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Serum uric acid is an independent predictor for all major forms of cardiovascular death in 28,613 elderly women: A prospective 21-year follow-up study

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Abstract

Background: The role of serum uric acid (SUA) as a risk factor for cardiovascular disease (CVD) remains controversial. Little is known about its predictive value for mortality from congestive heart failure (CHF) and stroke, particularly in elderly, post-menopausal women.
Methods: The relation of SUA to risk of death from total CVD, CHF, stroke and coronary heart disease (CHD) was examined prospectively in a large cohort of 28613 elderly Austrian women (mean age 62.3 years), followed-up for a median of 15.2 years. Adjusted Cox proportional hazards models were calculated to evaluate SUA as an independent predictor for fatal CVD events.
Results: SUA in the highest quartile (≥5.41 mg/dL) was significantly associated with mortality from total CVD ($p<0.0001$), showing a clear dose–response relationship; the adjusted hazard ratio (95%CI) in comparison to the lowest SUA quartile was 1.35 (1.20–1.52). In subgroup analyses SUA was independently predictive for deaths from acute and subacute ($p<0.0001$) and chronic forms ($p=0.035$) of CHD, yielding adjusted hazard ratios for the highest versus lowest SUA quartile of 1.58 (1.19–2.10) and 1.25 (1.01–1.56), respectively. SUA was further significantly related to fatal CHF ($p<0.0001$) and stroke ($p=0.018$); the adjusted hazard ratios for the highest versus lowest SUA quartile were 1.50 (1.04–2.17) and 1.37 (1.09–1.74), respectively.
Conclusions: These findings, for the first time, demonstrate that SUA is an independent predictor for all major forms of death from CVD including acute, subacute and chronic forms of CHD, CHF and stroke in elderly, post-menopausal women.

Keywords: Cardiovascular mortality; Serum uric acid; Risk factors; Elderly women; Epidemiology

1. Introduction

Cardiovascular disease (CVD) is currently the major cause of mortality in women worldwide, coronary heart disease (CHD) and stroke being the most frequent causes of death in post-menopausal women in industrialised countries [1,2]. Serum uric acid (SUA) has consistently been described as a correlate for the development and progression of CVD and modestly higher SUA concentrations have been reported in patients with CHD than in healthy controls, over the past five decades [3–5]. However, despite effective means of safely lowering SUA [6], there is still no well-established patho-

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physiological link between hyperuricemia and subsequent cardiovascular complications [7]. Moreover, due to a lack of consistent epidemiologic evidence, the predictive value of SUA for cardiovascular events remains highly controversial [6,8].

On the one hand, several studies [9–17] have demonstrated an independent association between hyperuricemia and cardiovascular risk in general populations. Single studies have shown a stronger association in females than in males [13], while others found a gender specific relationship, only in women. In line with this, sex-specific differences in trends of CVD have previously been well-established, although the precise underlying mechanisms remain unclear [18,19]. On the other hand, results from different epidemiologic investigations [20–26] indicate that SUA does not have a predictive role in the development of CHD, death from CVD, or death from all causes in men and/or women, after adjustment for established risk factors. Differences in the composition of the populations studied, length of follow-up, study end points and statistical adjustment for confounding may all have contributed to the conflicting conclusions drawn from earlier studies. Consistent evidence may also be lacking to due insufficient sample sizes and infrequent events in several previous investigations. Additionally, many earlier studies exclusively focused on males or failed to conduct sex-specific analyses in women, although mortality rates from heart disease differ across the life course of men and women, both in timing of incidence and in clinical presentation [27].

In the present 21-year follow-up study we aimed to prospectively investigate the predictive power of SUA for cardiovascular death in a large cohort of 28,613 elderly Austrian women, using health examination data from the Vorarlberg Health Monitoring and Promotion Program (VHM&PP), one of the world's largest ongoing population-based risk factor surveillance programs. Although previous studies have investigated the relationship between SUA and death from specific subforms of CVD or CVD mortality in total, to the best of our knowledge, this study comprises the first epidemiologic investigation, to explore the predictive significance of SUA for all major subforms of fatal CVD, including death from acute, subacute and chronic forms of CHD, CHF and stroke in a general population of apparently healthy, postmenopausal women. Regarding CHF, no previous study has investigated this association so far.

2. Materials and methods

2.1. Study population

The VHM&PP [28–30] is a prospective, multicentre, population-based risk factor surveillance program, located in Vorarlberg, the westernmost province of Austria. It is routinely performed by the Agency for Social- and Preventive Medicine and basically addresses all adults of the entire province. Participation in the health examination is voluntary and conducted in a standardized manner by trained local physicians and internists only. The program routinely includes the recording of socio-demographic data, a physical examination with a fasting blood sample, and consultation with a physician. Costs are covered by the participant's (compulsory) health insurance. All adults of the regions were invited to participate by a combination of different measures such as written invitations, television, radio and newspaper reports. A more detailed description of the program methodology has been reported elsewhere [28–30]. All participants signed informed consents to have personal data stored and processed. For this study, institutional review board approval was obtained by the Ethics Committee of the province of Vorarlberg. Between 1985 and 2005, 99739 female adult Vorarlberg residents (age >18 years) were enrolled in the VHM&PP cohort. However, as SUA routinely was determined only in all women aged ≥50 years at screening, but not measured in women at younger ages, the current investigation was restricted to all 28,613 elderly female participants (age >50 years) with complete and valid data on SUA at enrolment.

