

Association of a Polymorphism in a Gene Encoding a Urate Transporter with CKD Progression

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Abstract

Background and objectives Hyperuricemia predicts a high risk for CKD progression but there is no large clinical trial in humans indicating that this relationship is causal in nature. The rs734553 single-nucleotide polymorphism (SNP) of the GLUT9 urate transporter gene was strongly associated with uric acid (UA) levels in a large meta-analysis.

Design, setting, participants, & measurements This prospective study adopted the Mendelian randomization approach. The rs734553 SNP was used as an instrumental variable to investigate the relationship between UA and renal outcomes in a cohort of 755 patients with CKD who were enrolled between October 18, 2005, and October 2, 2008. The association between the polymorphism and UA was preliminary confirmed in a series of 211 healthy volunteers enrolled between January 1, 2001, and July 12, 2011, from the same geographic area as the patients with CKD. The study end point was a composite renal-end point (*i.e.*, >30% decrease in the GFR, dialysis, or transplantation). Patients were followed up for a median of 36 months.

Results In healthy individuals, serum UA levels were highest in homozygotes for the T allele (risk allele), intermediate in heterozygotes for the same allele, and lowest in those without the risk allele ($P < 0.001$), but no such relationship was found in patients with CKD. In the CKD cohort, homozygotes (TT) and heterozygotes (GT) for the risk allele had a 2.35 times higher risk (hazard ratio, 2.35; 95% confidence interval, 1.25 to 4.42; $P = 0.008$) of CKD progression. The risk for CKD progression by rs734553 remained unmodified in analyses adjusting for proteinuria, GFR, and other classical and CKD-peculiar risk factors.

Conclusions A GLUT9 polymorphism, which is strongly associated with serum UA levels in healthy individuals of the general population with normal renal function, holds a strong predictive power for CKD progression. These findings are compatible with the hypothesis that the link between UA and CKD progression is causal in nature.

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Introduction

Uric acid has long been suspected as a causal risk factor for renal damage and progression to kidney failure, but definitive proof that it is causally implicated in CKD is still lacking (1). Some cohort studies reported a relationship between uric acid plasma levels and the risk of CKD progression (2–5) but such an association was negated in other follow-up studies (6,7). Small clinical trials (8–10) and experimental studies in animal models (11–13) suggest a benefit of uric acid-lowering interventions on renal disease progression. However, because of the lack of large-scale clinical trials testing the effect of these interventions on major clinical end points (*e.g.*, progression to kidney failure), it remains unresolved whether uric acid is causally implicated in CKD progression.

The inherent variability of uric acid over time is considered a plausible explanation for the inability of observational studies to capture the link between uric acid and CKD (1). Indeed, uric acid levels in CKD

depend on several factors that are not stable over time in this population, including hydration status and the use of diuretics, allopurinol, and other drugs, acid base status, and GFR loss. Therefore, prevailing uric acid levels may not reflect the true uric acid burden in CKD. The concentration of uric acid in plasma has an important genetic control (14). GLUT9 is a major, high-capacity urate transporter in the proximal nephron that exchanges both glucose and fructose for urate (15). Loss-of-function heterozygous mutations in GLUT9 severely impair urate reabsorption and determine hypouricemia, and mutated GLUT9 isoforms display markedly reduced transport activities in oocyte studies *in vitro* (16). On the other hand, a very large meta-analysis in 28,000 individuals showed that the T allele in the intronic single-nucleotide polymorphism (SNP) rs734553 of GLUT9 (17) is the strongest marker of hyperuricemia described thus far. Because genes are randomly transmitted at mating (Mendelian randomization) (18), the T allele of the

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rs734553 polymorphism of the GLUT9 gene may be applied as a surrogate of hyperuricemia to further explore the link between uric acid and renal outcomes in cohort studies. With this background in mind, we investigated the relationship between uric acid, the rs734553 polymorphism in the GLUT9 gene, and the progression toward kidney failure in a sizable cohort of patients with CKD.

