiles in women and men respectively) and a nonsignificant increased CVD risk in those with low SUA levels (<3.2 and <4.5 mg/dL in women and men, respectively). Different characteristics of the study populations and lower baseline SUA levels in the study by Verdecchia et al[37] may have contributed to the partial discrepancy in the study results. Kuo et al[6] confirmed the presence of a U-shaped association between SUA levels and CVD mortality, with a significant increased CVD mortality also for SUA levels below 4.9 mg/dL. Although this latter study[6] the mortality end point was reported and analyses were not stratified by sex, this results are in line with our findings. Based on these elements, we should underline that sex-based and cutoff-based differences between our and other findings deserve further clarification. In particular, use of stratified cutoff levels for SUA and controlling for factors that might lead to lower SUA levels (eg, malnourishment, lung disease, or frailty) should be considered in future studies. Our study highlighted a strong U-shaped association between SUA levels and the risk of cerebrovascular events. Subjects with SUA levels in the 1st quartile (lower than 295.1 μmol/L [5.0 mg/dL]) and those in the fourth quartile of SUA levels (>395 μmol/L [6.5 mg/dL]) had 5.3- and 4.4-times higher risk of cerebrovascular events than those with SUA levels within the second quartile, respectively.

Previous epidemiological studies and meta-analyses have shown an association between SUA levels and stroke.[43,44] However, the independent association between SUA levels and cerebrovascular disease remains controversial, as other studies failed to confirm such association.[9] Generic proatherothrombotic mechanisms by which hyperuricemia can independently predict an increased incidence of stroke have been proposed. Increased lipid peroxidation and platelet adhesiveness, stimulation of vascular smooth cell proliferation, vascular inflammation, and endothelial cells injury are just some of proposed mechanisms.[45] However, oppositely to cerebrovascular risk, the association between elevated SUA levels and CHD risk did not reach statistically significance in the whole IMPROVE cohort, albeit a sort of U-shaped relationship between SUA levels and CHD events was still evident in men. Therefore, alternative mechanisms explaining the greater detrimental impact of UA on cerebrovascular rather than on CHD events should be hypothesized. In this regard, UA has been prospectively and pathogenetically associated with the development of hypertension,[46,47] which is associated more strongly with the risk of cerebrovascular diseases, rather than with that of CHD. Also, it has been found that the brain is extremely susceptible to oxidative stress.[48] This is important in the light of the frequently reported prooxidative effects of UA.[1] Finally, an association between SUA levels and the incidence of atrial fibrillation has been reported,[49] thus possibly contributing to increase the risk of cardioembolic cerebrovascular events in hyperuricemic subjects. The proposed mechanisms by which UA might exert its detrimental impact preferentially at the cerebrovascular rather than at the coronary level need to be verified in specifically designed large prospective studies, allowing for more reliable analysis of separate end points.

A significant influence of sex into the relationship between SUA and cardiovascular events has been observed in this study, with SUA levels being associated with risk of cardiovascular events only in men. In agreement with our result, previous studies found an association between SUA levels and stroke in men but not in women.[7,50] However, other studies conducted in different populations have shown a stronger association between hyperuricemia and CVD risk in women than in men.[51,52] In the meta-analysis by Zhong et al,[44] the increase in SUA levels was instead associated with an increased risk of stroke in both men and women. Large differences in age, prevalence of cardiovascular risk factors, and menopausal status can be noticed among populations recruited in the different studies. In our population, a high prevalence of hypertension and dyslipidemia was observed and almost all women were in menopause. Thus, results of previous studies are hardly comparable to ours, with respect to sex-related differences in the association between SUA levels and CVD risk. A pathophysiological hypothesis emerging from our study can be proposed to explain these differences.

We found that a significant independent association between SUA levels and Fastest-cIMT$_{max\text{-}progr}$ was present in men, whereas such association did not reach statistical significance in women. This may suggest that the harmful impact of UA on the progression of carotid atherosclerosis may be attenuated in women, albeit the interaction between sex and SUA did not reach formally statistical significance. How this can happen cannot be deduced directly from our results, but some speculative hypotheses can be suggested. UA metabolism is genetically regulated and sex differences in the regulation of SUA concentrations

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have been reported.[53] For example, variants of *SLC2A9* and *ABCG2* genes, which regulate renal and extrarenal urate excretion respectively, influence SUA levels differently in men and women.[53] Furthermore, distinct patterns of metabolic alteration between sexes, likely because of different exposure to sex hormones, might have an impact on the greater susceptibility of men to the deleterious effects of SUA levels on atherosclerosis risk.[54–56] Nevertheless, it must be considered that event rates in women are lower than in men, therefore we cannot exclude that an association between SUA levels, atherosclerosis progression, and CVD risk in women would emerge with longer follow-up.