2.2. Measurements and definitions

Measurements of height, weight, blood pressure, total cholesterol, triglycerides, blood glucose, gamma–glutamyltransferase (GGT), SUA and smoking status (current, former, never) routinely were obtained for each participant. Individuals who reported smoking of at least one cigarette per day during the year before examination were classified as current smokers. Occupational status (blue collar, white collar or self-employed) was determined by the insurance number of participants and was included in the models as a surrogate measure of socioeconomic status. Participants who were retired at baseline were classified according to their former occupation and housewife's according to their husband's occupation. Two central laboratories undergoing regular internal and external quality procedures enzymatically determined total cholesterol, triglycerides, GGT and blood glucose and performed SUA measurements on fasting blood samples. Within 60 to 240 min, the blood was centrifuged for 15 min at 4000 rotations per minute. Subsequently, uric acid concentration of all samples was determined immediately on a RXL (DADE). In order to check calibration, 3 daily control samples were included. If average values of the control samples of each run were not within 3% of the true value, the run was repeated. Day-by-day variation had to be within 5%. Consequently, all subjects were stratified according to quartiles of SUA distribution with cut-off values ranging from 3.70 (lowest quartile), 4.50, 5.40 to >5.40 mg/dL (highest quartile). Systolic and diastolic blood pressures were measured twice in sitting position on the right arm with a mercury sphygmomanometer. The average of these two measurements was used for each blood pressure variable. Hypertension was defined as a diastolic blood pressure of ≥95 mmHg or a systolic blood pressure of ≥160 mmHg.

Table 1
Characteristics of study population, VHM&PP 1985–2005

Characteristic	(n=28,613)
Age, mean±SD (range), years	62.3±8.8 (50.0–95.3)
Age >75 years—no.(%)	3073 (10.7)
Cigarette smoking—no.(%)	2536 (8.9)
Weight, mean±SD (median), kg	67.9±12.4 (66.0)
BMI, mean±SD (median), kg/m^2	26.5±4.6 (25.9)
Glucose, mean±SD (median), mg/dL	96.1±30.1 (90.0)
Serum uric acid, mean±SD (median), mg/dL	4.6±1.3 (4.5)
Triglycerides, mean±SD (median), mg/dL	138.6±81.5 (118.0)
Total cholesterol, mean±SD (median), mg/dL	246.1±46.6 (243.0)
GGT, mean±SD (median), U/L	32.2±41.9 (21.5)
Systolic blood pressure, mean±SD (median), mm Hg	145.2±22.5 (140.0)
Diastolic blood pressure, mean±SD (median), mm Hg	85.1±11.1 (84.0)
Hypertension—no.(%)	7072 (24.7)
Total mortality—no (%)	5702 (19.9)
Cardiovascular/cerebrovascular deaths—no. (%)	2874 (10.0)
Other death cause—no. (%)	2828 (9.9)
Follow-up, mean±SD (median), years	13.6±6.0 (15.2)
Person years at risk	387,731

BMI indicates body mass index, GGT gamma-glutamyltransferase.

2.3. End points

By the end of 2005, 5702 deaths were recorded in our database of which 2874 (50.4%) were cardiovascular or cerebrovascular related deaths. Date and cause of death information was provided by the local health authority and was linked in the database with the use of a validated procedure. All deaths were identified from death certificates that were confirmed by authorized physicians only. In case of unclear causes of death, autopsies were performed. For analyses, deaths from CVD were classified into the following subgroups according to the International Classification of Diseases, 9th & 10th Revision (ICD-9, ICD-10): acute and subacute forms of CHD (ICD-9 410, 411; ICD-10 I21–I24), chronic forms of CHD including occlusive CHD and its complications (ICD-9 412–414; ICD-10 I20, I25 [except I25.5]), CHF (ICD-9 425, 428, 429.0, 429.1, 429.3; ICD-10 I25.5, I42, I43, I50, I51.5, I51.7), hemorrhagic stroke (ICD-9 430–432; ICD-10 I60–I62), ischemic stroke (ICD-9 433–435, 437, 438; ICD-10 I63, I65–I69), undefined stroke (ICD-9 436; ICD–10 I64) and other CVD (ICD-9 390–399, 401–405, 420–424, 426, 427, 429.9, 440–447; ICD-10 I0–I15, I30–I41, I44–I49, I51.0, I51.4, I51.8, I51.9, I70–I74).