Materials and Methods

The study protocol conformed with the ethical guidelines of our institution and adhered to the Declaration of Helsinki. This study was approved by the ethics committees of all participating nephrology units, and written informed consent was obtained from each study participant.

Patients with CKD

All patients with stages 2–5 CKD were consecutively recruited from 22 nephrology units in Southern Italy. Patient enrollment was performed between October 18, 2005, and October 2, 2008. All patients were in stable clinical condition and none had intercurrent infections or acute inflammatory processes. Inclusion criteria were as follows: nonacute or rapidly evolving renal diseases, age ranging from 18 to 75 years, nontransplanted, nonpregnant, and not affected by cancer or diseases in the terminal phase.

Healthy Population

To confirm the link between uric acid levels and the rs734553 polymorphism in the GLUT9 gene (17), we studied 211 consecutive normotensive volunteers (43% men) without renal disease ($GFR_{CKD-EPI} > 60$ ml/min per 1.73 m², estimated by the Chronic Kidney Disease in Epidemiology [CKD-EPI] study equation), and no proteinuria, enrolled between January 1, 2001, and July 12, 2011. None of the individuals in this group were taking drugs of any sort. These normotensive volunteers are part of a growing cohort of healthy individuals who contribute to a biobank established in our unit for comparative studies in individuals with hypertension and patients with CKD.

Study Outcomes

Patients were followed up until August 2011 (median follow-up time of 36 months; range, 1.4–48 months). The study end point was a composite renal-end point, *i.e.*, a $>30\%$ decrease in GFR (estimated by the Modification of Diet in Renal Disease [MDRD₁₈₆] study equation formula), dialysis, or transplantation.

Heart Rate, BP, and Laboratory Measurements

BP measurements were performed after a 20-minute period of quiet resting in a semi-recumbent position immediately before blood sampling. Blood sampling was performed after 20–30 minutes of quiet resting in a semi-recumbent position, and plasma was stored at -80°C until analysis. Serum creatinine, lipids, albumin, calcium, and hemoglobin were measured by standard methods in the routine clinical laboratory. Serum C-reactive protein (CRP) was measured by a high-sensitivity commercially available RIA kit (intra-assay and interassay coefficients of variation, 3.5% and 3.4%, respectively; Dade Behring, Inc., Marburg, Germany). All patients with CKD also

underwent a 24-hour urine collection for the measurement of proteinuria.

Genotyping of the GLUT9 Gene Polymorphism

Genomic DNA was extracted from peripheral blood leukocytes by the salting-out technique. The participants were genotyped for the rs734553 GLUT9 polymorphism, studied by a validated TaqMan SNP genotyping assay. SNP genotyping was performed by an ABI PRISM 7900HT sequence detection system according to the manufacturer's recommendations (Life Technologies, Carlsbad, CA). The assay mix (including unlabeled PCR primers, and FAM and VIC dye-labeled TaqMan MGB probes) was designed by Life Technologies. The reaction system contained 1–5 ng of genomic DNA, 12.5 μl of TaqMan Universal PCR Master Mix, $2\times$ No AmpErase UNG, and 1.25 μl 40 \times Assay Mix and was adjusted with H₂O for a total volume of 25 μl . Alleles were scored using allelic discrimination software (Sequence Detection System, version 2.2; Life Technologies). A random 5% of samples were independently repeated to confirm genotyping results. The genotype results for these samples were completely consistent.

Statistical Analyses

Data are expressed as the mean \pm SD, median (interquartile range [IQR]), or percent frequency. Comparisons between two groups were made by the *t* test, Mann–Whitney test, or chi-squared test, as appropriate. Comparisons among more than two groups were made by *P* for trend.

The relationship between GLUT9 SNP and the incidence rate of renal events was investigated by Kaplan–Meier survival curves and univariate and multivariate Cox regression analyses. As potential confounders (hierarchical model), we considered traditional risk factors (age, sex, smoking, diabetes, cholesterol, BP), uric acid, body mass index, antihypertensive and allopurinol treatment, factors peculiar to CKD (hemoglobin, albumin, phosphate, urinary protein, and eGFR), and other emerging risk factors in this population (CRP). The internal validation of study results was carried out by a bootstrapping resampling technique (19).

