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Uric acid is independent and inversely associated to glomerular filtration rate in young adult Brazilian individuals

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Abstract *Background and aims:* Uric acid, the end-product of human purine metabolism, is associated with hypertension, diabetes and obesity. It has also been independently associated with the onset of chronic kidney disease in several populations. In this study, the association between serum uric acid (SUA) level and estimated glomerular filtration rate (eGFR) was investigated in healthy individuals belonging to two Brazilian birth cohorts.
Methods and results: Data from 3541 to 3482 individuals, aged 30 and 22-years old, respectively, was included. eGFR was calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation based on creatinine measurement. Regression analyses were sex-stratified due to interaction between SUA and sex ($p < 0.001$) and adjusted for perinatal, cardiometabolic and behavioral variables.

We observed an inverse association between eGFR and SUA even after adjustment. In the highest tertile (3rd) of SUA, the eGFR coefficients at 30-years were-0.21 (95%CI -0.24;-0.18) for men and −0.20 (95%CI -0.23; −0.17) for women; at 22-years, were −0.09 (95%CI -0.12;-0.05) for men and −0.13 (95%CI -0.15; −0.10) for women. Higher differences among exponential means (95% CI) of eGFR between the 1st and the 3rd tertile of SUA were seen in older participants, being more pronounced in men. At 22-years, the highest difference was found in women.
Conclusions: In young healthy individuals from a low-middle income country, SUA level was inversely associated with eGFR. Gender-related differences in eGFR according tertiles of SUA were higher in men at 30-years and in women at 22-years.
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Abbreviations: AUDIT, Alcohol Use Disorder Identification Test; BMI, Body Mass Index; CKD, Chronic Kidney Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; DBP, Diastolic Blood Pressure; eGFR, estimated Glomerular Filtration Rate; GLUT-9, Glucose transporter-9; HDL-c, High Density Lipoprotein-cholesterol; IQR, Interquartile Range; LDL-c, Low Density Lipoprotein-cholesterol; MR, Mendelian Randomization; RAS, Renin-Angiotensin-System; Scr, serum creatinine; SUA, serum Uric Acid; SD, Standard Deviation; SBP, Systolic Blood Pressure; TC, Total Cholesterol; URAT1, Uric acid transporter 1; WC, waist circumference.

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Introduction

Uric acid is the end-product of human purine metabolism since the loss of uricase gene functions as a thrifty gene in humans and ape ancestors has occurred almost 15 million years ago [1]. The increase of SUA level results from a decrease of renal excretion or as an overproduction from several pathways such as: purine rich food intake, alcohol abuse, excessive fructose consumption or high cell turnover conditions [2].

Uric acid seems to play oxidant properties in the presence of an unfavorable hydrophobic environment created especially by the lipids [3]. In this context, uric acid has been related to hypertension, dyslipidemia, obesity, impaired glucose metabolism and metabolic syndrome contributing to pathophysiology of cardiovascular disease [4] as well as to the early development of Type 2 Diabetes [5]. Nowadays, the increase of SUA has called special epidemiological attention as an independent risk factor for the onset of chronic kidney disease (CKD) [6], a big burden on health and economy worldwide [7]. However, despite of all knowledge, many controversial data still exist about the real role of SUA in chronic diseases, especially in CKD.

Taking into account that birth cohorts are considered excellent models to study risk factors related to chronic diseases, this study aimed to assess the association between SUA level and estimated glomerular filtration rate (eGFR) in healthy individuals at 30 and 22-years old belonging to two Brazilian birth cohorts.

Methods

Birth cohort studies

Pelotas is a medium-sized city, with nearly 330,000 inhabitants, located in south of Brazil. In 1982 and 1993, all maternity hospitals in the city were visited daily and the births were identified. Those liveborns whose families lived in the urban area of the city were evaluated and their mothers interviewed including a total of 5914 children in the 1982 cohort and 5249 children in the 1993 cohort. Participants have been followed-up on several occasions and further details of the methodology have been described elsewhere for the 1982 [8] and the 1993 cohort studies [9]. Between June 2012 and February 2013, at a mean age of 30.2 years, all participants of the 1982 cohort were searched and 3701 were interviewed and examined in the research clinic, who adding to those known to have died, represented a follow-up rate of 68.1% of the original cohort [10]. A similar attempt was made for the 1993 cohort between October 2015 and July 2016, at a mean age of 22.6 and a response rate of 76.3% was obtained considering 3810 interviews performed and 193 registered deaths [11]. The present study is based on data from the last follow-up of each cohort including participants who had blood samples and laboratory measurements. The exclusion criterion for the blood sample was pregnancy in women. Refusal for collecting blood was the main cause of losses. Both studies were approved by the Research Ethics Committee of the Medical School of the Federal University of Pelotas (UFPel) and the interviews and blood collections were carried out after the participants provided written consent.

