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Serum Uric Acid and Risk of Cardiovascular Mortality: A Prospective Long-Term Study of 83 683 Austrian Men

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BACKGROUND: The role of serum uric acid (SUA) as an independent risk factor for cardiovascular disease (CVD) remains controversial, and little is known about its prognostic importance for mortality from congestive heart failure (CHF) and stroke. Few large-scale epidemiologic studies with sufficient follow-up have addressed the association of SUA and CVD mortality in apparently healthy men across a wide age range.

METHODS: A cohort of 83 683 Austrian men (mean age, 41.6 years) was prospectively followed for a median of 13.6 years. We used Cox proportional hazards models adjusted for established risk factors to evaluate SUA as an independent predictor for CVD mortality.

RESULTS: The highest quintile of SUA concentration (>398.81 μmol/L) was significantly related to mortality from CHF ($P = 0.03$) and stroke ($P < 0.0001$); adjusted hazard ratios (95% confidence interval) for the highest vs lowest quintiles of SUA were 1.51 (1.03–2.22) and 1.59 (1.23–2.04), respectively. SUA was not associated, however, with mortality from acute, subacute, or chronic forms of coronary heart disease (CHD) after adjustment for potential confounding factors ($P = 0.12$). Age was a significant effect modifier for the relation of SUA to fatal CHF ($P = 0.05$), with markedly stronger associations found in younger individuals.

CONCLUSIONS: Our study demonstrates for the first time in a large prospective male cohort that SUA is independently related to mortality from CHF and stroke. Although increased SUA is not necessarily a causal risk factor, our results suggest the clinical importance of monitoring and intervention based on the presence of an increased SUA concentration, especially because SUA is routinely measured.

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Despite recent substantial decreases in age-standardized mortality in Western countries, cardiovascular disease (CVD)[7] remains the leading cause of mortality worldwide, and cardiac failure is increasingly prevalent, particularly among older people *(1, 2)*. Increased serum uric acid (SUA) concentrations have consistently been reported to be associated with the progression of CVD, and SUA concentrations have been documented over the past 5 decades to be modestly higher in patients with coronary heart disease (CHD) than in healthy control individuals *(3–5)*. Much controversy exists, however, as to whether SUA is an independent risk factor, because a pathophysiological link between hyperuricemia and subsequent cardiovascular complications has yet to be confirmed and because SUA is related to many of the established risk factors, including hypertension, dyslipidemia, obesity, and excessive alcohol consumption *(6)*. Because of very controversial epidemiologic findings and a lack of consistent evidence, the role of SUA as an independent and causal risk factor for cardiovascular events remains unclear *(7, 8)*.

On the one hand, several studies *(9–18)* have demonstrated an independent association between SUA and cardiovascular risk in general populations, suggesting that SUA may be an important causal agent for adverse cardiovascular outcomes. Conversely, different epidemiologic investigations *(19–24)*, including the Framingham Heart Study *(20)*, have indicated that

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[7] Nonstandard abbreviations: CVD, cardiovascular disease; SUA, serum uric acid; CHF, congestive heart failure; CHD, coronary heart disease; VHM&PP, Vorarlberg Health Monitoring & Promotion Program; GGT, γ-glutamyltransferase; ICD-9, ICD10, International Classification of Diseases, 9th and 10th Revisions; CAD, coronary artery disease.

uric acid per se does not play a causal role in the development of CHD, death from CVD, or death from all causes, after adjustment for well-established cardiovascular risk factors. Instead, these studies suggested that apparent associations are likely attributable to a correlation of SUA with other confounding risk factors for CVD *(25, 26)*. Differences in the compositions of the populations studied, length of follow-up, study endpoints, and statistical adjustment for confounding variables may all have contributed to the conflicting conclusions that have been drawn from earlier studies; the lack of consistent evidence in several previous investigations may also have been due to insufficient sample sizes and infrequent events.

In the present long-term study, we prospectively investigated the relationship of SUA concentration with mortality from CHF, CHD, and stroke in a large cohort of Austrian men by analyzing 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 CHD, stroke, and CVD in total, this study is the first large-scale investigation to explore the association of SUA with CHF mortality in a general population of apparently healthy men across a wide age range.

Materials and Methods

STUDY POPULATION

The VHM&PP *(27–29)* is a prospective, multicenter, population-based risk-factor surveillance program located in Vorarlberg, the westernmost province of Austria. The VHM&PP is routinely performed by the Agency for Social and Preventive Medicine and essentially addresses all adults in the entire province. Participation in the health examination is voluntary and conducted in a standardized manner only by trained local physicians and internists. The program routinely includes the recording of sociodemographic data, a physical examination with a fasting blood sample, and consultation with a physician. Costs are covered by the participant's health insurance (compulsory). All adults of the region were invited to participate via a combination of different measures, such as written invitations and television, radio, and newspaper reports. A more detailed description of the program methods has been reported elsewhere *(27–29)*. For this study, institutional review board approval was obtained by the Ethics Committee of the province of Vorarlberg.

Between 1985 and 2005, 85 035 male adult Vorarlberg residents (age >18 years; mean, 41.6 years) were enrolled in the VHM&PP cohort. Relative to the population numbers measured at the national census in 1991 (Statistik Austria), nearly 74% of all resident men in the province underwent at least 1 examination during the study period. The vast majority of study participants were of Austrian origin. Although migrant workers were also included, the proportion of participants of non-Austrian origin is <10%. All participants gave signed informed consent to have personal data stored and processed. The current analyses were restricted to 83 683 participants with complete and valid SUA data at enrollment. For this reason, 1 352 participants (1.6%) were excluded from the present study.