2.4. Statistical analysis

To determine associations of SUA with established cardiovascular risk factors, partial correlation coefficients, adjusted for age, and multiple regression models were calculated. In order to utilize parametric analytic techniques GGT and triglycerides were logarithmically transformed. Cox proportional hazards models, adjusted for age, body mass index, systolic and diastolic blood pressure, total cholesterol, triglycerides, GGT, blood glucose, smoking status, occupational status and year of examination were used to compute hazard ratios with 95% confidence intervals for SUA quartiles. In addition, hazard ratios were estimated for unit increases of SUA and significance testing was performed with a Wald χ^2 test on SUA unit changes as well. Subgroup analyses for subforms of CVD mortality, specific age groups and in hypertensive study participants were performed with the same Cox models. The proportional hazards assumption was checked and found to be fulfilled for all models. Significance testing of age as an effect modifier of the relation between SUA and CVD mortality was done through the assessment of interaction terms in the models. Probability values <0.05 were considered to indicate statistical significance. All statistical analyses were performed using SPSS 14.0 (Chicago, Illinois).

3. Results

3.1. Characteristics of study population

Demographic and clinical characteristics of the study population are shown in Table 1. The cohort consisted of 28613 elderly female participants with complete data on SUA, prospectively followed-up for a median of 15.2 years, with a total time at risk of 387,731 person–years. The vast majority of participants (95.9%) were followed-up for at least two years after baseline SUA measurement and 70.6% had follow-up times of 10 or even more years. Mean age at study entry was 62.3 years. Total mortality was 19.9%, and mortality from CVD corresponded to 10.0%. Baseline SUA concentrations were approximately normally distributed, ranging from 1.1 to 14.0 mg/dL with a mean±SD of 4.6±1.3 mg/dL.

Table 2
Clinical correlates of serum uric acid, VHM&PP 1985–2005

	Correlation coefficient*	p-value	Standardized regression coefficient†	p-value
Body–mass index (kg/m^2)	0.30	<0.0001	0.22	<0.0001
Triglycerides (mg/dl)	0.30	<0.0001	0.22	<0.0001
Gamma–glutamyltransferase (U/L)	0.21	<0.0001	0.13	<0.0001
Systolic blood pressure (mmHg)	0.14	<0.0001	0.04	<0.0001
Diastolic blood pressure (mmHg)	0.13	<0.0001	0.001	0.91
Total cholesterol (mg/dl)	0.09	<0.0001	−0.002	0.79
Glucose (mg/dl)	0.06	<0.0001	−0.06	<0.0001
Cigarette smoking	0.04	<0.0001	0.03	0.001

*Age-adjusted partial correlation coefficients. Gamma–glutamyl transferase (GGT) and triglycerides were log-transformed.
†Multiple regression analysis including age, GGT, triglycerides, BMI, total cholesterol, systolic blood pressure, diastolic blood pressure, cigarette smoking and glucose. GGT and triglycerides were log-transformed. R^2=0.20.

3.2. Association of SUA with established cardiovascular risk factors

Table 2 shows that SUA was significantly correlated with established cardiovascular risk factors and components of the metabolic syndrome. The strongest age-adjusted correlation was observed between SUA and body–mass index ($r=0.30$, $p<0.0001$). SUA was further positively correlated with triglycerides ($r=0.30$), GGT ($r=0.21$), systolic blood pressure ($r=0.14$), diastolic blood pressure ($r=0.13$), total cholesterol ($r=0.09$), blood glucose ($r=0.06$) and smoking ($r=0.04$, all $p<0.0001$). In multiple regression analysis using SUA as dependent variable, body mass index, triglycerides, GGT, systolic blood pressure, blood glucose (all $p<0.0001$) and smoking ($p=0.001$) were independent explanatory variables. However, altogether these factors explained only about 20% in the variation of SUA.

Table 3
Mortality from cardiovascular disease according to serum uric acid, VHM&PP 1985—2005