Clinical measurements

In both cohorts, weight was measured using a scale from an air-displacement plethysmography (BodPod scale - BOD POD® Composition System; COSMED) and height using a portable stadiometer (accuracy of 0.1 cm). Waist circumference (WC, in cm) was measured with the subject standing, with the arms hanging freely and next to the body, using a non-elastic measuring tape in the horizontal plane around the narrowest part of the waist. In obese subjects, the measure was taken in the horizontal plane at the point between the last rib and the iliac crest. Body Mass Index (BMI) was calculated dividing weight in Kg by the square of height in meters. All pregnant women or up to 3 months post-partum at the time of the measurements were excluded.

Blood pressure was measured twice at the beginning and at the end of the interview using the Omron HEM 742 blood pressure monitoring device. The mean value obtained for systolic (SBP) and diastolic blood pressure (DBP), respectively, was used in the present analysis.

Biochemical measurements

Random non-fasting blood samples were drawn by venipuncture into clot activator collection tubes, which were left at room temperature for 30 min and then centrifuged for 15 min at 2000*g*. Serum samples were stored at −80 °C until analyses. Serum creatinine (Scr) was measured by Jaffe method in the 1982 cohort samples whereas an enzymatic colorimetric method was used in the 1993 cohort. In both cohorts, urea and SUA acid were analyzed by enzymatic methods in an automatic analyzer (LabMax 240, Labtest Diagnóstica S.A., Lagoa Santa, MG, Brazil). The inter-assay coefficient of variation (CV) for Scr, urea and SUA in the 1982 cohort was, respectively, 1.9%, 1.6% and 1.9%. In the 1993, the inter-assay CV was 4.5%, 6.4% and 3.6% respectively. In the 1982 cohort, measurements of glucose, total cholesterol (TC), HDL-cholesterol (HDL-c), LDL-cholesterol (LDL-c) and triglycerides were processed through automatic enzymatic colorimetric methods in a chemistry analyzer (BS-380, Mindray, Shenzhen Mindray Bio-Medical Electronics Co., Ltd, China). The inter-assay CV obtained for each parameter was 1.6%, 2.0%, 4.5%, 5.0% and 2.4%, respectively. In the 1993 cohort, biochemical measurements were processed in an automatic analyzer (LabMax 240, Labtest Diagnóstica S.A., Lagoa Santa, MG, Brazil). The inter-assay CVs obtained for glucose, TC, HDL-c, LDL-c and triglycerides were 1.4%, 1.6%, 2.2%, 2.3%, and 4.0%, respectively.

Glomerular filtration rate (GRF) is defined as the total amount of fluid filtered through all of the functioning

nephrons per unit of time. GFR can be estimated from different equations including Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [12]. In the present study, renal function was evaluated by creatinine-based eGFR according to CKD-EPI equation using Scr (mg/dL), age (years) and sex as follow: women/Scr ≤0.7 mg/dL, [GFR = 144 × (Scr/0.7)$^{-0.329}$ × (0.993) Age]; women/Scr >0.7 mg/dL, [GFR = 144 × (Scr/0.7)$^{-1.209}$ × (0.993)Age]; men/Scr ≤0.9 mg/dL, [GFR = 141 × (Scr/0.9)$^{-0.411}$ × (0.993)Age]; men/Scr >0.9 mg/dL, [GFR = 141 × (Scr/0.9)$^{-1.209}$ × (0.993)Age]. The results were expressed as mL/min/per 1.73 m^2. Taking into account the miscegenation present in the Brazilian population and as suggested in previous study [13], adjustment for ethnicity was done only in regression analyses.

Statistical analyses

A cross-sectional association analysis between eGFR and SUA was performed in individuals at 30 and 22-years, respectively. Taking into consideration possible confounders [6,14], we included the following covariates in the adjusted regression analyses after testing collinearity (mean VIF<3): *demographic* [self-reported skin color: white; black; brown; others]; *perinatal* [family income (minimum wages): ≤1; 1.1–3; 3.1–6; >6]; [maternal schooling (years): 0; 1–4; 5–8; ≥9]; [maternal pregestational BMI (Kg/m2): <18.5; 18.5–24.9; 25–29.9; ≥30]; [maternal smoking during pregnancy: no; yes]; [birth weight (g): <2500; 2500–2999; 3000–3499; ≥3500]; *behavioral variables at 30- and 22-years follow-ups* [Alcohol Use Disorder Identification Test (AUDIT), harmful

Table 1 Description of the participants at 30 and 22-years old according to covariates, stratified by sex.