MEASUREMENTS AND DEFINITIONS

Measurements of height, weight, blood pressure, total cholesterol, triglycerides, blood glucose, γ-glutamyltransferase (GGT), SUA, and smoking status were routinely obtained for each participant. Individuals who reported smoking at least 1 cigarette per day during the year before examination were classified as current smokers. Two central laboratories that underwent regular internal and external quality-control procedures carried out enzymatic measurements of total cholesterol, triglycerides, GGT, and blood glucose and performed SUA measurements on fasting blood samples. Blood samples were centrifuged for 15 min at 3309*g* within 60–240 minutes of venipuncture. Subsequently, we enzymatically measured uric acid concentrations of all samples on an RXL Chemistry Analyzer (Dade) by monitoring the loss of absorbance at 293 nm following uricase treatment *(30)*. To check calibration, we included 3 control samples daily. If the mean values for the control samples of each run were not within 3% of the expected value, the run was repeated. Day-to-day variation (CV) was <5%. Study participants were classified according to the quintiles of the SUA concentration distribution with the following cutoff values: 273.81 μmol/L (lowest quintile), 315.48 μmol/L, 351.19 μmol/L, 398.81 μmol/L, and >398.81 μmol/L (highest quintile).

Systolic and diastolic blood pressures were measured twice with a mercury sphygmomanometer on the right arm of study participants after they had assumed a sitting position. The mean of the 2 measurements was used for each blood pressure variable. Hypertension was defined as a diastolic blood pressure ≥95 mmHg or a systolic blood pressure ≥160 mmHg.

ENDPOINTS

By the end of 2005, our database had recorded 7 243 deaths, of which 3 007 (41.5%) were related to cardiovascular or cerebrovascular events. The date and cause of death were provided by the local health authority and were linked in the database with the use of a validated procedure. All deaths were identified from death certificates that were confirmed by authorized physi-

cians only. Autopsies were performed in cases of an unclear cause of death. For analyses, we grouped deaths from CVD into the following subgroups according to the International Classification of Diseases, 9th and 10th Revisions (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 related to coronary artery disease (CAD) (ICD-9 428; ICD-10 I25.5, I50); CHF unrelated to CAD (ICD-9 425, 429.0, 429.1, 429.3; ICD-10 I42, I43, 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).

STATISTICAL ANALYSIS

To evaluate associations of SUA concentration with established cardiovascular risk factors, we calculated age-adjusted partial correlation coefficients and used stepwise multiple regression models. GGT and triglyceride data were logarithmically transformed so that parametric analytical techniques could be used. We used Cox proportional hazards models adjusted for age, body mass index, systolic and diastolic blood pressure, total cholesterol, triglycerides, GGT, blood glucose, smoking status, and year of examination to compute hazard ratios with 95% confidence intervals for SUA quintiles. In addition, we estimated hazard ratios for unit increases in SUA concentration and carried out significance testing with a Wald χ^2 test on SUA unit changes. We used the same Cox models in subgroup analyses for different categories of fatal CVD events in hypertensive study participants and according to age groups. The proportional hazards assumption was fulfilled for all models. The significance testing of age as an effect modifier of the relationship between SUA and CVD mortality was done through the assessment of multiplicative interaction terms in the models. Probability values ≤ 0.05 were considered to indicate statistical significance. All statistical analyses were performed with SPSS software, version 14.0.

Results

CHARACTERISTICS OF THE STUDY POPULATION AT BASELINE

The demographic and clinical characteristics of the study population are summarized in Table 1. The study cohort consisted of 83 683 male adult participants with complete and valid SUA data; the participants were prospectively followed up for a median of 13.6 years (total time at risk, 1.04×10^6 person-years). The vast majority of participants (94.1%) were followed up for at least 2 years after baseline SUA measurements, and 64.1% had follow-up times of 10 years or more. The mean age at study entry was 41.6 years. The total mortality was 8.7%, and the mortality from CVD was 3.6%. The distribution of SUA concentrations at baseline is shown in Fig. 1. SUA concentration showed an approximately gaussian distribution (range, 65.5–1 071.4 μmol/L; mean (SD), 338.2 (76.5) μmol/L).

ASSOCIATION OF SUA WITH ESTABLISHED RISK FACTORS

SUA concentration was significantly correlated with most established cardiovascular risk factors (Table 2). The strongest age-adjusted correlation was observed between SUA and GGT ($r = 0.28$; $P < 0.001$). SUA was also positively correlated with triglycerides ($r = 0.27$), body mass index ($r = 0.25$), total cholesterol ($r = 0.18$), systolic and diastolic blood pressure (both $r = 0.15$), and smoking ($r = 0.11$; all P values < 0.001) and negatively correlated with blood glucose ($r = -0.14$; $P = 0.004$). In a stepwise, multiple regression analysis that used SUA concentration as the dependent variable, GGT, triglycerides, body mass index, total cholesterol, systolic and diastolic blood pressure, smoking, and blood glucose were all independent explanatory variables (all P values < 0.0001). Altogether, however, these factors explained only about 15% of the variation in SUA concentration.

ASSOCIATIONS OF SUA WITH CVD MORTALITY

The relationship between baseline SUA concentration and subsequent CVD mortality is shown in Table 3 and Fig. 2. In age-adjusted Cox proportional hazards models, a high SUA concentration was significantly associated with an increased risk of mortality from CHD ($P < 0.0001$): the hazard ratio (95% confidence interval) for the highest SUA quintile vs the lowest quintile was 1.55 (1.27–1.91) for acute and subacute CHD forms and 1.34 (1.10–1.63) for chronic forms of CHD. A high SUA concentration was also associated with an increased risk of mortality from CHF ($P < 0.001$) and stroke ($P < 0.0001$), with age-adjusted hazard ratios for the highest SUA quintile vs the lowest quintile of 1.60 (1.12–2.27) and 1.62 (1.30–2.04), respectively. In subgroup analyses, this hazard ratio increased to 1.78 (1.11–2.84) for fatal ischemic strokes but was attenuated to borderline significance for hemorrhagic strokes [1.45 (0.90–2.33); $P = 0.08$]. Concerning the association of SUA concentration with mortality from other cardiovascular events, we found an age-adjusted hazard ratio of 1.79 (1.31–2.45; $P < 0.0001$) for the highest SUA quintile vs the lowest quintile.