	Serum uric acid (SUA)					
	≤3.70 mg/dL ($n=7404$)	3.71—4.50 mg/dL ($n=7611$)	4.51—5.40 mg/dL ($n=6976$)	≥5.41 mg/dL ($n=6622$)	Total per unit increase ($n=28,613$)	p for unit increase
All cardiovascular/cerebrovascular events						
Fatal events—no.(%)	515 (7.0)	636 (8.4)	725 (10.4)	998 (15.1)	2874 (10.0)	
HR 1 (95% CI)*	1.00 (Ref)	1.14 (1.02–1.29)	1.32 (1.18–1.48)	1.52 (1.37–1.70)	1.13 (1.10–1.16)	<0.0001
HR 2 (95% CI)†	1.00 (Ref)	1.08 (0.96–1.22)	1.22 (1.08–1.37)	1.35 (1.20–1.52)	1.10 (1.06–1.13)	<0.0001
Coronary heart disease						
Fatal events—no.(%)	235 (3.2)	273 (3.6)	324 (4.6)	497 (7.5)	1329 (4.6)	
HR 1 (95% CI)*	1.00 (Ref)	1.08 (0.91–1.29)	1.29 (1.09–1.53)	1.68 (1.43–1.96)	1.17 (1.13–1.21)	<0.0001
HR 2 (95% CI)†	1.00 (Ref)	1.02 (0.85–1.23)	1.17 (0.98–1.39)	1.37 (1.15–1.63)	1.11 (1.06–1.16)	<0.0001
Acute and subacute forms of coronary heart disease						
Fatal events—no.(%)	83 (1.1)	100 (1.3)	131 (1.9)	204 (3.1)	518 (1.8)	
HR 1 (95% CI)*	1.00 (Ref)	1.14 (0.85–1.52)	1.51 (1.15–2.00)	2.08 (1.60–2.69)	1.27 (1.19–1.34)	<0.0001
HR 2 (95% CI)†	1.00 (Ref)	1.02 (0.75–1.38)	1.27 (0.95–1.70)	1.58 (1.19–2.10)	1.19 (1.11–1.27)	<0.0001
Chronic forms of coronary heart disease						
Fatal events—no.(%)	152 (2.1)	173 (2.3)	193 (2.8)	293 (4.4)	811 (2.8)	
HR 1 (95% CI)*	1.00 (Ref)	1.05 (0.84–1.30)	1.18 (0.95–1.45)	1.47 (1.20–1.79)	1.11 (1.06–1.16)	<0.0001
HR 2 (95% CI)†	1.00 (Ref)	1.02 (0.81–1.28)	1.11 (0.89–1.39)	1.25 (1.01–1.56)	1.06 (1.00–1.12)	0.035
Congestive heart failure						
Fatal events—no.(%)	50 (0.7)	79 (1.0)	63 (0.9)	103 (1.6)	295 (1.0)	
HR 1 (95% CI)*	1.00 (Ref)	1.44 (1.01–2.06)	1.16 (0.80–1.69)	1.55 (1.10–2.18)	1.10 (1.01–1.19)	0.023
HR 2 (95% CI)†	1.00 (Ref)	1.34 (0.93–1.93)	1.09 (0.74–1.60)	1.50 (1.04–2.17)	1.10 (1.00–1.20)	0.04
Stroke						
Fatal events—no.(%)	134 (1.8)	183 (2.4)	218 (3.1)	241 (3.6)	776 (2.7)	
HR 1 (95% CI)*	1.00 (Ref)	1.26 (1.01–1.58)	1.51 (1.22–1.88)	1.40 (1.13–1.74)	1.08 (1.03–1.14)	0.003
HR 2 (95% CI)†	1.00 (Ref)	1.25 (0.99–1.57)	1.48 (1.18–1.86)	1.37 (1.09–1.74)	1.07 (1.01–1.13)	0.018
Hemorrhagic stroke						
Fatal events—no.(%)	25 (0.3)	28 (0.4)	32 (0.5)	29 (0.4)	114 (0.4)	
HR 1 (95% CI)*	1.00 (Ref)	1.10 (0.64–1.89)	1.32 (0.78–2.23)	1.14 (0.66–1.97)	1.04 (0.91–1.20)	0.56
HR 2 (95% CI)†	1.00 (Ref)	1.14 (0.65–2.01)	1.47 (0.83–2.52)	1.29 (0.71–2.40)	1.06 (0.91–1.23)	0.46
Ischemic stroke						
Fatal events—no.(%)	42 (0.6)	53 (0.7)	54 (0.8)	62 (0.9)	211 (0.7)	
HR 1 (95% CI)*	1.00 (Ref)	1.13 (0.76–1.70)	1.15 (0.77–1.73)	1.06 (0.71–1.58)	1.00 (0.91–1.11)	0.94
HR 2 (95% CI)†	1.00 (Ref)	1.17 (0.76–1.79)	1.19 (0.76–1.84)	1.15 (0.74–1.79)	1.02 (0.91–1.14)	0.74
Undefined stroke						
Fatal events—no.(%)	67 (0.9)	102 (1.3)	132 (1.9)	150 (2.3)	451 (1.6)	
HR 1 (95% CI)*	1.00 (Ref)	1.40 (1.03–1.90)	1.82 (1.35–2.44)	1.71 (1.28–2.29)	1.13 (1.06–1.20)	<0.0001
HR 2 (95% CI)†	1.00 (Ref)	1.33 (0.97–1.83)	1.66 (1.22–2.26)	1.53 (1.11–2.09)	1.10 (1.02–1.18)	0.014
Other cardiovascular events						
Fatal events—no.(%)	96 (1.3)	101 (1.3)	120 (1.7)	157 (2.4)	474 (1.7)	
HR 1 (95% CI)*	1.00 (Ref)	0.98 (0.74–1.30)	1.18 (0.90–1.55)	1.30 (1.01–1.69)	1.12 (1.05–1.19)	0.001
HR 2 (95% CI)†	1.00 (Ref)	0.89 (0.67–1.19)	1.06 (0.80–1.41)	1.15 (0.87–1.53)	1.09 (1.02–1.17)	0.017

*Hazard ratios (95% confidence intervals) from Cox proportional hazards models adjusted for age.

†Hazard ratios (95% confidence intervals) from Cox proportional hazards models adjusted for age, body—mass index, systolic and diastolic blood pressure, total cholesterol, triglycerides, gamma-glutamyltransferase (GGT), glucose, smoking status, occupational status and year of examination. Triglycerides and GGT were logarithmically transformed.