Strengths of this study need to be acknowledged. In the present analyses, we have explored the associations between SUA levels and multiple atherosclerosis-related end points, both clinical and subclinical. These associations were adjusted for a large number of confounders including several CVD risk factors, some dietary habits potentially affecting SUA levels and CVD risk, and multiple drugs, including those affecting SUA levels. Finally, a large representative population of subjects at moderate-to-high CVD risk factors, recruited simultaneously across 5 European countries, has been studied. Some limitations of our study must be mentioned as well. First, 1 single measurement of SUA levels was performed at baseline, thus exposing this measurement to a potential bias deriving from day-to-day variability of SUA levels. Second, although statistical adjustments have been made for a considerable number of potential confounding factors, residual confounding from unconsidered variables cannot be excluded. Finally, our study included subjects at moderate-to-high CVD risk, thus all the results should be extrapolated with caution to populations at different CVD risk.

CONCLUSIONS

In conclusion, in patients at moderate-to-high CVD risk, free from overt CVD at baseline, both low and high SUA levels were associated with an increased CVD risk in men irrespective of a large number of potential confounders. Accelerated cIMT progression may support the association between elevation of SUA levels and CVD risk, mostly in men. Further, specifically designed studies are warranted to clarify the biological mechanisms underlying sex- and organ-specific patterns of the association of SUA levels and CVD risk and the impact of modulating SUA levels on different CVD end points.

APPENDIX

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None.

Supplementary Material

Tables S1–S2

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SUPPLEMENTAL MATERIAL

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Table S1. Characteristics according to SUA quartiles in women.

	Serum Uric Acid (SUA) quartiles					
	1st	2nd	3rd	4th	P value for trend	Between groups difference P value
SUA range, μmol/L (mg/dl)	<244 (<4.1)	244, 284 (4.1, 4.8)	284, 328 (4.8, 5.5)	>328 (>5.5)	N.A.	N.A.
Number of patients	480	480	481	480	N.A.	N.A.
Age, years	64.5 (59.8, 67.1)	63.8 (59.4, 67.0)	65.0 (60.3, 67.5)	64.6 (59.6, 68.2)	0.24	0.31
Current smoke, %	17.7	21.9	24.7	27.3	<0.001	<0.001
Diabetes, %	15.0	13.3	20.2	32.7	<0.001	<0.001
Hypertension, %	64.9	70.4	73.2	86.3	<0.001	<0.001
Obesity, %	12.8	22.9	26.4	43.5	<0.001	<0.001
Gout, %	0.6	0.2	1.0	2.3	<0.001	<0.001
Cardiac diseases, %	4.0	6.2	6.3	7.7	<0.001	<0.001

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Diuretics, %	14.4	24.2	25.6	47.9	<0.001	<0.001
Allopurinol/cholchicin, %	0.6	0.2	1.2	1.0	0.20	0.27
Lipid-lowering, %	56.5	47.5	51.4	44.8	0.002	0.002
Statins, %	46.3	40.6	46.2	37.5	0.040	0.012
Fibrate, %	8.8	5.6	4.2	5.0	0.008	0.015
Anti-platelet, %	14.0	14.4	13.7	16.5	0.34	0.62
Ace-inhibitors, %	13.3	15.8	18.3	23.1	<0.001	0.001
Angiotensin receptor blockers, %	11.1	12.1	17.7	19.6	<0.001	0.001
Beta-blockers, %	20.0	23.1	24.5	37.1	<0.001	<0.001
Calcium-antagonists, %	14.0	14.2	15.6	16.9	0.16	0.56
Anti-inflammatory, %	16.7	17.3	17.0	22.7	0.024	0.049
Meat consumption, portions/week	3 (2, 4)	3 (2, 5)	3 (2, 5)	4 (2, 5)	<0.001	0.002