After additional adjustment for potential confounding factors, the associations mentioned above remained stable in terms of statistical significance, with

Table 1. Characteristics of the study population by quintile of SUA concentration, VHM&PP 1985–2005.

Characteristic	All participants	SUA quintile 1 (≤273.81 μmol/L)	2 (273.82–315.48 μmol/L)	3 (315.49–351.19 μmol/L)	4 (351.20–398.81 μmol/L)	5 (>398.81 μmol/L)
	(n = 83 683)	(n = 17 121)	(n = 17 942)	(n = 16 356)	(n = 16 626)	(n = 15 638)
Age, mean (SD), range, years	41.6 (14.7), 18–96	41.4 (14.5), 18–96	40.7 (14.5), 18–91	40.7 (14.6), 19–96	41.6 (14.7), 19–92	44.1 (14.9), 18–95
Age >65 years, n (%)	6 528 (7.7)	1 246 (7.3)	1 255 (7.0)	1 121 (6.9)	1 275 (7.7)	1 546 (9.9)
Age >75 years, n (%)	1 810 (2.2)	337 (2.0)	324 (1.8)	340 (2.1)	361 (2.2)	448 (2.9)
Cigarette smoking, n (%)	25 163 (29.6)	5 097 (29.8)	5 262 (29.3)	4 783 (29.2)	4 974 (29.9)	4 630 (29.6)
Weight, mean (SD), median, kg	77.9 (12.3), 77.0	73.9 (11.0), 73.0	76.2 (11.3), 75.0	77.8 (11.5), 77.0	79.5 (12.2), 78.0	83.0 (13.5), 82.0
BMI[a], mean (SD), median, kg/m^2	25.3 (3.6), 24.9	24.2 (3.3), 23.9	24.7 (3.3), 24.4	25.2 (3.4), 24.9	25.8 (3.6), 25.4	27.0 (3.9), 26.6
Glucose, mean (SD), median, mmol/L	4.98 (1.34), 4.83	5.14 (1.81), 4.88	4.97 (1.32), 4.83	4.91 (1.17), 4.77	4.92 (1.14), 4.83	4.99 (1.17), 4.83
SUA, mean (SD), median, μmol/L	338.2 (76.5), 333.3	238.1 (29.8), 250.0	297.6 (11.9), 297.6	333.3 (11.9), 333.3	375.0 (11.9), 375.0	452.4 (47.6), 440.5
Triglycerides, mean (SD), median, mmol/L	1.72 (1.21), 1.37	1.42 (0.98), 1.15	1.51 (1.00), 1.22	1.63 (1.10), 1.34	1.82 (1.24), 1.49	2.26 (1.54), 1.84
Total cholesterol, mean (SD), median, mmol/L	5.63 (1.24), 5.54	5.35 (1.18), 5.25	5.48 (1.17), 5.30	5.59 (1.19), 5.51	5.75 (1.21), 5.67	6.02 (1.34), 5.93
GGT, mean (SD), median, U/L	24.4 (34.6), 16.0	19.0 (29.6), 13.0	20.0 (25.3), 14.0	21.9 (27.0), 15.0	25.3 (32.0), 17.0	36.8 (51.3), 23.0
Systolic blood pressure, mean (SD), median, mmHg	132.0 (18.8), 130.0	128.7 (17.8), 129.0	130.1 (18.0), 130.0	131.1 (18.1), 130.0	133.0 (18.8), 130.0	137.6 (20.1), 135.0
Diastolic blood pressure, mean (SD), median, mmHg	81.6 (10.8), 80.0	79.5 (10.3), 80.0	80.6 (10.4), 80.0	81.2 (10.5), 80.0	82.3 (10.8), 80.0	84.8 (11.6), 80.0
Hypertension, n (%)	9 896 (11.6)	1 357 (7.9)	1 644 (9.2)	1 644 (10.1)	2 100 (12.6)	3 049 (19.5)
Total mortality, n (%)	7 243 (8.7)	1 379 (8.1)	1 302 (7.3)	1 257 (7.7)	1 421 (8.5)	1 884 (12.0)
Cardiovascular/cerebrovascular deaths, n (%)	3 007 (3.6)	564 (3.3)	508 (2.8)	540 (3.3)	562 (3.4)	833 (5.3)
Other cause, n (%)	4 236 (5.1)	815 (4.8)	794 (4.4)	717 (4.4)	859 (5.2)	1 051 (6.7)
Follow-up, mean (SD), median, years	12.4 (6.2), 13.6	12.5 (6.3), 13.6	12.3 (6.2), 13.4	12.4 (6.2), 13.6	12.4 (6.1), 13.6	12.4 (6.0), 13.6
Person-years at risk	1 038 070	214 393	221 391	202 375	206 630	193 281

[a] BMI, body mass index.