Data analysis was performed by commercially available statistical software including SPSS for Windows (version 9; SPSS, Inc., Chicago, IL) and STATA 9 (StataCorp LP, College Station, TX).

Results

The cohort of CKD patients was extracted from a total population of 826 patients with stages 3 and 4 CKD. Among these, 34 patients were lost to observation after the baseline visit, 33 were erroneously enrolled (*i.e.*, had a $GFR > 60$ ml/min per 1.73 m²), and 4 did not have available DNA samples. Thus, 755 patients with stages 2–5 CKD were included in this analysis. Their mean age was 61 ± 11 years, average eGFR (eGFR₁₈₆) was 36 ± 13 ml/min per 1.73 m², and the median proteinuria was 0.6 g/24 h (IQR, 0.2–1.5 g/24 h). Sixty percent of participants were men, 50% were smokers, and 35% were patients with diabetes. Overall, 237 patients (31%) had background cardiovascular comorbidities. There were 691 patients (91%) who were taking antihypertensive treatment: 144 patients were receiving monotherapy with angiotensin converting enzyme inhibitors, AT-1 antagonists, diuretics,

calcium antagonists, and sympatholytic agents, whereas the remaining 547 patients were receiving double ($n=217$), triple ($n=208$), or more than triple ($n=122$) therapy with various combinations of these drugs. Of 755 patients, 38 (5%) had a clinical diagnosis of gout. There were 320 patients (42%) who were receiving treatment with allopurinol. The main demographic, clinical, and biochemical characteristics of the CKD population are summarized in Table 1. In patients with CKD, uric acid levels were directly associated with male sex ($r=0.09$, $P=0.01$), body mass index ($r=0.13$, $P=0.001$), triglycerides ($r=0.11$, $P=0.004$), phosphate ($r=0.14$, $P<0.001$), and high-sensitivity CRP ($r=0.09$, $P=0.02$), and were inversely associated with $GFR_{MDRD186}$ ($r=-0.16$, $P<0.001$) and HDL cholesterol ($r=-0.09$, $P=0.02$).

Correlates of GLUT9 SNP in Patients with CKD

In patients with CKD, the polymorphism frequency distribution (rs734553, GG: 8.1%; GT: 35.4%; TT: 56.6%) slightly deviated from Hardy–Weinberg equilibrium ($\chi^2=4.30$, $P=0.04$), whereas this was not true in healthy normotensive individuals (rs734553, GG: 8.0%; GT: 47.0%; TT: 47.0%) ($\chi^2=1.15$, $P=0.28$). In patients with CKD, 24-hour urinary protein excretion was more than 2 times higher ($P=0.01$) in homozygotes and heterozygotes (GT+TT) (0.7 g/24 h; IQR, 0.2–1.4) for the T allele compared with patients without such an allele (GG) (0.3 g/24 h; IQR, 0.1–1.10) (Table 1). With the exception of smoking, no difference for demographic, clinical, and biochemical risk factors was found between GG and GT/TT CKD patients (Table 1).

Healthy Population

In healthy Caucasian individuals of the general population in the same geographic area as the patients with CKD (Table 2), uric acid was higher ($P=0.02$) in those with at least one T allele. Further testing by a codominant model showed a dose-response relationship between the number of T alleles and uric acid levels ($P<0.001$) (Figure 1).

Kidney Disease Progression in the CKD Cohort

During the follow-up period (mean 29 ± 11 months; range, 1.4–47.0 months), 244 patients had renal events. In a Kaplan–Meier analysis, the incidence rate of renal outcomes was significantly higher in patients with GT and TT genotypes compared with patients with the GG genotype (Figure 2). Therefore, patients harboring the T allele had a hazard ratio (HR) for renal events that was approximately 2 times higher (HR, 2.35; 95% confidence interval [95% CI], 1.25 to 4.42; $P=0.01$) than the HR in patients without this allele (HR, 1; reference group). The association between the GLUT9 polymorphism and renal outcomes also remained significant (Table 3) in a multiple Cox regression model adjusting for traditional and non-traditional risk factors. Such an association was unmodified in a bootstrapping validated model confirming the high internal validity of the same association (Table 3, last column).