	Men		Women	
	30 years (N = 1747)	22 years (N = 1660)	30 years (N = 1794)	22 years (N = 1822)
	N (%)	N (%)	N (%)	N (%)
Self reported skin color[a]				
White	1314 (75.2)	992 (63.6)	1373 (76.5)	1090 (62.6)
Black	276 (15.8)	232 (14.9)	282 (15.7)	270 (15.5)
Brown	98 (5.6)	267 (17.1)	85 (4.7)	321 (18.5)
Others	59 (3.4)	69 (4.4)	54 (3.0)	59 (3.4)
Perinatal				
Family income (minimum wages)[c a]				
≤1	348 (20.0)	291 (17.5)	348 (19.5)	324 (17.8)
1.1–3	851 (48.9)	718 (43.3)	898 (50.3)	777 (42.7)
3.1–6	346 (19.9)	398 (24.0)	341 (19.1)	449 (24.6)
>6	195 (11.2)	253 (15.2)	198 (11.1)	272 (14.9)
Maternal				
Pregestational BMI (Kg/m^2)[c a]				
<18.5	112 (7.4)	161 (10.0)	104 (6.8)	143 (8.0)
18.5–24.9	1059 (70.4)	1086 (67.4)	1055 (69.4)	1217 (68.3)
25–29.9	266 (17.7)	289 (17.9)	288 (18.9)	338 (19.0)
≥30	68 (4.5)	75 (4.7)	74 (4.9)	83 (4.7)
Maternal smoking during pregnancy[c]				
No	1140 (65.3)	1140 (68.7)	1168 (65.1)	1209 (66.4)
Yes	607 (34.8)	520 (31.3)	626 (34.9)	613 (33.6)
Birth weight (g)[c a]				
<2500	100 (5.7)	114 (6.9)	151 (8.4)	194 (10.7)
2500–2999	359 (20.6)	363 (21.9)	483 (26.9)	506 (27.8)
3000–3499	654 (37.4)	655 (39.5)	677 (37.8)	708 (38.9)
≥3500	634 (36.3)	526 (31.7)	482 (26.9)	412 (22.6)
Behavioral				
Smoking status[a]				
Never smoker	982 (56.8)	1149 (69.2)	1063 (60.0)	1385 (76.2)
Former	297 (17.2)	167 (10.1)	325 (18.3)	184 (10.1)
Current smoker	450 (26.0)	344 (20.7)	384 (21.7)	248 (13.7)
Harmful alcohol intake (AUDIT ≥ 8 points)				
no	1114 (64.5)	1158 (69.8)	1591 (89.7)	1557 (85.7)
yes	614 (35.5)	501 (30.2)	182 (10.3)	260 (14.3)
Physical activity[a,b]				
Inactive	1056 (61.8)	421 (25.4)	1399 (79.4)	762 (42.0)
Active	654 (38.3)	1234 (74.6)	363 (20.6)	1054 (58.0)

[c] Variables collected at perinatal follow-up.
[a] Maximum of missing values 273 for the variable maternal pregestational BMI in the 1993 Birth Cohort.
[b] Classified as inactive those who do not reach 150 min/week of physical activities in leisure time. AUDIT (Alcohol Use Disorders Identification Test). BMI (Body Mass Index).

Table 2 Description of the participants at 30 and 22-years old according to clinical characteristics by sex.

	Men		Women	
	30 years	22 years	30 years	22 years
	(N = 1747)	(N = 1660)	(N = 1794)	(1822)
	mean (SD)	mean (SD)	mean (SD)	mean (SD)
BMI (kg/m^2)[a]	27.0 (5.0)	25.0 (4.8)	26.7 (6.0)	25.5 (5.7)
WC (cm)[a]	89.2 (11.8)	82.9 (10.8)	80.6 (12.0)	77.3 (11.7)
SBP (mmHg)[a]	128.1 (12.2)	131.6 (12.4)	114.5 (11.9)	116.9 (11.0)
DBP (mmHg)[a]	76.9 (9.3)	73.8 (8.6)	73.9 (9.1)	72.3 (8.7)
Glucose (mmol/L)	5.1 (1.7)	5.1 (1.4)	4.8 (1.1)	4.9 (1.2)
TC (mmol/L)	5.0 (1.0)	4.0 (0.9)	4.9 (0.9)	4.3 (1.0)
HDL-c (mmol/L)	1.4 (0.3)	1.2 (0.3)	1.6 (0.4)	1.4 (0.3)
LDL-c (mmol/L)	2.9 (0.8)	2.3 (0.6)	2.8 (0.7)	2.5 (0.7)
Triglycerides (mmol/L - median - IQR)	1.2 (0.8; 1.9)	1.0 (0.7; 1.4)	1.0 (0.7; 1.4)	1.0 (0.7; 1.3)
Urea (mmol/L)[a]	5.0 (1.3)	5.1 (1.4)	4.0 (1.1)	4.1 (1.2)
SUA (μmol/L)[a]	267.7 (68.9)	311.3 (73.8)	185.0 (52.3)	233.2 (63.8)
Scr (μmol/L)[a]	83.7 (18.0)	83.0 (24.6)	63.3 (15.9)	61.4 (14.5)
eGFR (ml/min/173m^2 - median - IQR)[a]	107.8 (90.3; 119.4)	119.6 (103.7; 125.6)	114.9 (95.0; 123.1)	124.3 (111.0; 129.2)