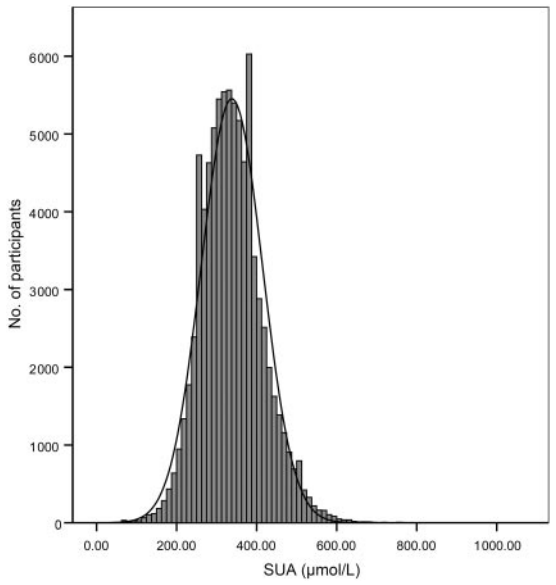

Fig. 1. Histogram of baseline SUA concentrations in 83 683 study participants, VHM&PP 1985–2005.

only slight attenuation for CHF, stroke, and other cardiovascular events (Table 3 and Fig. 2). Cox proportional hazards models adjusted for age, body mass index, systolic and diastolic blood pressure, total cholesterol, triglycerides, GGT, glucose, smoking status, and year of examination yielded hazard ratios (95% confidence interval) for the highest SUA quintile vs the lowest quintile of 1.51 (1.03–2.22) for CHF, 1.59 (1.23–2.04) for all strokes, and 1.39 (0.99–1.94) for other cardiovascular events. The initially observed significant association of SUA concentration with mortality from CHD entirely disappeared, however, with the fully adjusted hazard ratio for the highest SUA quintile vs the lowest quintile decreasing to 1.05 (0.90–1.22; $P = 0.12$). Fig. 3 displays the adjusted cumulative survival curves for CHD, CHF, and all strokes within the 21-year follow-up period according to SUA quintile.

Participant age was a significant effect modifier for the relationship of SUA concentration with total CVD mortality (P for multiplicative interaction = 0.049). When we considered subgroups, the significant multiplicative interaction of SUA concentration with age was confined to fatal CHF ($P = 0.05$), whereas we observed no significant interaction for the relationship with fatal CHD ($P = 0.41$), stroke ($P = 0.55$), or other CVD events ($P = 0.11$). After we stratified participants into age groups according to a cutoff value of 65 years, the initially observed significant association of SUA concentration with fatal CHF became less striking. The association was statistically nonsignificant in participants >65 years old but was even more striking in participants ≤65 years old [the fully-adjusted hazard ratios for the highest vs lowest SUA quintiles were 1.19 (0.71–1.97; $P = 0.50$) and 2.32 (1.23–4.34; $P = 0.008$), respectively]. To further eliminate the possible effects of very old participants, we excluded all participants >75 years old in another subgroup analysis. With this reanalysis, however, the statistical significance remained unchanged for all associations that were statistically significant in the main analysis.

Because of the assumed relevance of hypertension in the pathogenesis of uric acid–induced CVD *(31, 32)*, we separately investigated all previous reported associations in hypertensive study participants. These analyses did not reveal substantial changes in hazard ratios or statistical significance with respect to the results of the main analyses that included all participants; how-

Table 2. Clinical correlates of SUA concentration, VHM&PP 1985–2005.

	Correlation coefficient[a]	*P*	Standardized regression coefficient[b]	*P*
GGT, (U/L)	0.28	<0.001	0.17	<0.0001
Triglycerides (mmol/L)	0.27	<0.001	0.15	<0.0001
Body mass index (kg/m^2)	0.25	<0.001	0.14	<0.0001
Total cholesterol (mmol/L)	0.18	<0.001	0.05	<0.0001
Systolic blood pressure (mmHg)	0.15	<0.001	0.05	<0.0001
Diastolic blood pressure (mmHg)	0.15	<0.001	0.03	<0.0001
Cigarette smoking	0.11	0.004	−0.03	<0.0001
Glucose (mmol/L)	−0.14	<0.001	−0.13	<0.0001

[a] Age-adjusted partial correlation coefficients. GGT and triglyceride data were log-transformed.
[b] Stepwise multiple regression analysis including age, GGT, triglycerides, body mass index, total cholesterol, systolic blood pressure, diastolic blood pressure, cigarette smoking, and glucose. GGT and triglyceride data were log-transformed. $R = 0.15$.

Table 3. Mortality from CVD according to SUA concentration, VHM&PP 1985–2005.