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Alcohol consumption, g/day	0 (0, 15)	0 (0, 10)	0 (0, 10)	0 (0, 11)	0.80	0.37
Systolic Blood Pressure, mmHg	140 (127, 152)	140 (130, 152)	141 (130, 152)	140 (130, 153)	0.014	0.055
Diastolic Blood Pressure, mmHg	80 (74, 86)	80 (74, 88)	81 (75, 88)	81 (75, 88)	0.014	0.07
Body Mass Index, kg/m^2	24.8 (22.6, 27.3)	25.7 (23.2, 28.9)	26.8 (23.9, 29.7)	28.8 (26.0-32.4)	<0.001	<0.001
Waist/Hip ratio	0.85 (0.81, 0.90)	0.86 (0.81, 0.91)	0.87 (0.83, 0.91)	0.89 (0.84, 0.94)	<0.001	<0.001
Blood glucose, mmol/L	5.1 (4.6, 5.6)	5.2 (4.8, 5.9)	5.3 (4.8-6.0)	5.6 (5.1, 6.7)	<0.001	<0.001
Total Cholesterol, mg/dl	214 (185, 244)	222 (189, 252)	218 (190, 249)	223 (191, 251)	0.022	0.030
Triglyceride, mg/dl	90 (67, 126)	102 (77, 142)	113 (86, 159)	142 (97, 196)	<0.001	<0.001
HDL-Cholesterol, mg/dl	54 (44, 64)	52 (44, 62)	51 (43, 61)	49 (40, 58)	<0.001	<0.001
LDL-Cholesterol, mg/dl	138 (109, 167)	144 (116, 172)	139 (113, 168)	140 (113, 167)	0.603	0.16
GFR, ml/min	76 (65, 91)	75 (65, 88)	74 (63, 89)	77 (63, 93)	0.65	0.47

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IMT_{mean}, mm	0.804 (0.715, 0.919)	0.804 (0.717, 0.939)	0.803 (0.709, 0.925)	0.804 (0.714, 0.923)	0.82	0.94
IMT_{max}, mm	1.74 (1.34, 2.32)	1.74 (1.30, 2.31)	1.74 (1.30, 2.31)	1.69 (1.35, 2.31)	0.71	0.89
$IMT_{mean-max}$, mm	1.27 (1.08, 1.50)	1.26 (1.06, 1.52)	1.25 (1.07-1.50)	1.26 (1.08, 1.55)	0.97	0.91
PF CC-IMT_{mean}, mm	0.693 (0.633, 0.746)	0.683 (0.641, 0.748)	0.689 (0.640, 0.740)	0.692 (0.637, 0.745)	0.74	0.95
Fastest-c$IMT_{max-progr}$, mm/year	0.166 (0.100, 0.301)	0.158 (0.087, 0.286)	0.207 (0.104, 0.338)	0.169 (0.087, 0.314)	0.37	0.010

Values are median (25^{th}, 75^{th} percentile) or percentage. P Values were calculated by Kruskal Wallis and Jonckheere-Terpstra tests. CC, common carotid; GFR, glomerular filtration rate; HDL, high density lipoproteins; IMT, intima media thickness; LDL, low density lipoprotein; N.A., not applicable, PF, plaque-free; SUA, serum uric acid.

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Table S2. Characteristics according to SUA quartiles in men.

	Serum Uric Acid (SUA) quartiles					
	1st	2nd	3rd	4th	P value for trend	Between groups difference P value
SUA range, μmol/L (mg/dl)	<295 (<5.0)	295, 336 (5.0, 5.7)	337, 385 (5.7, 6.5)	>385 (>6.5)	N.A.	N.A.
Number of patients	441	441	442	441	N.A.	N.A.
Age, years	65.0 (59.7, 67.3)	64.6 (59.4, 67.1)	64.0 (59.3, 67.0)	63.9 (59.3, 67.1)	0.24	0.60
Current smoke, %	46.5	50.3	51.6	60.8	<0.001	<0.001
Diabetes, %	27.0	32.7	26.5	31.5	0.45	0.099
Hypertension, %	62.8	70.3	73.1	77.3	<0.001	<0.001
Obesity, %	14.7	21.3	26.7	33.8	<0.001	<0.001
Gout, %	1.6	2.5	3.2	7.0	<0.001	<0.001
Cardiac diseases, %	5.0	5.2	5.9	13.6	<0.001	<0.001

