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Elevated serum uric acid level predicts rapid decline in kidney function

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Abstract

Background—While elevated serum uric acid level (SUA) is a recognized risk factor for chronic kidney disease (CKD), it remains unclear whether change in SUA is independently associated with change in estimated glomerular filtration rate (eGFR) over time. Accordingly, we examined the longitudinal associations between change in SUA and change in eGFR over 5-years in a general Japanese population.

Methods—This was a large, single-center, retrospective 5-year cohort study at St. Luke's International Hospital, Tokyo, Japan, between 2004 and 2009. We included 13,070 subjects (30–85 years) in our analyses whose data were available at 2004 and 2009. Of those, we excluded 492 subjects with eGFR <60 mL/min/1.73m² at baseline. In addition to examining the entire cohort (n=12,578), we stratified our analyses by baseline eGFR groups; 60–90 mL/min/1.73m², 90–120 mL/min/1.73m², and 120 mL/min/1.73m². Linear and logistic regressions models were applied to examine the relationships between baseline and change in SUA, change in eGFR and rapid eGFR decline (defined as the highest quantile of change in eGFR), adjusted for age, sex, body mass index, abdominal circumference, hypertension, dyslipidemia, and diabetes mellitus.

Results—After multivariable adjustments including baseline eGFR, 1 mg/dL increase in baseline SUA was associated with greater odds of developing rapid eGFR decline (OR: 1.27, 95% CI: 1.17–1.38), and 1 mg/dL increase in SUA over 5-years was associated with 3.77-fold greater odds of rapid eGFR decline (OR: 3.77, 95% CI: 3.35–4.26).

Conclusions—Elevated baseline SUA and increasing SUA over time were independent risk factors for rapid eGFR decline over 5-years.

Keywords

Uric acid; Epidemiology; risk factors; chronic kidney failure

Introduction

Serum uric acid level (SUA) is associated with cardiovascular diseases (CVD).[1,2] Elevated SUA is an independent risk factor for hypertension and chronic kidney disease (CKD)[3], and SUA is also a strong predictor of development of diabetic kidney disease.[4,5] Early progressive decline in estimated glomerular filtration rate (eGFR) is associated with greater risk of macrovascular complications.[6] CKD remains a leading risk factor for CVD and all-cause mortality.[7,8] In normal physiology, GFR declines with aging by approximately 1 mL/min/1.73m² annually.[9,10] Rapid GFR decline, an early and progressive decline in GFR, is thought to be an early marker of progressive kidney disease, and has also been shown to be associated with CVD and all-cause mortality.[10] It remains unclear what initiates rapid GFR decline.

The mechanisms responsible for the association between SUA and kidney disease are not well understood. Possible mechanisms include inflammation, production of reactive oxygen species, activation of renin–angiotensin–aldosterone system (RAAS) and direct effects on intrarenal hemodynamics.[10] SUA may also directly affect the glomerular hemodynamic profile of patients.[11] Transient uricosuria with crystal formation in subjects with hyperuricemia may also be a potential mechanism for tubular injury with retrograde glomerular disease. [12]

In this study, we examined the relationships between baseline SUA, change in SUA and rapid eGFR decline over 5-years in Japanese adults. We hypothesized that greater baseline SUA and increase in SUA over time would be associated with greater odds of rapid eGFR decline, independent of other risk factors of CKD.

Materials and methods

Study design and study subjects

This study was a large, single-center, retrospective cohort study. We used the database at St. Luke's International Hospital Center for Preventive Medicine, Tokyo, Japan. We analyzed the medical records of study subjects who underwent annual medical examination at the hospital both 2004 and 2009. When the study subjects had more than one annual exam, we only used the first examination of that year to avoid double counts. While the general public had free access to the center, the cost of these medical examinations was covered by the participating subjects or their respective employers. Every subject had a general work-up, including taking current and past medical history, measuring vital signs, and performing a physical exam, having blood tests, respiratory evaluation, electrocardiogram, and chest X-ray performed. A few studies have been published from this database.[13–15] For our

analyses, we included only subjects between 30 and 85 years of age and excluded subjects with CKD (eGFR <60 mL/min/1.73m²) at baseline exam (2004).

We evaluated the change of eGFR over 5 years, and stratified study subjects into quartile of change in eGFR. We compared the highest (4th) quartile of change in eGFR (defined as rapid eGFR decline) with the lowest (1st) quartile of change in eGFR to investigate which risk factors were associated with greater change in eGFR over time. Moreover, we stratified the study subjects into three groups by their baseline eGFR: 60–90 mL/min/1.73m², 90–120 mL/min/1.73m², and 120 mL/min/1.73m² as eGFR measurements could be less accurate at high eGFR ranges. Furthermore, because the distribution of SUA differed between male and female, regression analyses were also stratified by sex. We also checked the correlation between change in SUA and change in eGFR over 5 years.