	SUA						
	Quintile						
	1 (≤273.81 μmol/L) (n = 17 121)	2 (273.82–315.48 μmol/L) (n = 17 942)	3 (315.49–351.19 μmol/L) (n = 16 356)	4 (351.20–398.81 μmol/L) (n = 16 626)	5 (>398.81 μmol/L) (n = 15 638)	Total per-unit increase (n = 83 683)	*P* for unit increase
CHD							
Fatal events, n (%)	326 (1.9)	277 (1.5)	322 (2.0)	321 (1.9)	453 (2.9)	1 699 (2.0)	
HR 1[a] (95% CI)	1.00 (Ref)	0.90 (0.77–1.06)	1.17 (1.00–1.36)	1.10 (0.94–1.28)	1.44 (1.25–1.66)	1.11 (1.08–1.15)	<0.0001
HR 2 (95% CI)	1.00 (Ref)	0.81 (0.69–0.96)	1.04 (0.88–1.21)	0.89 (0.76–1.05)	1.05 (0.90–1.22)	1.03 (0.99–1.07)	0.12
Acute and subacute CHD forms							
Fatal events, n (%)	149 (0.9)	136 (0.8)	164 (1.0)	169 (1.0)	226 (1.4)	844 (1.0)	
HR 1 (95% CI)	1.00 (Ref)	0.95 (0.76–1.20)	1.28 (1.03–1.60)	1.24 (0.99–1.54)	1.55 (1.27–1.91)	1.16 (1.10–1.21)	<0.0001
HR 2 (95% CI)	1.00 (Ref)	0.80 (0.63–1.01)	1.07 (0.85–1.34)	0.94 (0.75–1.18)	1.02 (0.81–1.27)	1.05 (1.00–1.11)	0.07
Chronic CHD forms							
Fatal events, n (%)	177 (1.0)	141 (0.8)	158 (1.0)	152 (0.9)	227 (1.5)	855 (1.0)	
HR 1 (95% CI)	1.00 (Ref)	0.86 (0.69–1.08)	1.08 (0.87–1.33)	0.98 (0.79–1.21)	1.34 (1.10–1.63)	1.07 (1.02–1.12)	0.006
HR 2 (95% CI)	1.00 (Ref)	0.83 (0.66–1.04)	1.01 (0.81–1.27)	0.85 (0.67–1.07)	1.10 (0.87–1.3)	1.01 (0.96–1.06)	0.73
CHF							
Fatal events, n (%)	51 (0.3)	46 (0.3)	46 (0.3)	58 (0.3)	79 (0.5)	280 (0.3)	
HR 1 (95% CI)	1.00 (Ref)	0.97 (0.65–1.45)	1.08 (0.72–1.61)	1.28 (0.88–1.86)	1.60 (1.12–2.27)	1.13 (1.04–1.22)	0.004
HR 2 (95% CI)	1.00 (Ref)	0.97 (0.64–1.47)	1.14 (0.75–1.71)	1.24 (0.83–1.84)	1.51 (1.03–2.22)	1.10 (1.01–1.20)	0.03
CHF related to CAD							
Fatal events, n (%)	30 (0.2)	31 (0.2)	28 (0.2)	38 (0.2)	38 (0.2)	165 (0.2)	
HR 1 (95% CI)	1.00 (Ref)	1.14 (0.69–1.88)	1.13 (0.68–1.90)	1.45 (0.90–2.35)	1.32 (0.82–2.13)	1.06 (0.95–1.17)	0.32
HR 2 (95% CI)	1.00 (Ref)	1.25 (0.74–2.10)	1.33 (0.78–2.23)	1.64 (0.99–2.72)	1.49 (0.88–2.50)	1.07 (0.95–1.19)	0.27
CHF unrelated to CAD							
Fatal events, n (%)	21 (0.1)	15 (0.1)	18 (0.1)	20 (0.1)	41 (0.3)	115 (0.1)	
HR 1 (95% CI)	1.00 (Ref)	0.75 (0.39–1.46)	1.00 (0.53–1.88)	1.04 (0.56–1.92)	2.00 (1.18–3.38)	1.23 (1.09–1.39)	0.001
HR 2 (95% CI)	1.00 (Ref)	0.67 (0.34–1.34)	0.93 (0.49–1.78)	0.82 (0.43–1.58)	1.49 (0.84–2.65)	1.15 (1.01–1.32)	0.04

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Table 3. Mortality from CVD according to SUA concentration, VHM&PP 1985–2005. *(Continued)*

	SUA						
	Quintile						
	1 (≤273.81 μmol/L) (n = 17 121)	2 (273.82–315.48 μmol/L) (n = 17 942)	3 (315.49–351.19 μmol/L) (n = 16 356)	4 (351.20–398.81 μmol/L) (n = 16 626)	5 (>398.81 μmol/L) (n = 15 638)	Total per-unit increase (n = 83 683)	*P* for unit increase
Stroke							
Fatal events, n (%)	124 (0.7)	110 (0.6)	107 (0.7)	111 (0.7)	193 (1.2)	645 (0.8)	
HR 1 (95% CI)	1.00 (Ref)	0.96 (0.75–1.25)	1.04 (0.80–1.35)	1.02 (0.79–1.31)	1.62 (1.30–2.04)	1.13 (1.07–1.19)	<0.0001
HR 2 (95% CI)	1.00 (Ref)	1.00 (0.76–1.30)	1.05 (0.80–1.38)	1.02 (0.78–1.34)	1.59 (1.23–2.04)	1.11 (1.05–1.18)	<0.0001
Hemorrhagic stroke							
Fatal events, n (%)	29 (0.2)	29 (0.2)	23 (0.1)	26 (0.2)	40 (0.3)	147 (0.2)	
HR 1 (95% CI)	1.00 (Ref)	1.05 (0.62–1.75)	0.93 (0.54–1.60)	0.99 (0.58–1.68)	1.45 (0.90–2.33)	1.11 (0.99–1.25)	0.08
HR 2 (95% CI)	1.00 (Ref)	1.02 (0.60–1.72)	0.89 (0.51–1.57)	0.92 (0.53–1.60)	1.18 (0.70–2.01)	1.06 (0.93–1.20)	0.39
Ischemic stroke							
Fatal events, n (%)	28 (0.2)	23 (0.1)	26 (0.2)	23 (0.1)	47 (0.3)	147 (0.2)	
HR 1 (95% CI)	1.00 (Ref)	0.91 (0.52–1.57)	1.13 (0.66–1.93)	0.95 (0.55–1.65)	1.78 (1.11–2.84)	1.14 (1.02–1.27)	0.02
HR 2 (95% CI)	1.00 (Ref)	0.92 (0.52–1.63)	1.19 (0.68–2.07)	1.01 (0.57–1.80)	1.81 (1.07–3.04)	1.13 (1.00–1.27)	0.048
Undefined stroke							
Fatal events, n (%)	67 (0.4)	58 (0.3)	58 (0.4)	62 (0.4)	106 (0.7)	351 (0.4)	
HR 1 (95% CI)	1.00 (Ref)	0.96 (0.67–1.36)	1.05 (0.74–1.50)	1.06 (0.75–1.50)	1.64 (1.21–2.23)	1.13 (1.06–1.22)	<0.0001
HR 2 (95% CI)	1.00 (Ref)	1.02 (0.71–1.47)	1.07 (0.73–1.55)	1.06 (0.73–1.55)	1.66 (1.18–2.34)	1.12 (1.04–1.21)	0.004
Other cardiovascular events							
Fatal events, n (%)	63 (0.4)	75 (0.4)	65 (0.4)	72 (0.4)	108 (0.7)	383 (0.5)	
HR 1 (95% CI)	1.00 (Ref)	1.27 (0.91–1.78)	1.23 (0.87–1.74)	1.28 (0.92–1.80)	1.79 (1.31–2.45)	1.17 (1.09–1.25)	<0.0001
HR 2 (95% CI)	1.00 (Ref)	1.17 (0.83–1.65)	1.11 (0.78–1.59)	1.05 (0.74–1.50)	1.39 (0.99–1.94)	1.09 (1.01–1.18)	0.03