SD (Standard Deviation); IQR (interquartile range); BMI (Body Mass Index); WC (waist circumference); SBP (Systolic Blood Pressure); DBP (Diastolic Blood Pressure); TC (total cholesterol); HDL-c (HDL-cholesterol); LDL-c (LDL-cholesterol); T(triglycerides); SUA (serum Uric Acid); Scr (serum creatinine); eGFR (estimate Glomerular Filtration Rate).

[a] Variables showing missing values-maximum 27 missing values for BMI (Kg/m^2) in the 1982 cohort at 30 years.

intake ≥ 8 points: no/yes]; [smoking status: none; >0 to 1 cigarette/day; >1 cigarette/day]; [physical activity: inactive (<150 min/week); active (≥150 min/week); and *cardiometabolic variables* [current BMI; WC; SBP and DBP; glucose, total cholesterol (TC), HDL-cholesterol (HDL-c), triglycerides and urea]. All continuous variables were expressed as mean and standard deviation (SD) or median and interquartile range (IQR). Logarithm transformation was used for triglycerides and eGFR. Conversion factors of International System units were applied in regression analyses: TC, HDL-c, LDL-c: 1 mg/dL = 0.0259 mmol/L; Triglycerides:1 mg/dL = 0.0113 mmol/L; Glucose:1 mmol/L = 18 mg/dL; Scr:1 mg/dL = 88.4 μmol/L; Urea:1 mg/dL = 0.166 mmol/L; SUA:1 mg/dL = 59.5 μmol/L.

The association between eGFR or SUA with each one of the covariates was investigated using correlation or linear regression analyses. The adjusted models proposed were: model 1 (demographic and perinatal covariates); model 2 (model 1 plus cardiometabolic and behavioral covariates). The results of eGFR were reported as exponential mean with its 95% confidence interval (95% CI) according to SUA tertiles. All analyses were sex-stratified due to the significant interaction between SUA and sex ($p < 0.001$). Birth weight and AUDIT were included as continuous variables in the regression analyses. Data were processed using the statistical package STATA, version 12.0. Values of $p < 0.05$ in the Wald test for linear regression or heterogeneity were considered statistically significant.

Table 3 Adjusted linear regression analyses between eGFR and tertiles of serum uric acid (SUA) in individuals at 30 and 22 years of age.

MEN	30 years				22 years			
	Model 1		Model 2		Model 1		Model 2	
	Coef. (95% CI)	p	Coef. (95% CI)	p	Coef. (95% CI)	p	Coef. (95% CI)	p
SUA (tertiles)								
1st	Ref.		Ref.		Ref.		Ref.	
2nd	−0.11 (−0.14; −0.08)	<0.001	−0.11 (−0.13; −0.08)	<0.001	−0.05 (−0.08; −0.01)	0.007	−0.04 (−0.08; −0.01)	0.007
3rd	−0.23 (−0.26; −0.20)	<0.001	−0.21 (−0.24; −0.18)	<0.001	−0.10 (−0.13; −0.07)	<0.001	−0.09 (−0.12; −0.05)	<0.001
WOMEN	30 years				22 years			
	Coef. (CI95%)	p	Coef. (CI95%)	p	Coef. (CI95%)	p	Coef. (CI95%)	p
SUA (tertiles)								
1st	Ref.				Ref.		Ref.	
2nd	−0.12 (−0.14; −0.10)	<0.001	−0.11 (−0.13; −0.09)	<0.001	−0.05 (−0.07; −0.03)	<0.001	−0.05 (−0.07; −0.04)	<0.001
3rd	−0.24 (−0.27; −0.21)	<0.001	−0.20 (−0.23; −0.17)	<0.001	−0.15 (−0.17; −0.13)	<0.001	−0.13 (−0.15; −0.10)	<0.001