3.3. Associations of SUA with CVD mortality

The relationship between baseline SUA concentrations and subsequent cardiovascular death is shown in Table 3 and Fig. 1. In age-adjusted Cox proportional hazards models, SUA levels were independently predictive for mortality from all cardiovascular events ($p<0.0001$), showing a clear dose–response relationship; the hazard ratio (95%CI) for the highest versus lowest SUA quartile was 1.52 (1.37–1.70). In subgroup analyses, SUA was significantly related to mortality from acute and subacute forms of CHD ($p<0.0001$) and chronic forms of CHD ($p<0.0001$), yielding age-adjusted hazard ratios for the highest versus lowest SUA quartile equalling 2.08 (1.60–2.69) and 1.47 (1.20–1.79), respectively. SUA was further independently related to fatal CHF ($p=0.023$), stroke mortality ($p=0.003$) and other fatal cardiovascular events ($p=0.001$); hazard ratios (95%CI) for the highest versus lowest SUA quartile were 1.55 (1.10–2.18), 1.40 (1.13–1.74) and 1.30 (1.01–1.69), respectively.

After additional adjustment for potential confounding, the above reported associations only slightly attenuated, remaining stable in terms of statistical significance (Table 3, Fig. 1). Cox proportional hazards models adjusted for age, body-mass index, systolic and diastolic blood pressure, total cholesterol, triglycerides, GGT, glucose, smoking status, occupational status and year of examination yielded hazard ratios (95%CI) for the highest versus lowest SUA quartile equalling 1.35 (1.20–1.52) for all fatal cardiovascular events ($p<0.0001$), 1.37 (1.15–1.63) for CHD ($p<0.0001$), 1.50 (1.04–2.17) for CHF ($p=0.04$) and 1.37 (1.09–1.74) for all strokes ($p=0.018$). Fig. 2 displays the adjusted cumulative survival from all fatal cardiovascular/cerebrovascular events within the 21-year follow-up period according to quartiles of SUA.

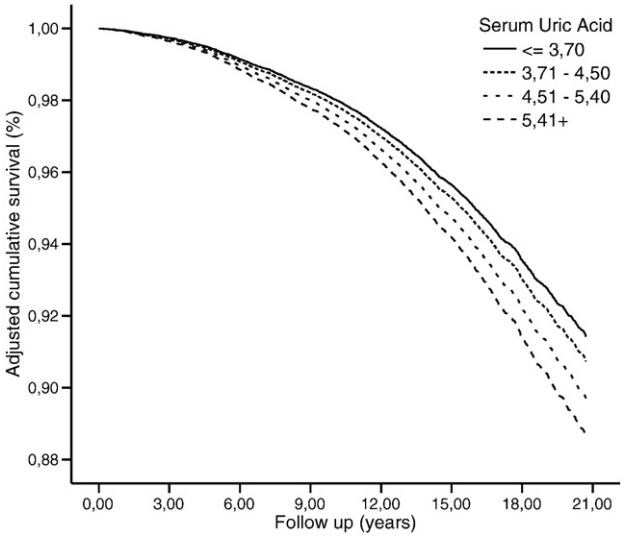

Fig. 2. Adjusted cumulative survival from all cardiovascular/cerebrovascular events according to quartiles of SUA among 28,613 elderly female Austrian adults (mean age 62.3 years) in the VHM&PP estimated at the average values of covariates. Survival curves were calculated with Cox proportional hazards models adjusted for age, body–mass index, systolic and diastolic blood pressure, total cholesterol, triglycerides, gamma glutamyltransferase, glucose, smoking status, occupational status and year of examination.

In order to eliminate possible effects of very old participants, we excluded all individuals aged >75 years for a subgroup analysis. However, all associations that were

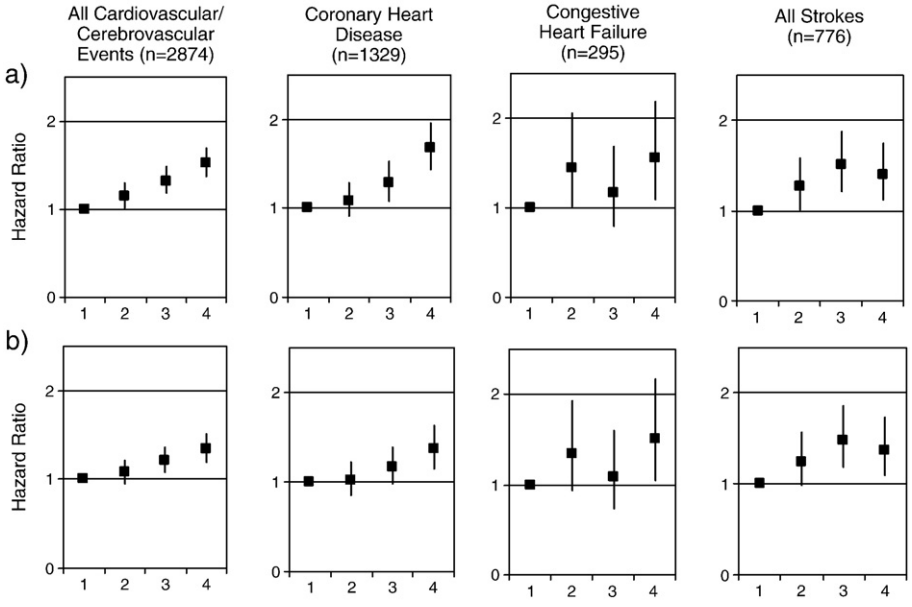

Fig. 1. Hazard ratios with 95%CIs for the association between SUA and CVD mortality from a) Cox proportional hazards models adjusted for age and b) Cox proportional hazards models adjusted for age, body–mass index, systolic and diastolic blood pressure, total cholesterol, triglycerides, gamma-glutamyltransferase, glucose, smoking status, occupational status and year of examination. Boxes present consecutive quartiles of SUA.