[a] HR 1, hazard ratio from Cox proportional hazards models adjusted for age; HR 2, hazard ratio from Cox proportional hazards models adjusted for age, body mass index, systolic and diastolic blood pressure, total cholesterol, triglycerides, GGT, glucose, smoking status, and year of examination (triglyceride and GGT data were log-transformed); CI, confidence interval; Ref, reference.

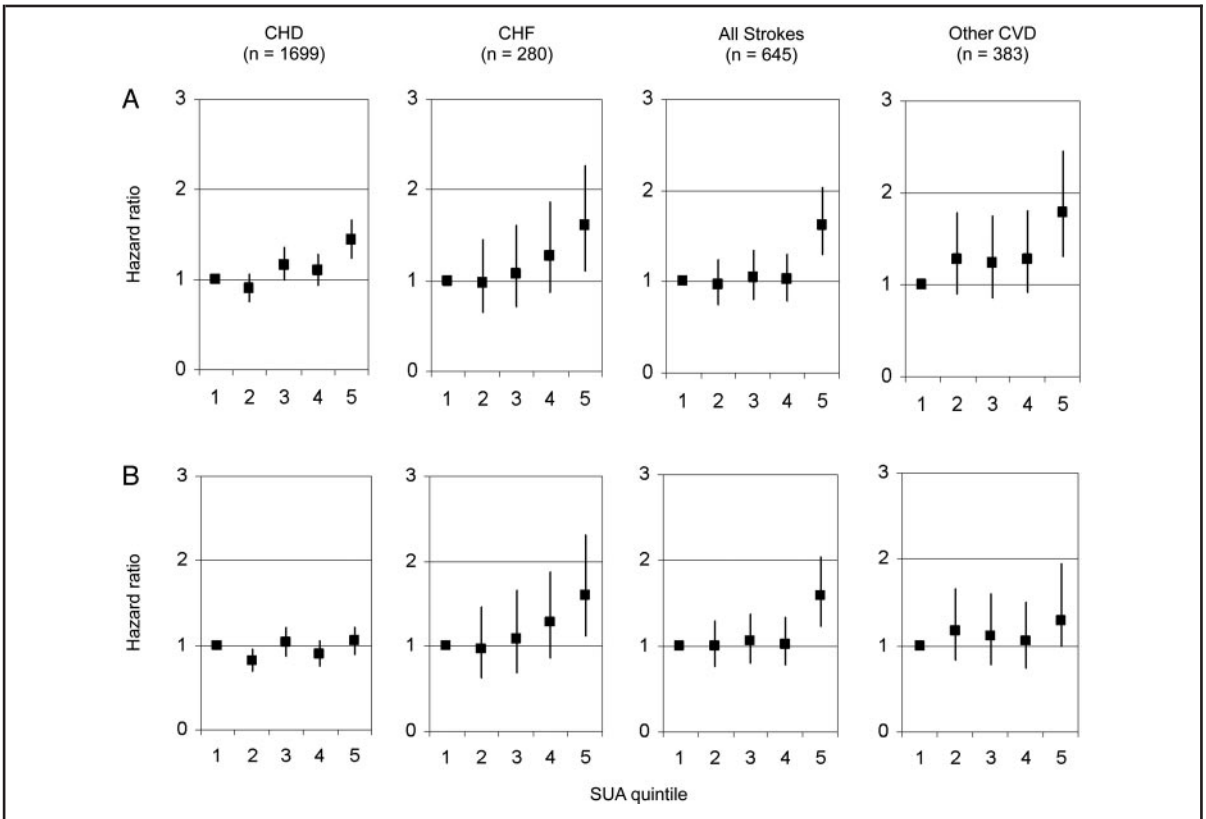

Fig. 2. Hazard ratios with 95% confidence intervals for the association between SUA and CVD mortality from Cox proportional hazards models adjusted for age (A) and Cox proportional hazards models adjusted for age, body mass index, systolic and diastolic blood pressure, total cholesterol, triglycerides, GGT, glucose, smoking status, and year of examination (B).

Boxes present consecutive quintiles of SUA concentration.

ever, we found that SUA concentrations were moderately higher in hypertensive patients than in healthy study participants, especially in the younger age groups (data not shown).

