URIC ACID AND CARDIOVASCULAR EVENTS - A MENDELIAN RANDOMISATION STUDY

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Background: Obesity and diet rich in uric acid (UA) raising components have led to high prevalence of hyperuricemia in Westernized populations. This is in parallel with increasing prevalence rates of hypertension, diabetes mellitus, chronic kidney disease, and cardiovascular disease. Whether UA truly represents an independent risk factor for the development of these diseases is still a matter of hot debate. Recently, a large meta-analysis including >140.000 individuals identified 28 genetic loci that were genome-wide significantly associated with serum UA concentration (1). Based on these SNPs we constructed a genetic risk score (GRS) and used it in a Mendelian Randomization study to examine whether uric acid represents an independent and causal vascular risk factor.

Methods: UA was measured in patients of the Ludwigshafen Risk and Cardiovascular Health Study (LURIC) using a photometric colour test on a Hitachi 717 analyzer (Roche, Mannheim, Germany) with reagents from Rolf Greiner Biochemica (Flacht, Germany). We first tested all 28 UA SNPs from the meta-analysis for pleiotropic effects in LURIC. From 14 SNPs with no evidence of peiotropy we used eight SNPs that showed an effect in accordance to the meta-analysis to calculate a weighted genetic risk score (GRS) for UA concentration. Causal hazard ratios (CHR) were calculated using a two-stage regression estimate (2) with the GRS as instrumental variable to examine association with mortality, cardiovascular mortality (CVM) and sudden cardiac death (SCD). In the first stage a linear regression of UA on GRS was performed. The predicted UA values from the first stage were then used for Cox regression analysis.

Table 1: Patient characteristics according to quartiles of urate genetic risk score

	GRS				
	1st quartile (<= 0.63)	2nd quartile (0.64 - 0.94)	3rd quartile (0.95 - 1.03)	4th quartile (1.04+)	P value*
Uric acid mg/dl	4.90±1.61	5.02±1.69	5.20±1.74	5.33±1.71	<0.001
Sex (male)%	71.6	67.5	71.3	69.8	0.253
Age (yr)	62.6±10.6	62.7±11.0	63.0±10.6	62.7±10.4	0.912
Body mass index (kg/m^2)	27.6±4.13	27.5±4.1	27.2±3.9	27.6±4.0	0.233
eGFR (ml/min/1.73m^2)	82.0±20.2	81.9±20.9	81.9±20.0	82.0±19.7	0.987
Diastolic blood pressure (mmHg)	81.1±11.3	80.9±11.6	80.9±11.5	80.6±11.1	0.900
Systolic blood pressure (mmHg)	141.1±23.0	140.1±24.0	142.2±24.0	140.1±23.6	0.364
Fasting glucose(mg/dL)	102.1 (93.2-116.8)	103.0 (94.2-120.6)	102.6 (94.7-119.4)	101.0 (93.4-116.0)	0.241
LDL cholesterol (mg/dL)	115.5±34.2	117.9±35.5	117.0±35.1	115.4±32.7	0.411
HDL cholesterol (mg/dL)	38.7±11.0	38.7±10.0	38.7±11.0	38.6±10.7	0.993
Triglycerides (mg/dL)	141.0 (106.0-195.0)	147.0 (110.0-202.0)	143.0 (106.0-189.7)	145.5 (110.0-208.3)	0.086
C-reactive protein (mg/L)	3.93 (1.36-9.59)	3.38 (1.34-8.52)	2.96 (1.17-8.40)	3.75 (1.46-8.61)	0.033
Coronary artery disease (%)	79.7	78.6	77.5	80.6	0.889
Hypertension (%)	74.0	71.0	75.0	70.4	0.524
Diabetes (%)	40.1	43.4	38.6	39.2	0.308

*Chi-square test for categorical variables, ANOVA for continuous variables. Variables with skewed distribution were log transformed before entering analysis.