eGFR (mL/min/per 1.73 m^2): estimate glomerular filtration rate; SUA (μmol/L): serum uric acid. Regressions performed with eGFR and triglycerides on logarithmic scale and SUA concentration in tertiles. Regression analyses were adjusted according: Model 1[self reported skin color, family income, maternal pregestational body mass index (BMI), maternal smoking during pregnancy; birth weight]; Model 2 [Model 1 + systolic blood pressure, diastolic blood pressure, BMI (except for individuals at 22 years), waist circumference, glucose, total cholesterol, HDL-c, triglycerides, urea, difference of time between blood collection and last meal, harmful alcohol intake (AUDIT), smoking status, and physical activity].

Table 4 Exponential means (95%) of eGFR according tertiles of SUA in individuals at 30 and 22 years of age: adjusted regression analyses.

	eGFR (mL/min/per 1.73m^2)			
	MEN			
	30 years (N = 1746)		22 years (N = 1660)	
	Model 1	Model 2	Model 1	Model 2
	Mean (95%CI)	Mean (95%CI)	Mean (95%CI)	Mean (95% CI)
SUA (tertiles)	**p < 0.001**	**p < 0.001**	**p < 0.001**	**p < 0.001**
1st	122.3 (119.1; 125.6)	120.7 (117.7; 123.8)	120.0 (116.5; 123.5)	118.9 (115.6; 122.3)
2nd	109.2 (107.6; 110.8)	108.7 (107.2; 110.2)	114.5 (112.6; 116.5)	113.8 (111.9; 115.6)
3rd	97.3 (96.2; 98.5)	97.7 (96.7; 98.8)	108.5 (107.1; 110,0)	109.2 (107.8; 110.6)
	WOMEN			
	30 years (N = 1794)		22 years (N = 1822)	
	Model 1	Model 2	Model 1	Model 2
	Mean (95%CI)	Mean (95%CI)	Mean (95%CI)	Mean (95%CI)
SUA (tertiles)	**p < 0.001**	**p < 0.001**	**p < 0.001**	**p < 0.001**
1st	114.5 (113.1; 115.9)	113.8 (112.5; 115.1)	121.3 (120.0; 122.5)	121.1 (119.9; 122.3)
2nd	101.7 (100.2; 103.3)	102.2 (100.7; 103.6)	115.5 (113.9; 117.1)	115.0 (113.5; 116.5)
3rd	90.4 (87.8; 93.3)	93.1 (90.4; 95.8)	104.5 (102.2; 106.8)	106.4 (104.1; 108.8)

eGFR (mL/min/per 1.73 m^2): estimate glomerular filtration rate; SUA (μmol/L): serum uric acid. Regressions performed with eGFR and triglycerides on logarithmic scale and SUA concentration in tertiles. Results presented in exponential means (95%CI). P-value by the Wald's test for linear tendency. Regression analyses were adjusted according: Model 1[self reported skin color, family income, maternal pregestational body mass index (BMI), maternal smoking during pregnancy; birth weight]; Model 2 [Model 1 + systolic blood pressure, diastolic blood pressure, BMI (except for individuals at 22 years), waist circumference, glucose, total cholesterol, HDL-c, triglycerides, urea, difference of time between blood collection and last meal, harmful alcohol intake (AUDIT), smoking status, and physical activity].

Results

The present study included 3541 individuals from the 1982 cohort and 3482 from the 1993 cohort. Male participants represented 49.3% and 47.3% of the sample population from the 1982 and the 1993 cohorts, respectively.

Sample description according to demographic, perinatal and behavioral covariates at respective follow-ups is showed in Table 1. In both cohorts, most of the individuals were white and had family income at birth between 1.1 and 3.0 minimum wages. The majority of mothers of the cohort participants had normal pregestational BMI and did not smoke during pregnancy. The birth weight distribution of participants was similar between the cohorts and the larger amount of them presented birth weight between 3000−3499 g. Regarding lifestyle, more individuals have declared to be non smokers independently of sex and age. Men showed higher harmful alcohol intake and were more physically active compared to women in both ages.