Discussion

This prospective, long-term study is the largest single investigation undertaken to date to assess the association between baseline SUA concentration in men and their risk of subsequent mortality from CHF, CHD, and stroke. As expected, our findings confirm that SUA concentrations are directly associated with most established cardiovascular risk factors, including systolic blood pressure, total cholesterol, triglycerides, body mass index, and GGT. After fully adjusting for these confounding variables, however, we found that men with baseline SUA values >398.81 μmol/L have about a 50% greater risk for fatal CHF and stroke and about a 40% greater risk for mortality from other cardiovascular events than do men with SUA concentrations ≤273.81 μmol/L. That our results were stable after exclusion of participants >75 years old accented the prognostic significance of SUA for mortality from CHF and stroke, although not necessarily as a causal risk factor. Conversely, after fully adjusting for potential confounding variables, we found that increased SUA concentration was not significantly related to mortality from acute, subacute, or chronic forms of CHD.

Concordantly with our results, recent in vitro and in vivo findings suggest that SUA contributes directly to endothelial dysfunction by inducing antiproliferative effects and impairing nitric oxide production *(33)*, thus causing a deterioration in CHF. To date, however, little epidemiologic evidence supports the role of SUA as an independent risk factor for CHF, and we know of no other similar published epidemiologic reports with which to compare our results. Our study results demonstrate a positive and merely linear association, indicating a moderate but clear dose–response relationship

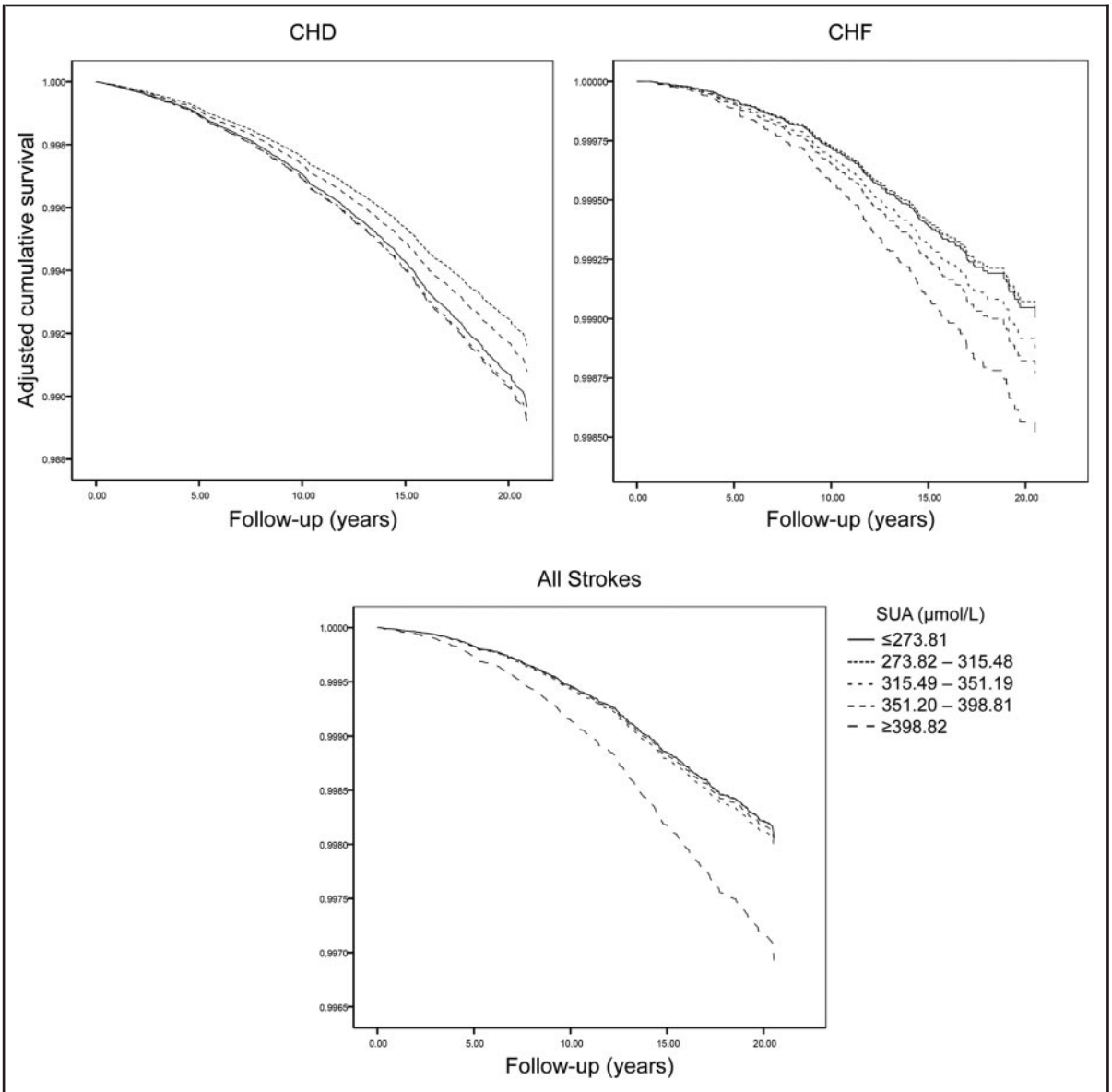

Fig. 3. Adjusted cumulative survival from CHD, CHF, and all strokes according to SUA quintile for 83 683 Austrian men (mean age, 41.6 years) in the VHM&PP estimated at the mean values of covariates.