Definition of rapid eGFR decline, chronic kidney disease, hypertension, diabetes, and dyslipidemia

GFR was calculated using the Japanese GFR equation: $\text{eGFR (mL/min/1.73m}^2\text{)} = 194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287} (\times 0.739 \text{ if female})$. [16] Rather than arbitrary defining rapid eGFR decline as >3 mL/min/1.73m²/year, we defined rapid eGFR decline as the highest quartile of eGFR observed over 5-years in this study. Hypertension was defined as being on antihypertensive medication and/or systolic blood pressure (BP) of 140 mmHg and/or diastolic BP of 90 mmHg according to the Japanese Society of Hypertension guidelines (JSH 2014). [17] BP readings were obtained using an automatic brachial sphygmomanometer. Diabetes mellitus status was defined by current history of diabetes mellitus and/or HbA1c (National Glycohemoglobin Standardization Program (NGSP)) of 6.5% according to International Expert Committee. [18]. Dyslipidemia was defined by current medication for dyslipidemia and/or whose low-density lipoprotein cholesterol (LDL-C) 140 mg/dL, high-density lipoprotein cholesterol (HDL-C) < 40 mg/dL, and/or triglyceride 150 mg/dL according to Japan Atherosclerosis Society guidelines. [19]

Statistical analysis

Statistical analyses were performed using the SPSS Statistics software (IBM SPSS Statistics version 22 for Windows; IBM, New York). The statistically significant level was set as $\alpha = 0.05$, and all statistical analyses were two-sided. Data are expressed as mean $\pm$ standard derivation (SD) or as percent frequency, unless otherwise specified. Comparisons between two groups were performed with *t*-tests for normally distributed variables and χ^2 analyses for categorical data. Comparisons among four groups (quartile of change in eGFR) were performed by one-way analysis of variance (ANOVA) with Tukey's post hoc method. The risk factor for rapid eGFR decline was evaluated by univariable and multivariable logistic regression models; between the lowest (1st) quartile and highest (4th) quartile of change in eGFR. Multivariable logistic regression models included the following covariates: age, sex, BMI, smoking status, hypertension, diabetes mellitus status, dyslipidemia, baseline eGFR, baseline SUA, and change in SUA. The correlations between change in SUA and change in eGFR over 5-years were investigated by Pearson's correlation. We analyzed the odds ratios (ORs) of developing rapid eGFR decline in each quartile with the lowest quartile as the reference group. Due to sex-difference in SUA distribution, we also stratified our

multivariable regression analyses by sex. These logistic regression analyses were also adjusted for age, BMI, smoking habits, hypertension, diabetes mellitus status, dyslipidemia, and baseline eGFR,

Ethical considerations

All data were collected and compiled in a protected computer database. Individual data were anonymized without identifiable personal information. St. Luke's International Hospital Ethics Committee approved the protocol for this study. Informed consent was obtained from all the subjects by comprehensive agreement method in the hospital.

Results

Study characteristics

There were 13,201 subjects who underwent annual medical examination at the hospital both in 2004 and in 2009. We excluded 121 subjects who were younger than 30 years of age and 10 subjects who were older than 85 years old in 2004. Of 13,070 subjects between 30 and 85 years of age in 2004, we excluded an additional 492 subjects with CKD (eGFR <60 mL/min/1.73m²) in 2004. Consequently, 12,578 subjects were included in the analyses of this study. Study subjects' demographic data are shown in Table 1.

Risk factors for rapid eGFR decline

In this study subjects, the baseline (2004) eGFR was 86.7±14.8 mL/min/1.73m² (male: 84.3±14.1 mL/min/1.73m², female: 89.0±15.0 mL/min/1.73m²) and follow-up (2009) eGFR was 71.2±11.6 mL/min/1.73m² (male: 70.1±11.4 mL/min/1.73m², female: 72.1±11.8 mL/min/1.73m²) (Table 1). The quartiles of change in eGFR over 5 years included 3,145 subjects in 1st quartile (eGFR change < 9.57 mL/min/1.73m²), 3,144 subjects in 2nd quartile (9.57–14.83 mL/min/1.73m²), 3,145 subjects in 3rd quartile (14.83–20.56 mL/min/1.73m²), and 3,144 subjects in 4th quartile (20.56–25.83 mL/min/1.73m² eGFR change) (Figure 1). Subjects in the rapid eGFR decline group (4th quartile group) tended to be female, younger, with lower BMI, non-smokers with less dyslipidemia, lower baseline SUA levels, and higher baseline eGFR.