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Results: The GRS was not associated with any biochemical marker except for UA and high-sensitivity C-reactive protein (hsCRP) (**Table 1**). While UA itself was significantly associated with prevalent coronary artery disease, hypertension, diabetes mellitus and other cardiovascular diseases the GRS was not (**Table 1**). UA as well as GRS were both associated with CVM and SCD. CHR were significant for CVD and SCD in a multivariate adjusted model including medication with HRs of 1.77 (1.12-2.81) and 2.41 (1.16-5.00), respectively (**Figure 1**, **Table 2**).

Table 2: Patient characteristics according to quartiles of urate genetic risk score

	Causal odds ratio per 1 mg/dl increase in uric acid (95% CI)		Hazard ratio per 1 mg/dl increase in uric acid (95% CI)	
Model 1				
All-cause mortality	1.05 (0.74-1.49)	0.777	1.22 (1.18-1.26)	<0.001
Cardiovascular mortality	1.62 (1.02-2.56)	0.041	1.27 (1.28-1-32)	<0.001
Sudden Cardiac Death	2.06 (1.00-4.24)	0.051	1.31 (1.23-1.39)	<0.001
Model 2				
All-cause mortality	1.04 (0.73-1.49)	0.814	1.17 (1.13-1.21)	<0.001
Cardiovascular mortality	1.61 (1.02-2.57)	0.043	1.22 (1.18-1.27)	<0.001
Sudden Cardiac Death	1.94 (0.93-4.03)	0.076	1.26 (1.18-1.34)	<0.001
Model 3				
All-cause mortality	1.11 (0.78-1.58)	0.553	1.08 (1.03-1.12)	<0.001
Cardiovascular mortality	1.79 (1.13-2.83)	0.014	1.12 (1.07-1.18)	<0.001
Sudden Cardiac Death	2.18 (1.05-4.51)	0.036	1.14 (1.05-1.23)	0.001

Model 1: unadjusted; Model 2: adjusted for age, sex; Model 3: additionally adjusted for LDL-C, HDL-C, smoking, bmi, diabetes, hypertension, eGFR, TG, friesinger score, hsCRP

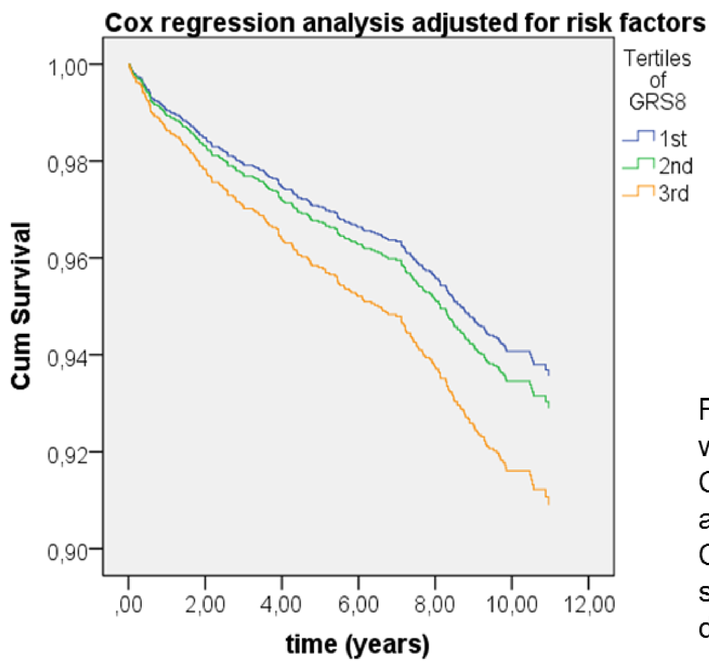

Fig 1: Association of GRS with sudden cardiac death. Cox regression analysis adjusted for: sex age LDL-C, HDL-C, TG, BMI, smoking, hyptertension, diabetes, friesinger score

Discussion: We found an association of a genetic risk score composed of uric acid increasing SNPs with cardiovascular mortality and sudden cardiac death which remained significant after multivariate adjustment. This exactly replicates previous prospective findings for UA in LURIC (3). In contrast, we did not find an association of the GRS with prevalent coronary artery disease. UA might thus be causally involved in long-term adverse cardiovascular outcomes by causal mechanisms that are independent of atherosclerosis.

References:

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