In contrast with the GLUT9 polymorphism, circulating levels of uric acid largely failed to predict renal events HR (1 g/dl): 1.01; 95% CI, 0.94–1.09; $P=0.72$.

Table 1. Main clinical and biochemical data of the study population (stages 2–5 CKD)

Characteristic	Whole Group (N=755)	GLUT9		P Value
		GG (n=61)	GT+TT (n=694)	
Age (yr)	62±11	61±11	62±11	0.56
Men	60	54	61	0.33
Smoker	50	34	51	0.01
Diabetes	35	31	35	0.51
With cardiovascular comorbidities	31	26	32	0.36
On antihypertensive treatment	97	94	97	0.33
On treatment with allopurinol	42	38	43	0.44
Body mass index (kg/m ²)	28±5	27.6±3.8	28.2±4.7	0.26
Systolic BP (mmHg)	134±18	133±16	134±18	0.60
Diastolic BP (mmHg)	78±11	77±9	78±11	0.80
Heart rate (beats/min)	72±10	71±12	72±9	0.40
Cholesterol (mg/dl)	187±45	179±49	187±44	0.20
HDL cholesterol (mg/dl)	50±17	49±14	50±17	0.49
LDL cholesterol (mg/dl)	112±42	109±47	112±42	0.62
Triglycerides (mg/dl)	152±80	162±80	151±80	0.33
Hemoglobin (g/dl)	12.8±1.8	12.7±1.6	13.0±1.8	0.48
Albumin (g/dl)	4.2±0.5	4.2±0.4	4.2±0.5	0.95
Phosphate (mg/dl)	3.73±0.78	3.63±0.86	3.73±0.77	0.35
High-sensitivity C-reactive protein (mg/dl)	2.4 (1.0–5.5)	1.9 (0.7–5.3)	2.4 (1.1–5.4)	0.19
Uric acid (mg/dl)	6.7±1.8	6.5±1.6	6.7±1.8	0.30
$GFR_{MDRD186}$ (ml/min per 1.73 m ²)	36±13	37±15	36±13	0.39
Urinary protein (mg/24 h)	0.6 (0.2–1.5)	0.3 (0.1–1.1)	0.7 (0.2–1.4)	0.01

Data are expressed as mean±SD, median (interquartile range), or percent frequency, as appropriate. $GFR_{MDRD186}$, GFR measured by the Modification of Diet in Renal Disease study formula.

Table 2. Main clinical and biochemical data of the healthy normotensive population (n=211)

Characteristic	GLUT9			P Value
	GG (n=17)	GT (n=97)	TT (n=97)	
Age (yr)	44±16	35±14	40±16	0.51
Men	7 (41)	44 (45)	40 (41)	0.74
Smoker	5 (29)	23 (24)	19 (20)	0.34
Diabetes	2 (12)	3 (3)	6 (6)	0.94
BMI (kg/m ²)	28±8	26±5	27±5	0.63
Cholesterol (mg/dl)	164±35	168±35	175±36	0.11
Triglycerides (mg/dl)	116±89	85±42	92±54	0.52
Uric acid (mg/dl)	4.10±1.49	4.46±1.34	4.92±1.40	<0.001

Data are expressed as mean±SD or n (%). BMI, body mass index.