statistically significant in the main analysis remained unchanged in terms of statistical significance when reanalyzed. Additionally, adjusted hazard ratios for the highest versus lowest SUA quartile increased to 1.51 (1.31–1.75) for all fatal cardiovascular events, 1.57 (1.27–1.93) for CHD, 1.75 (1.09–2.81) for CHF and 1.57 (1.17–2.10) for all strokes, suggesting a more prominent effect in women 50–75 years of age. Because of the assumed relevance of hypertension in the pathogenesis of uric acid-induced CVD [31,32], in a further subgroup analysis, we investigated all above associations in hypertensive study participants separately. Although this analysis did not reveal substantial changes in terms of statistical significance, we found infirmly increased hazard ratios for the association of SUA and CVD mortality, in respect to the results of the main analysis including all participants (data not shown).

4. Discussion

The present study comprises the first large-scale epidemiologic investigation to evaluate the predictive value of SUA on subsequent total cardiovascular death and all major subforms in elderly, post-menopausal women. As expected, our findings confirm that SUA levels are correlated with most established cardiovascular risk factors and components of the metabolic syndrome. However, after full adjustment for these risk factors in our multivariate models, we still found that older females with baseline SUA concentrations >5.41 mg/dL have a 35% greater risk for mortality from all cardiovascular events, in comparison to women with SUA concentrations ≤3.70 mg/dL. In subgroup analyses, this risk substantially increased to 50% for mortality from CHF and to nearly 60% for mortality from acute and subacute forms of CHD. The latter finding is in strong contrast with the results of our recently published investigation on the relationship of SUA with CVD mortality in a large cohort of more than 83000 men, where no effect of SUA on fatal CHD could be demonstrated after adjustment for major risk factors [33].

Given the epidemiological nature of our observations, the underlying biological mechanisms causing SUA to be independently related to all forms of cardiovascular death in our large cohort of elderly women cannot be certainly answered in the present investigation. However, in respect to the finding of a more prominent role of SUA in women 50–75 years of age, in comparison to its predictive significance in the total cohort, from a statistical point of view, one might argue that with highest age more individuals are at risk for the development of fatal CVD in general, attenuating the excess effect of SUA. Recent in vitro and in vivo findings, concordantly with our results, suggest that SUA may contribute directly to endothelial dysfunction by inducing antiproliferative effects and impairing nitric oxide production [34], thus causing a deterioration in CHF. Until now, however, no epidemiological evidence was available to support the role of SUA as an independent risk factor for CHF in elderly women, and we do not know of other similar published epidemiologic reports with which to compare our results. It has been shown that human atherosclerotic plaque contains a considerable amount of uric acid, and hyperuricemia, via purine metabolism, may promote thrombus formation [35,36]. SUA concentrations were found to be associated with increased production of oxygen free radicals, to promote oxygenation of low-density lipoprotein cholesterol and to facilitate lipid peroxidation [37,38]. Each of these factors is known to play a crucial role in the progression of atherosclerosis. Consistently, Aboa Eboule and colleagues [39] reported a significant relationship between SUA and CHD mortality in 9701 randomly selected Belgians and Puddu and colleagues [40] found SUA to be independently predictive for CHD events in healthy middle-aged Italians. Bos and colleagues [16] recently demonstrated a significant relationship between SUA and incident risk of stroke events in older females from the Netherlands. Alternatively, in the Framingham study [20,22], univariate associations of SUA with CHD in healthy middle-aged females appeared largely to be explained by the relation of SUA with other CHD risk factors, rather suggesting SUA to act as a marker for increased risk of CVD than a causal risk factor.

Our study had several strengths and potential limitations that should be considered. Major strengths are the prospective design, the large sample size, length of follow-up, and the standardized protocol. In addition, examinations were only performed by experienced physicians. Even though information on major risk factors was collected, our study was unable to account for additional factors that further might have residually confounded the relationship between SUA and CVD mortality. Uric acid is the main end product of metabolism of purines, which in turn are derived mostly from diet, and increases especially with higher red meat intake [41,42]. In our cohort, diet was not recorded during baseline screening and thus, could possibly explain differences in SUA levels among the study population. Additionally, alcohol consumption, medication use (e.g. diuretics, statins) and other causes of high SUA, including increased endogenous production of urate, decreased excretion of monosodium urate by the kidneys, or decreasing renal function were not directly adjusted for in our models. However, our cohort consisted of an apparently healthy elderly population, rather than a sick hospital sample and 75% of all VHM&PP study participants were examined before the implementation of statin therapy in Austria in 1995.