Clinical characteristics of the studied sample are observed in Table 2. Prevalence of overweight and obesity were 34.7% and 23.0% in the 1982 cohort, respectively; in the 1993 cohort, it was observed 27.0% of overweight and 16.2% of obesity. Men at the age of 30 showed higher measurements of BMI, WC, DBP, TC, HDL-c, LDL-c and triglycerides than those observed in men at the age of 22. Similar pattern of results was observed among women. On the other hand, SUA levels were higher among young individuals, although mean values were inside a normal reference range (202.3−416.5 μmol/L and 142.8−339.15 μmol/L, for men and women, respectively). Men at 22-years old presented a mean SUA level equals 311.3 (±73.8) μmol/L whereas a mean level of 267.7 (±68.9) μmol/L was found in men at 30-years; in women at 22-years old, mean SUA level was 233.2 (±63.8) μmol/L whereas at the age of 30 was 185.0 (±52.3) μmol/L. Similar pattern was seen comparing SBP at the ages of 22 and 30 in men [131.6 (±12.4) mmHg *vs* 128.1 (±12.2) mmHg] and in women [116.9 (±11.0) mmHg *vs* 114.5 (±11.9) mmHg].

According to the estimative of GFR, the median (IQR) at 30-years of age was 110.8 (92.7; 121.7) mL/min/1.73 m^2, being 107.8 (90.3; 119.4) mL/min/1.73 m^2 in men and 114.9 (95.0; 123.1) mL/min/1.73 m^2 in women. A higher eGFR was found at 22-years compared to those at 30-years [122.4 (107.1; 127.7) mL/min/1.73 m^2], and lower in men [119.6 (103.7; 125.6) mL/min/1.73 m^2] than in women [124.3 (111.0; 129.2 mL/min/1.73 m^2].

Results of correlation and regression analyses of eGFR or SUA with each one of the covariates are shown as supplementary tables. Uric acid was positively associated with family income in men at both ages, but only in women at 30 years (S1). Further, an increase in family income in both sexes at 30 years was associated with lower eGFR (S3). Uric acid was also found positive and significantly correlated with cardiometabolic factors in both sexes and ages, but negatively correlated with HDL-c at 30-years old (S2). In respect to kidney function, negative and significant correlations were observed with SBP, glucose, total cholesterol, triglycerides and urea in almost all groups of individuals (S4). In respect to lifestyle, more consistent associations were observed in men at 30-years. In these individuals, harmful alcohol intake was found positively associated with SUA levels (S1) and inversely associated with eGFR (S3). Also, those classified as active

showed lower SUA levels compared to inactive individuals (S1), but no association of physical activity was found with eGFR (S4).

Focusing on the study main association, the Pearson correlation coefficients found between eGFR and SUA for men and women were the followings, respectively: −0.442 (<0.001) and −0.417 (<0.001) at 30-years; −0.315 (<0.001) and −0.367 (<0.001) at 22-years. To better explore this association we investigated eGFR means according to SUA tertiles.) In the highest tertile of SUA (3rd tertile), the crude regression coefficients for men and women at 30-years were −0.23 (−0.25;-0.20) and −0.22 (−0.25;-0.19), respectively; and at 22-years, they were −0.04 (−0.07;-0.01) for men and −0.05 (−0.07;-0.03) for women, being p-value <0.001 in all analyses. The results from adjusted analyses kept the same direction and significance as these in the crude ones (Table 3). In order to minimize difficulties of interpreting model estimates from log-transformed data we described the exponential means of eGFR according tertiles of SUA (Table 4). The means of eGFR decreased according to tertiles of SUA in men and women, at ages of 30 and 22-years, even after adjustment for demographic/perinatal covariates (model 1) or adding the cardiometabolic and behavioral covariates (model 2). The inverse association between SUA and eGFR was maintained significant in both sexes and ages. A higher eGFR mean difference between the lowest (1st) and the highest (3rd) tertile of SUA was observed for individuals at 30-years than for those at 22-years. This difference of eGFR means between tertiles of SUA (1st to 3rd), according to adjusted regression analyses (model 2), was higher among men than among women at 30-years (23.0 mL/min/per 1.73 m^2 *vs.* 20.7 mL/min/per 1.73 m^2) but lower at 22-years old, being 9.7 mL/min/per 1.73 m^2 in men and 14.7 mL/min/per 1.73 m^2 in women.

Discussion

In a cross-sectional analysis, we observed a strong and inverse association between eGFR and SUA levels in 30 and 22-years old individuals belonging to the 1982 and the 1993 Pelotas birth cohort, respectively. A lower mean of eGFR was found for those individuals who had SUA level in the highest tertile, independently of age and sex, even after adjusting for perinatal, cardiometabolic and behavioral confounders. Lower values of eGFR mean associated with SUA levels at the 3rd tertile were observed in older individuals compared to younger ones. At the same age, a lower eGFR mean associated to the highest tertile of SUA was seen in women.