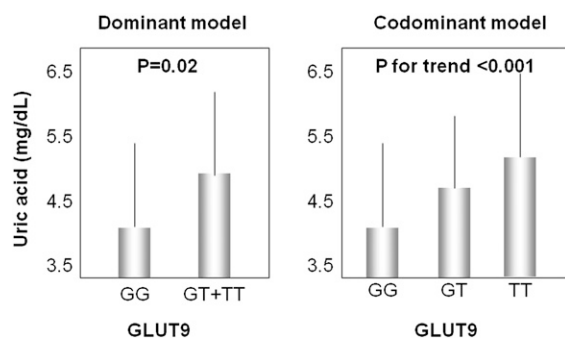


Figure 1. | Uric acid levels and GLUT9 genotypes divided according to dominant and codominant models in healthy individuals. Data are expressed as mean (and SD) and P value.

Discussion

This study shows that a polymorphism in the GLUT9 gene, a major genetic regulator of serum acid levels, predicted renal outcomes in patients with stages 2–5 CKD, while no such relationship was found with uric acid levels.

Uric acid has long been suspected as a risk factor for renal damage (1,20) and hyperuricemia has been associated with a variety of adverse renal outcomes, including the incident risk for CKD in the general population (5,21–26), progression of renal insufficiency in patients with pre-existing CKD (2) or IgA nephropathy (5), or the risk of diabetic nephropathy in patients with type 1 diabetes (27) or with albuminuria in type 2 diabetes (28). However, other studies in CKD failed to confirm (6,7) the relationship between renal function decline and uric acid in patients with CKD. Importantly, in the MDRD study (29), which applied a state-of-the-art measurement of the GFR (iothalamate clearance), no association was found between uric acid levels and the rate of renal function loss over time. The effect of uric acid lowering with allopurinol has been tested in a limited number of clinical trials. A favorable effect of allopurinol was reported in a short-term, uncontrolled study in patients with asymptomatic hyperuricemia (8) and in two small randomized trials (9,10) in patients with CKD. To date, no large-scale clinical trial has tested whether uric acid level lowering may affect relevant kidney outcomes in patients with CKD.

Uric acid is mainly excreted by the kidney (70%) and a minor fraction is eliminated by the intestinal route. Urate transporters, particularly GLUT9, are key players in the renal handling of this anion. GLUT9, a major determinant of serum uric acid, has two alternatively spliced variants. GLUT9a, encoded by 12 exons, is a 540 amino acid protein, whereas GLUT9b, encoded by 13 exons, includes 512 amino acids. In humans, GLUT9b expression is restricted to the liver and kidney, whereas GLUT9a has a broad tissue distribution including the liver, kidney, intestine, leukocytes, and chondrocytes. This transporter is required for hepatic uric acid uptake, and elective inactivation of the gene coding for the same transporter in mice liver induces severe hyperuricemia (30). In the kidney, GLUT9 has a major influence on uric acid reabsorption (15). Indeed, loss-of-function mutations in GLUT9 severely impair urate reabsorption *in vitro* and determine marked hypouricemia *in vivo* in humans (16). On the other hand, various polymorphisms in the GLUT9 gene have been linked with altered serum uric acid levels in humans. The T allele of the rs734553 polymorphism was the genetic variant that was most consistently associated with hyperuricemia ($P=10^{-201}$) in a large meta-analysis including >28,000 participants encompassing individuals in the general population and patients with hypertension and metabolic syndrome (17). Because transmission of the allele responsible for hyperuricemia (the T allele) occurs randomly at mating (Mendelian randomization), this genetic polymorphism may be useful for testing the hypothesis that hyperuricemia is causally implicated in CKD progression. This approach has already been applied for testing the link between uric acid and BP (31). As in the above-mentioned meta-analysis (17), the T allele of GLUT9 gene was strongly and dose dependently associated with serum acid levels in healthy individuals of the general population in our study. Although the link of such an allele with uric acid levels is very robust, the mechanistic implication of this finding in the renal handling of uric acid has not been investigated as yet. This SNP may underlie a gain of function in urate transport favoring tubular reabsorption of this anion, or this polymorphism itself may not be the cause of hyperuricemia but may simply be a marker of an effect mediated by another gene in linkage disequilibrium with the rs734553 polymorphism and/or this polymorphism