In summary, this study aimed to investigate the predictive value of SUA on subsequent cardiovascular death in a large population-based cohort of more than 28,000 elderly women. Our findings, for the first time, demonstrate that SUA is an independent predictor for all major forms of CVD mortality including acute, subacute and chronic forms of CHD, CHF and stroke in post-menopausal women. Given that measurement of SUA is a routine procedure with repeatable results in clinical laboratories and short-term fluctuations in individuals being non-significant and without age-specific or diurnal pattern [43,44], our findings strongly suggest the

clinical importance of monitoring and intervention on the basis of increased SUA.

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References

[1] Lawlor DA, Ebrahim S, Davey Smith G. A life course approach to coronary heart disease and stroke. In: Kuh D, Hardy R, editors. A life course approach to women's health. Oxford: Oxford University Press; 2002. p. 86–119.
[2] Ulmer H, Kelleher C, Fitzsimon N, Diem G, Concin H. Secular trends in cardiovascular risk factors: an age–period-cohort analysis of 698954 health examinations in 181350 Austrian men and women. J Int Med 2007;261:566–76.
[3] Gertler MM, Garn SM, Levine SA. Serum uric acid in relation to age and physique in health and in coronary heart disease. Ann Int Med 1951;34:1421–31.
[4] Kohn PM, Prozan GB. Hyperuricemia — relationship to hypercholesteremia and acute myocardial infarction. JAMA 1959;170:1909–12.
[5] Beard JT. Serum uric acid and coronary heart disease. Am Heart J 1983;106:397–400.
[6] Baker JF, Krishnan E, Chen L, Schumacher HR. Serum uric acid and cardiovascular disease: recent developments, and where do they leave us? Am J Med 2005;118:816–26.
[7] Conen D, Wietlisbach V, Bovet P, et al. Prevalence of hyperuricemia and relation of serum uric acid with cardiovascular risk factors in a developing country. BMC Public Health 2004;4:9.
[8] Vaccarino V, Krumholz HM. Risk factors for cardiovascular disease: one down, many more to evaluate. Ann Intern Med 1999;131:62–3.
[9] Levine W, Dyer AR, Shekelle RB, Schoenberger JA, Stamler J. Serum uric acid and 11.5-year mortality of middle-aged women: findings of the Chicago Heart Association Detection Project in Industry. J Clin Epidemiol 1989;42:257–67.
[10] Freedman DS, Williamson DF, Gunter EW, Beyers T. Relation of serum uric acid to mortality and ischemic heart disease. The NHANES I Epidemiologic follow-up study. Am J Epidemiol 1995; 141:637–44.
[11] Liese AD, Hense HW, Lowel H, Doring A, Tietze M, Keil U. Association of serum uric acid with all-cause and cardiovascular disease mortality and incident myocardial infarction in the MONICA Augsburg cohort. Epidemiology 1999;10:391–7.
[12] Longo–Mbenza B, Luila EL, Mbete P, Vita EK. Is hyperuricemia a risk factor of stroke and coronary heart disease among Africans? Int J Cardiol 1999;71:17–22.
[13] Fang J, Alderman MH. Serum uric acid and cardiovascular mortality: the NHANES I epidemiologic follow up study. JAMA 2000;283:2404–10.
[14] Mazza A, Pessina AC, Pavei A, Scarpa R, Tikhonoff V, Casiglia E. Predictors of stroke mortality in elderly people from the general population. The cardiovascular study in elderly. Eur J Epidemiol 2001;17:1097–104.
[15] Niskanen LK, Laaksonen DE, Nyyssonen K, et al. Uric acid level as a risk factor for cardiovascular and all-cause mortality in middle-aged men: a prospective cohort study. Arch Intern Med 2004;164:1546–51.
[16] Bos MJ, Koudstall PJ, Hofman A, Witteman JCM, Breteler MMB. Uric acid is a risk factor for myocardial infarction and stroke. The Rotterdam study. Stroke 2006;37:1503–7.
[17] Hozawa A, Folsom AR, Ibrahim H, Nieto FJ, Rosamond WD, Shahar E. Serum uric acid and risk of ischemic stroke: the ARIC study. Atherosclerosis 2006;187:401–7.
[18] Wingard DL, Suarez L, Barrett–Connor E. The sex differential in mortality from all causes and ischemic heart disease. Am J Epidemiol 1983;117:165–72.
[19] Barrett–Connor E. Sex differences in coronary heart disease. Why are women so superior? The 1995 Ancel Keys Lecture. Circulation 1997;95:252–64.
[20] Brand FN, McGee DL, Kannel WB, Stokes III J, Castelli WB. Hyperuricemia as a risk factor of coronary heart disease: The Framingham Study. Am J Epidemiol 1985;121:11–8.
[21] Wannamethee SG, Shaper AG, Whincup PH. Serum urate and the risk of major coronary heart disease events. Heart 1997;78:147–53.
[22] Culleton BF, Larson MG, Kannel WB, Levy D. Serum uric acid and risk of cardiovascular disease and mortality: the Framingham Heart study. Ann Int Med 1999;31:7–13.
[23] Moriarity JT, Folsom AR, Iribarren C, Nieto FJ, Rosamond WE. Serum uric acid and risk of coronary heart disease: atherolsclerosis risk in communities (ARIC) study. Ann Epidemiol 2000;10: 136–43.
[24] Jee SH, Lee SY, Kim MT. Serum uric acid and risk of death from cancer, cardiovascular disease or all causes in men. Eur J Cardiovasc Prev Rehabil 2004;11:185–91.
[25] Sakata K, Hashimoto T, Ueshima H, Okayama A, for the NIPPON DATA 80 Research Group. Absence of an association between serum uric acid and mortality from cardiovascular disease: NIPPON DATA 80, 1980–1994. Eur J Epidemiol 2001;17:461–8.
[26] Wheeler JG, Juzwishin KDM, Eiriksdottir G, Gudnason V, Danesh J. Serum uric acid and coronary heart disease in 9,458 incident cases and 155,084 controls: prospective study and meta-analysis. Plos Medicine 2005;2:236–42.
[27] Meade TW, Dyer S, Howarth DJ, Imeson JD, Stirling Y. Antithrombin-III and procoagulant activity—sex differences and effects of the menopause. Br J Haematol 1990;74:77–81.
[28] Ulmer H, Kelleher C, Diem G, Concin H. Long-term tracking of cardiovascular risk factors among men and women in a large population-based health system: the Vorarlberg Health Monitoring & Promotion Programme. European Heart Journal 2003;24:1004–13.
[29] Ulmer H, Kelleher C, Diem G, Concin H. Why Eve is not Adam: prospective follow-up in 149650 women and men of cholesterol and other risk factors related to cardiovascular and all-cause mortality. Journal of Women's Health 2004;13:41–53.
[30] Ruttmann E, Brant LJ, Concin H, Diem G, Rapp K, Ulmer H, and the Vorarlberg Health Monitoring and Promotion Program Study Group. γ–Glutamyltransferase as an risk factor for cardiovascular disease mortality. An epidemiological investigation in a cohort of 163 944 Austrian adults. Circulation 2005;112:2130–7.
[31] Sundstrom J, Sullivan L, D'Agostino RB, Levy D, Kannel WB, Vasan RS. Relations of serum uric acid to longitudinal blood pressure tracking and hypertension incidence. Hypertension 2005;45:28–33.
[32] Alper Jr AB, Chen W, Yau L, Srinivasan SR, Berenson GS, Hamm LL. Childhood uric acid predicts adult blood pressure. The Bogalusa Heart Study. Hypertension 2005;45:34–8.
[33] Strasak A, Ruttmann E, Brant L, Kelleher C, Klenk J, Concin H, Diem G, Pfeiffer KP, Ulmer H and the VHM&PP Study Group. Serum uric acid and risk of cardiovascular mortality: A prospective long-term study in 83683 Austrian men. Clin Chem in press [2007 Nov 26, Electronic publication ahead of print].