A slow physiological decrease of kidney function is seen in ageing process, which is linked to cellular and organ senescence even in the absence of clinically evident comorbidities [15]. A decline in GFR of 0.75 mL/min per year was described in a longitudinal study of relatively normal men as reviewed by Hommos et al. (2017) [16]. Beyond age, main risk factors related to kidney dysfunction development have been identified from prospective studies such as: male gender, ethnicity, diabetes mellitus, hypertension, dyslipidemia, obesity and high-normal urinary albumin excretion [17]. Uric acid has been added to this list of factors since the focus on it has changed from just a marker of kidney dysfunction, but also as a disease predictor.

The mechanisms for uric acid enrolment in the kidney diseases were proposed from animal model studies which demonstrated that SUA could induce to oxidative stress and endothelial dysfunction resulting in systemic and glomerular hypertension [18]. It also could activate the renin-angiotensin system (RAS) resulting in vascular dysfunction of the afferent arteriolar system (arteriosclerosis) and glomerular hypertrophy [19]. In agreement with these, human studies showed SUA positively associated with serum renin concentration contributing to the intrarenal RAS activation [20] and with an increase in the afferent arteriolar resistance resulting in a negative correlation with GFR measured by clearance of inulin [21].

We present data showing SUA level consistent and inversely associated with eGFR in young adults without referring kidney disease. Despite the fact that our results are based on a cross-sectional analysis, they are in line with some studies which have pointed out SUA as a major predictor for the onset of CKD [22−24]. A meta-analysis of 15 cohort studies including 99,205 individuals and 3492 incident CKD cases showed that the relative risk of CKD was 1.22 (95%CI 1.16; 1.28) per 1 mg/dL SUA level increment [25]. Further, in another systematic review and meta-analysis it was observed an adjusted odds ratio (OR) for the association between elevated SUA and the development of new-onset CKD of 1.05 (95%CI, 1.02; 1.07). Although the OR was not high it was reported to be independent of sex, age, BMI, alcohol intake, smoking, hypertension, metabolic syndrome, hypertriglyceridemia, diabetes and medication [26]. The association between SUA and kidney function has also been reinforced by clinical trial studies which showed a significant decrease of Scr level and an increase of eGFR using uric acid lowering therapy [27]. Concordant results between randomized controlled trials and observational studies, but not supported by Mendelian Randomisation (MR) studies, were also showed in an umbrella review of meta-analyses [28]. According to the authors, although uric acid has an overall heritability of 40−60%, the strength of genetic instruments used in these MR studies has probably limited the power necessary to detect causal associations with CKD. The controversies concerning this association, especially related to progression of CKD or treatment of CKD patients with uric acid-lowering therapy, were more recently discussed by Johnson (2018) [6].

In the literature on Brazilian population, a significant inverse association was found between SUA and eGFR in a cross-sectional observational study including 756 non-hospitalized participants at mean age of 50 years. Those participants classified in the highest uric acid tertile showed the lowest eGFR [29]. Similar results were described in a sub-sample of 3412 apparently healthy men and women aged 40−62 years from the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) [30]. On the

other hand, in a retrospective cohort study of Brazilian office workers, including 1094 participants at 48.7 ± 8.8 years of age, no association of SUA and new-onset CKD was found when a multivariate logistic regression model was applied [1.12 (0.83−1.50)] even though a weak but significant correlation between baseline SUA and baseline eGFR was described ($r^2 = -0.21$, $p < 0.001$) [31].

Our data showed lower eGFR associated with higher SUA level in women comparing to the correspondent measurements in men at the same age. Gender differences on SUA level are well described [32]. In respect to eGFR, the results are not so clear. From direct measurement of GFR, no difference between eGFR in men and women up to the age of 50 years was observed however at ages above 50 years there is a tendency for a difference of 3.5 mL/min/1.73m2, with a faster renal decline in women than in men [33]. We described higher eGFR medians in women than those found in men from a healthy young population at 22 and 30-years of age. Differences about renal mass, sex hormones and renal hemodynamics between sexes are well known [34]. Women have fewer nephrons than men and may have less compensatory reserve [35]. On the other hand, there is a renal protection observed in women explained by estrogens which decreases the protein expression of uric acid transporters, like as URAT1 and GLUT9, decreasing its tubular reabsorption and increasing its renal excretion [36]; beyond its role on nitric oxide regulation and RAS inhibition at multiple sites [37]. As a consequence, the onset of menopause is associated with increased SUA levels [38]. In addition, the prevalence of CKD stages 3−5 in 2010 in different countries was reported to be higher in women, except for women at 20−29 years of age [39]. Therefore, at reproductive ages, woman seems to be protected against age−related kidney damage. As sexual hormone secretion declines, a decrease in the protective mechanism is suggested.