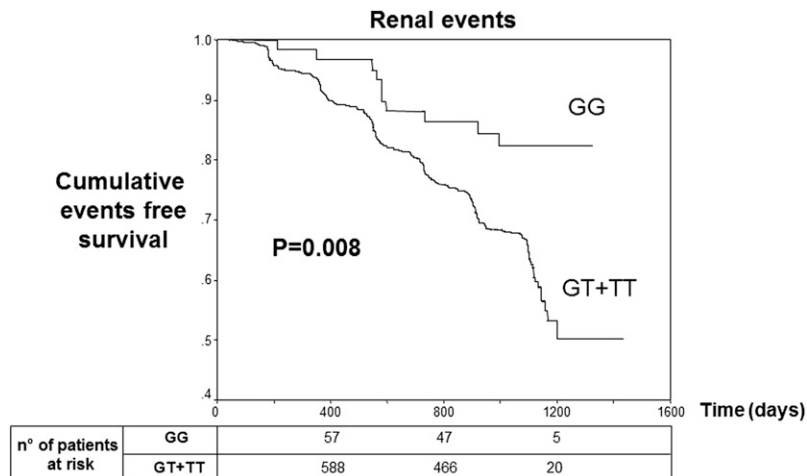


Figure 2. | Cumulative events-free survival (Kaplan–Meyer curves) for renal events in GG and GT+TT patients. The comparison between the two groups was made by the log-rank test. The table under the x axis indicates the number of patients at risk at relevant time points.

may predict adverse renal outcomes by other still unknown pathomechanism(s).

In contrast with findings in the general population, we did not detect any relationship between the T allele and serum acid levels in patients with CKD of a moderate to severe degree, a phenomenon suggesting that the link between uric acid levels and renal outcomes may be confounded by environmental factors such as reduced renal function, drug treatment, and other factors in this population. Thus, our findings are compatible with the hypothesis that long-term exposure to high uric acid (a predictable consequence of the rs734553 polymorphism) may accelerate CKD progression. Notably, no such link emerged when the analysis was run by testing uric acid levels rather than the rs734553 polymorphism. In this respect, our data may help to explain why some studies apparently negated that hyperuricemia may trigger and/or aggravate renal diseases. Our observation that the presence of the T allele also associated with proteinuria accords with the observation that hyperuricemia induced by oxonic acid in the remnant kidney model in the rat produces tubule-interstitial damage and augments proteinuria in this model (11).

The T allele is a quite common gene variant (prevalence of about 70%) in Caucasians; therefore, individuals harboring this variant might have had a survival advantage during the evolution of humankind. Of note, the distribution of this allele in our CKD cohort deviated from the Hardy–Weinberg equilibrium, further suggesting that this variant may be in the causative pathway leading to CKD progression (32). The T allele is not unique in being a common allele predicting adverse renal outcomes. For example, the APOL1 gene variant predisposing to a high risk of CKD progression in African Americans (*i.e.*, a variant that also confers resistance to lethal *Trypanosoma brucei* infections) has a 70% prevalence in this population (33). A given polymorphism may favor survival in a given high-risk environmental context but may turn out to be biologically dangerous in other, low-risk environmental contexts. It has to be noted that 42% of patients participating into this study were receiving allopurinol treatment. Notwithstanding the lack of

clinical trials supporting the use of allopurinol in CKD, most nephrologists in Italy prescribe this drug in asymptomatic hyperuricemia. This habit is not unique to Italian nephrologists or specific to our cohort. Indeed, in a cohort enrolling patients with CKD in central Europe (the Mild-to-Moderate Kidney Disease study), the proportion of patients treated with allopurinol was 30% (6). Such a high proportion is also common in other observation studies in European cohorts. Treatment with allopurinol was equally distributed across genotypes and did not influence the study outcomes.