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Diuretics, %	9.5	15.6	16.7	29.5	<0.001	<0.001
Allopurinol/cholchicin, %	3.4	3.6	3.8	4.8	0.298	0.740
Lipid-lowering, %	49.2	48.6	44.3	45.1	0.12	0.35
Statins, %	35.4	39.6	36.4	37.6	0.68	0.71
Fibrate, %	14.7	10.0	7.9	5.7	<0.001	<0.001
Anti-platelet, %	17.2	19.7	19.5	19.3	0.483	0.771
Ace-inhibitors, %	19.5	20.6	22.2	24.0	0.084	0.39
Angiotensin receptor blockers, %	11.1	15.0	14.3	19.3	0.002	0.008
Beta-blockers, %	16.1	18.8	21.5	27.4	<0.001	<0.001
Calcium-antagonists, %	16.6	15.4	18.3	19.7	0.13	0.35
Anti-inflammatory, %	18.4	21.1	20.4	22.2	0.21	0.55
Meat consumption, portions/week	4 (3, 5)	4 (2, 5)	4 (3, 6)	4 (3, 5)	0.099	0.14

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Alcohol consumption, g/day	10 (0, 38)	15 (0, 30)	15 (0, 40)	20 (0, 40)	<0.001	0.001
Systolic Blood Pressure, mmHg	140 (129, 153)	143 (130, 154)	140 (130, 152)	142 (130, 155)	0.31	0.10
Diastolic Blood Pressure, mmHg	81 (77, 88)	84 (78, 90)	83 (77, 90)	83 (77, 90)	0.17	0.15
Body Mass Index, kg/m^2	26.1 (24.7, 27.9)	26.8 (24.7, 28.9)	27.7 (25.4, 30.0)	28.0 (26.1-30.3)	<0.001	<0.001
Waist/Hip ratio	0.94 (0.91, 0.98)	0.96 (0.92, 1.00)	0.97 (0.93, 1.02)	0.99 (0.94, 1.03)	<0.001	<0.001
Blood glucose, mmol/L	5.7 (5.1, 6.5)	5.8 (5.2, 6.7)	5.7 (5.2-6.4)	5.8 (5.3, 6.9)	0.16	0.111
Total Cholesterol, mg/dl	196 (171, 222)	203 (176, 232)	199 (176, 228)	205 (174, 237)	0.005	0.009
Triglyceride, mg/dl	106 (76, 156)	113 (84, 172)	125 (85, 181)	138 (99, 201)	<0.001	<0.001
HDL-Cholesterol, mg/dl	44 (36, 51)	44 (37, 53)	42 (35, 49)	42 (36, 49)	0.014	0.005
LDL-Cholesterol, mg/dl	127 (104, 151)	131 (107, 155)	130 (107, 154)	131 (104, 151)	0.18	0.39
GFR, ml/min	88 (74, 101)	89 (74, 104)	88 (75-101)	84 (71, 97)	0.014	0.004

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IMT_{mean}, mm	0.908 (0.791, 1.067)	0.904 (0.774, 1.043)	0.885 (0.793, 1.055)	0.908 (0.777, 1.084)	0.85	0.71
IMT_{max}, mm	2.03 (1.55, 2.68)	2.12 (1.54, 2.78)	2.03 (1.57, 2.61)	2.04 (1.55, 2.78)	0.48	0.76
$IMT_{mean-max}$, mm	1.43 (1.20, 1.74)	1.47 (1.18, 1.77)	1.45 (1.23-1.70)	1.46 (1.20, 1.81)	0.36	0.75
PF CC-IMT_{mean}, mm	0.720 (0.660, 0.783)	0.719 (0.654, 0.779)	0.714 (0.657, 0.774)	0.719 (0.653, 0.779)	0.41	0.83
Fastest-c$IMT_{max-progr}$, mm/year	0.214 (0.109, 0.327)	0.208 (0.103-0.379)	0.222 (0.127, 0.395)	0.235 (0.134, 0.380)	0.004	0.03

Values are median (25^{th}, 75^{th} percentile) or percentage. P Values were calculated by Kruskal Wallis and Jonckheere-Terpstra tests. CC, common carotid; GFR, glomerular filtration rate; HDL, high density lipoproteins; IMT, intima media thickness; LDL, low density lipoprotein; N.A., not applicable, PF, plaque-free; SUA, serum uric acid.

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