A study including 6400 individuals with normal kidney function but SUA level >480 μmol/L (8.1 mg/dL) also showed an increase for kidney failure of 2.9-fold in men and 10.0-fold in women considering a follow-up of 2 years [40]. Further, a higher prevalence of target organ damage (including renal alteration) associated with hyperuricemia and hypertension was described in women [41]. A kidney function decline was even reported at uric acid levels inside a normal range in a study from a nationwide database of 165,847 individuals aged 29−74, which participated in the annual “Specific Health Check and Guidance in Japan” between 2008 and 2010. In this study, the cutoff of SUA level was ≥261.8 μmol/L (or 4 mg/dL) for women and ≥339.2 μmol/L (or ≥ 5.7 mg/dL) for men [42]. The deleterious effect of SUA levels increase seems to appear earlier in women than men as previously demonstrated by Akasaka et al. (2014) [43]. This evidence may suggest that women need to pay more attention to the potential risks of uric acid level increasing despite of known female mechanisms of protection.

The relationship between SUA and kidney function is far complex and affected by confounding. Recognizing this complexity, we performed adjustment models in order to guarantee adequate quality of our findings. A significant individual variation in age-related GFR decrease is observed in presence of risk factors, being hypertension and diabetes main risk factors for kidney disease [44]. Also cardiometabolic risk factors related to insulin resistance, isolated or in cluster as seen in the metabolic syndrome, have been associated with CKD in different populations [45−47]. In its turn, an elevated SUA concentration is independently associated with hypertension [48,49], metabolic abnormalities [50] and obesity [51]. Furthermore an elevated SUA level often precedes the development of insulin resistance and it is independent of insulin level present in serum [52], which is an observation that cannot always be considered as a secondary phenomenon. It is noteworthy to add that relationships between SUA and cardionephrometabolic variables were also described to be gender-related [53].

Concerning lifestyle characteristics, we found a higher influence of harmful alcohol intake on SUA levels and eGFR only in men at 30 years although it was significantly associated with SUA levels in women at both ages but not with eGFR. Alcohol intake, smoking, physical activity and diet are associated with uric acid in different studies [54,55] and they may affect renal function [17,56,57], even though some studies did not confirmed this association [58,59]. It is known that men tend to have an unhealthy lifestyle when compared to women. They tend to smoke and to intake alcohol more than women. They also tend to have unhealthy diet, with a greater ingested burden of protein, calories, sodium, phosphorus and potassium per milliliter per minute [60], representing a higher burden which could accelerate kidney dysfunction.

The findings of our study need to be interpreted in light of its limitations, as follow: 1) it is a cross-sectional analysis where causality could not be evaluated; 2) the use of estimated GFR as a marker of kidney function taking into consideration the imprecision associated with creatinine-based estimated GFR; creatinine excretion rates vary with age, sex, race, conditions associated with alteration in muscle mass, physical activity, meat intake, use of protein supplements, renal secretion or degradation of creatinine and fluid balance disorders such as dehydration [12]; the direct measurement of GFR is laborious and quite expensive for large epidemiological studies whereas eGFR based on creatinine is cheaper and widely used in clinical practice; 3) the measurement of eGFR and uric acid at one point in time not allowing to analyze physiological and pathological changes over time; 4) non fasting blood is another point to consider, although it is very difficult to obtain fasting blood samples in large health cohort studies; in order to minimize this limitation we applied an adjustment using the difference between time of blood collection and time of the last meal or snack consumed. The main strengths of this study were: 1) to present data of the association between eGFR and SUA in healthy young individuals at twenties and thirties showing the same direction and significance; 2) gender-related differences in the association studied; 3) the adjusted analysis for relevant confounders related to birth and current period of

life-course; 3) a good response rate for both cohorts during the period.

Conclusions

Uric acid level was inversely associated with eGFR in healthy individuals at 22 and 30 years of age from a low-middle income country. Even in the absence of causality, serum uric acid levels should receive more attention early in adulthood life, particularly in women. To improve the understanding about modifiable risk factors which have precocious and negative influence on kidney function, could help to prevent a clinical silent disease as CKD in the future.

Ethics approval and consent to participate

The 1982 (process n°: 16/12) and 1993 (protocol n°: 1,250,366) cohorts were approved by the Research Ethics Committee of the Federal University of Pelotas and, in each visit, the participants or their legal guardians signed the Free and Informed Consent Term.

Availability of data and materials

The database can be shared by corresponding author and Pelotas Cohorts Committee upon request.

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Declaration of Competing Interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2020.04.016.

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