Our study has limitations. Our sample size was not large. It was remarked that very large studies are needed to test the association between genetic polymorphisms and clinical outcomes. Additional limitations are the lack of data on urinary excretion of uric acid and of repeated measurements of serum uric acid and other variables. Furthermore, we cannot exclude residual confounding by unmeasured variables in the analyses based on serum uric acid data. A strength of our study is that it had a strong *a priori* rationale, and the polymorphism we used as an instrumental variable was consistently associated with uric acid levels in a large meta-analysis (17) and we once again replicated this association in healthy normotensive individuals of our geographic area. Furthermore, as demonstrated by bootstrap modeling, our findings had high internal validity. To note, our cohort was composed of patients of Caucasian descent only. Thus, our findings remain to be confirmed in other cohorts. Finally, although Mendelian randomization studies are useful for exploring putative causal associations, these studies in no way constitute definitive proof of causality. Appropriate clinical trials are needed to conclusively demonstrate that reducing uric acid levels may improve renal outcomes in patients with CKD.

In summary, a GLUT9 genetic variant predicts renal outcomes in patients with CKD. Our Mendelian randomization approach would support the interpretation that hyperuricemia may accelerate renal function loss in CKD. Functional studies aimed at elucidating the mechanism

Table 3. Univariate and multiple Cox regression models of GLUT9 polymorphism for explaining the incidence rate of renal events

Variable (Unit of Increase)	Fully Adjusted Analysis					
	Crude		Standard Model		Bootstrapping Validated Model	
	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
GLUT9 polymorphism ^a	2.35 (1.25 to 4.42)	0.008	2.17 (1.14 to 4.11)	0.02	2.17 (1.24 to 5.29)	0.02
Age (yr)			1.00 (0.98 to 1.01)	0.66	1.00 (0.98 to 1.01)	0.70
Men			1.04 (0.74 to 1.48)	0.81	1.04 (0.71 to 1.51)	0.81
Smoking ^b			1.23 (0.90 to 1.68)	0.19	1.23 (0.93 to 1.74)	0.21
Diabetes ^b			0.95 (0.69 to 1.30)	0.73	0.95 (0.67 to 1.33)	0.74
Cholesterol (1 g/dl)			1.00 (0.99 to 1.01)	0.59	1.00 (0.99 to 1.01)	0.59
Systolic BP (5 mmHg)			1.04 (1.01 to 1.07)	0.04	1.04 (0.99 to 1.08)	0.07
Antihypertensive treatment ^b			1.34 (0.49 to 3.64)	0.57	1.34 (0.52 to 6.12)	0.59
Body mass index (1 kg/m ²)			0.99 (0.96 to 1.02)	0.37	0.99 (0.95 to 1.02)	0.35
Hemoglobin (1 g/dl)			0.93 (0.85 to 1.02)	0.10	0.93 (0.84 to 1.02)	0.12
Albumin (1 g/dl)			0.65 (0.48 to 0.90)	0.01	0.65 (0.43 to 0.89)	0.02
Phosphate (1 mg/dl)			1.12 (0.94 to 1.33)	0.22	1.12 (0.91 to 1.38)	0.31
C-reactive protein (1 mg/L)			0.99 (0.98 to 1.00)	0.18	0.99 (0.97 to 1.00)	0.14
Uric acid (1 g/dl)			0.96 (0.89 to 1.03)	0.21	0.96 (0.89 to 1.03)	0.24
Urinary protein (1 g/24 h)			1.22 (1.14 to 1.31)	<0.001	1.22 (1.13 to 1.40)	0.001
Treatment with allopurinol ^b			0.98 (0.75 to 1.28)	0.88	0.98 (0.74 to 1.31)	0.89
eGFR _{MDRD186} (1 ml/min per 1.73 m ²)			0.96 (0.95 to 0.97)	<0.001	0.96 (0.94 to 0.97)	0.001

Data are expressed as the HR (95% confidence intervals) and *P* values. The bootstrapping validated 95% CIs are also given (see the Materials and Methods for more details about bootstrapping validation). 95% CI, 95% confidence interval; HR, hazard ratio.

^a0=GG; 1=GT+TT.

^b0=no; 1=yes.

whereby the rs734553 polymorphism affects the renal handling of urate may provide important clues to understand the interference of this anion with health outcomes, including CKD progression.

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Disclosures

None.

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