Survival curves were calculated with Cox proportional hazards models adjusted for age, body mass index, systolic and diastolic blood pressure, total cholesterol, triglycerides, GGT, glucose, smoking status, and year of examination.

between baseline SUA concentration and the risk of subsequent CHF mortality. This finding strongly suggests that SUA concentration plays an important role, especially in CHF unrelated to CAD in men ≤65 years old. The observed associations remained significant and stable, although slightly attenuated, even after adjustment for several confounding factors. Given the epidemiologic nature of our observations, the underlying biological mechanisms that cause SUA to be more strongly related to mortality from CHF in younger individuals (<65 years) than in older individuals (>65 years) remain uncertain, and providing a potential explanation for this finding would be rather speculative. From a statistical point of view, however, it is likely that, in general, the number of individuals at risk increases with age, a trend that would attenuate the excess effect of increased SUA concentration. In line with our results, Sakai and coworkers *(34)* recently demon-

strated in a Japanese population of 74 patients with mild to severe CHF that high serum concentrations of uric acid were important predictors of mortality, independently of clinical and neurohumoral factors previously associated with a poor prognosis. These investigators' results further indicate that not only high plasma concentrations of B-type natriuretic peptide but also high SUA concentrations are likely to be independently explanatory for mortality in CHF patients. SUA is a routinely measured variable in clinical laboratories, with repeatable results and nonsignificant short-term individual fluctuations without any age-specific or diurnal patterns *(35*, *36)*. Given these characteristics, SUA could feasibly be used as a helpful prognostic indicator in clinical practice.

In contrast to the merely linear association between SUA concentration and the risk of mortality from CHF, we found an increased risk for incident fatal strokes only for the highest SUA quintile (>398.81 μmol/L), suggesting a threshold effect. In our adjusted models, however, SUA concentration was independently predictive only in the subgroups of ischemic stroke and unidentified stroke and was not significantly related to mortality from hemorrhagic stroke. Although relatively little evidence exists on the role of SUA concentration as a risk factor for stroke mortality in men, this result was partly confirmed in the Rotterdam Study *(17)*. Participants in that investigation were all ≥55 years old, however, and in sex-specific analyses, the association of SUA concentration with ischemic stroke was inconsistent and fairly diminished in men. In line with our finding that the association of SUA concentration with the incident risk of fatal stroke may be subject to a threshold effect, Mazza and colleagues *(12)* reported a J-shaped relationship between SUA concentration and stroke mortality in elderly individuals from Italy, although the authors did not conduct sex-specific analyses for men. In regard to the underlying pathophysiological mechanism, human atherosclerotic plaque has been shown to contain a considerable amount of uric acid, and hyperuricemia may promote thrombus formation via purine metabolism *(37*, *38)*. In addition, increased uric acid concentrations are associated with the increased production of oxygen free radicals, promote oxygenation of LDL cholesterol, and facilitate lipid peroxidation *(15*, *39)*. Each of these factors is known to play a crucial role in the progression of atherosclerosis.

Concerning the relationship of SUA and risk of fatal CHD, our results are consistent with previous findings from the Framingham Heart Study *(20)* and an investigation by Wannamethee and coworkers *(19)* in that univariate associations appeared to be largely explained by the relation of SUA with other CHD risk factors and entirely disappeared after additional adjustment for confounding factors. In our multivariate models, the major risk factor was systolic blood pressure, which mostly attenuated the initially observed association. A similar result was observed in an investigation by Moriarity and colleagues *(21)*.

Although subgroup analyses of hypertensive study participants did not reveal substantial changes in terms of hazard ratios or statistical significance with respect to the results of the main analyses, we found SUA concentrations to be slightly increased in hypertensive study participants compared with nonhypertensive participants, especially for younger age groups. The mechanisms underlying the increase in SUA concentration and its potential prognostic implications in patients with essential hypertension are still not completely understood, although increased SUA concentrations in asymptomatic and uncomplicated cases with essential hypertension may reflect early renal vascular alterations, with reduction in cortical blood flow and depressed tubular secretion of urate caused by reduced delivery to the tubular secretory sites *(14)*. Excessive alcohol consumption may also play a contributory role.

Our study had several strengths and potential limitations that should be considered. Major strengths were the prospective design, large sample size, length of follow-up, and a standardized protocol performed by experienced physicians. Limitations included the inability to account for additional factors that might also have residually confounded the relationship between SUA concentration and CVD mortality (although information on major CVD risk factors was collected), including lipid subfractions or apolipoproteins, C-reactive protein, homocysteine, alcohol consumption, physical activity, diet, and genetic and psychosocial variables. SUA is the main end product of the metabolism of purines, which coderive from the diet and increase with a higher intake of red meat. Diet was not accounted for during baseline screening, and thus differences in diet may explain, at least in part, differences in SUA concentrations in the study population. Although our cohort consisted of an apparently healthy male population rather than a sick hospital sample, impaired renal function is common in CVD patients and is another codetermining factor of SUA concentration. Because creatinine or other measures of renal function were not routinely measured in all participants of this study, we were unable to directly adjust for these variables in the main analysis. We did, however, check for a cross-sectional correlation of SUA with serum creatinine in a subgroup of 838 participants who underwent a more detailed examination. We found only a weak age-adjusted correlation of SUA with creatinine (r = 0.13), which decreased to 0.11 after additional adjustment. Therefore, we believe that the prognostic power

of SUA for fatal CHF and stroke would remain significant after additional adjustment for renal function. A final limitation was the inability to examine the effect of medication use (e.g., statins and antihypertensive drugs) on the relationship of SUA concentration with CVD mortality. With regard to statins, however, little if any effect is possible because 75% of all VHM&PP study participants were examined before the implementation of statin therapy in Austria in 1995. In contrast, antihypertensive drugs, including diuretics, might have been used more frequently, thus providing a potential source for residual confounding of the results.

In conclusion, this long-term study of more than 80 000 Austrian men across a wide age range demonstrates for the first time that high SUA concentrations are independently associated with an increased risk of mortality from CHF and stroke in men. The finding of increased SUA concentrations in these individuals suggests the clinical importance of monitoring and intervention based on SUA measurement, particularly because SUA is easily and routinely measured.

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