[34] Kanellis J, Kang DH. Uric acid as a mediator of endothelial dysfunction, inflammation, and vascular disease. Semin Nephrol 2005;25:39–42.
[35] Suarna C, Dean RT, May J, Stocker R. Human atherosclerotic plaque contains both oxidized lipids and relatively large amounts of alpha–tocopherol and ascorbate. Arterioscler Thromb Vasc Biol 1995;15:1616–24.
[36] Visy J, LeCoz P, Chadefaux B, et al. Homocystinuria due to 5,10–methylenetetrahydrofolate reductase deficiency revealed by stroke in adult siblings. Neurology 1991;41:1313–5.
[37] Weir CJ, Muir SW, Walters MR, Lees KR. Serum urate as an independent predictor of poor outcome and future vascular events after acute stroke. Stroke 2003;34:1951–7.
[38] De Scheeder IK, van de Kraay AM, Lamers JM, Koster JF, deJong JW, Serruys PW. Myocardial malondialdehyde and uric acid release after short-lasting coronary occlusions during angioplasty: potential mechanisms for free radical generation. Am J Cardiol 1991;68:392–5.
[39] Aboa Eboule AC, De Smet P, Dramaix M, De Backer G, Kornitzer M. Relation between uricemia and all-causes cardiovascular and coronary mortality in both genders of non-selected sample of the Belgium population. Rev Epidemiol Sante Publique 2001;49:531–9.
[40] Puddu PE, Lanti M, Menotti A, et al. Serum uric acid for short-term prediction of cardiovascular disease incidence in the Gubbio population study. Acta Cardiol 2001;56:243–51.
[41] Choi HK, Liu S, Curhan G. Intake of purine-rich foods, protein, and dairy products and relationship to serum levels of uric acid: the Third National Health and Nutrition Examination Survey. Arthritis Rheum 2005;52:283–9.
[42] Schlesinger N. Dietary factors and hyperuricaemia. Curr Pharm Des 2005;11:4133–8.
[43] Kolonel LN, Yoshizawa C, Nomura AMY, et al. Relationship of serum uric acid to cancer occurrence in a prospective male cohort. Cancer Epidemiol Biomark Prev 1994;3:225–8.
[44] Searcy RL. Diagnostic biochemistry. New York: McGraw–Hill; 1969.