After multivariable adjustments, the risk factors of rapid eGFR decline were aging [OR per 1 year increase: 1.04; 95% confidence interval (CI), 1.03–1.04], female sex, hypertension, dyslipidemia, higher baseline eGFR, higher baseline SUA (OR per 1 mg/dL increase: 1.27, 95% CI: 1.17–1.38), and increase in change in SUA (OR per 1 mg/dL increase: 3.77, 95% CI: 3.35–4.26) (Table 2). Of note, diabetes mellitus status was not associated with greater odds of rapid eGFR decline (Table 2). Furthermore, excluding the 4.3% of participants with diabetes mellitus from the analyses did not attenuate the significance of the multivariable models (baseline SUA: OR 1.28, 95% CI 1.17–1.39, p<0.001, change in SUA: OR 3.76, 95% CI 3.32–4.25, p<0.001).

Stratifying the 12,578 subjects in three groups by their baseline eGFR, 7,914 subjects had eGFR from 60–90 mL/min/1.73m², 4,336 subjects with 90–120 mL/min/1.73m², and 328 subjects with >120 mL/min/1.73m². We examined each subgroup by their quartiles of

change in eGFR (Supplement 1). After multivariable adjustments, the risk factors of rapid eGFR decline in the group whose baseline eGFR was 60–90 mL/min/1.73m² were identical to the entire cohort; aging, female, hypertension, dyslipidemia, high baseline eGFR, high baseline SUA (OR per 1 mg/dL increase: 1.31; 95% CI, 1.22–1.40), and increased in change in SUA (OR per 1 mg/dL increase: 3.70; 95% CI, 3.32–4.11) (Supplement 2a - adjusted). The risk factors of rapid eGFR decline in the group whose baseline eGFR was 90–120 mL/min/1.73m² were aging, female, high baseline eGFR, high baseline SUA (OR per 1 mg/dL increase: 1.31, 95% CI: 1.17–1.47), and increased in change in SUA (OR per 1 mg/dL increase: 3.48, 95% CI: 3.02–4.25) (Supplement 2b - adjusted). In this group, hypertension and dyslipidemia were not significantly independent risk factors for rapid eGFR decline. The risk factors of rapid eGFR decline in the group whose baseline eGFR was 120 mL/min/1.73m² were female, dyslipidemia, high baseline eGFR, high baseline SUA (OR per 1 mg/dL increase: 1.83, 95% CI: 1.08–3.11), and increased in change in SUA (OR per 1 mg/dL increase: 5.93, 95% CI: 2.87–12.28) (Supplement 2c - adjusted). In this group, aging and hypertension were not independent risk factors for rapid eGFR decline, which were different from the entire cohort. Analyses in all subgroups demonstrated that increased baseline SUA and increase in SUA over time were strong risk factor for rapid eGFR decline, as well as female sex and high baseline eGFR.

Quartiles of SUA and rapid eGFR decline

Compared with the subjects in the lowest (1st) SUA quartile, those in the highest (4th) quartile had significantly greater odds (OR: 2.24; 95% CI, 1.66–3.02) of rapid eGFR decline after multivariable adjustments (Table 3). We calculated each SUA quartile for males and females to account for sex differences in SUA distribution. In male subjects, the subjects in the highest SUA quartile had 2.31-fold higher odds (95% CI, 1.62–3.30) of rapid eGFR decline compared to those in the lowest SUA quartile. In female subjects, the highest SUA quartile had 1.80-fold higher odds of rapid eGFR decline (95% CI, 1.28–2.55) compared to those in the lowest SUA quartile. Increased change SUA over 5 years was associated with greater odds of rapid eGFR decline both in male (OR per 1 mg/dL increase: 2.94, 95% CI: 2.53–3.43) and female (OR: 5.50, 95% CI: 4.53–6.68) (Table 3, **Male and Female**).

Correlations between change in SUA and change in eGFR over 5 years

Change in SUA was inversely correlated with change in eGFR over 5 years ($r = -0.305$, $p < 0.001$). In a linear regression model, a 1 mg/dL increase in SUA over 5 years was associated with an additional 3.59 mL/min/1.73m² decrease in eGFR over the mean 15.74 mL/min/1.73m² decrease in eGFR (Figure 2).

Discussion

In this study, baseline SUA and rise in SUA over time were independent risk factors for rapid eGFR decline along with aging, female sex, hypertension, dyslipidemia, and high baseline eGFR. The most important observation in this study was that not only baseline SUA, but also a rise in SUA was independently associated with greater odds of rapid eGFR decline. While increasing SUA over time could be partially attributed to the expected annual loss in GFR, mean SUA levels in all study subjects decreased from 5.30±1.38 to 5.25±1.32

mg/dL over 5 years, and mean eGFR decreased from 86.7 ± 14.8 to 71.2 ± 11.6 mL/min/ 1.73m^2 over 5 years. The observations that both mean SUA and eGFR declined over time suggest that the fall in GFR did not independently result in an increase in SUA in the subjects without CKD. In addition, we repeated our analyses in subgroups with different baseline eGFR, and both baseline SUA and rise in SUA over time were independent risk factors for rapid eGFR decline in all groups. Furthermore, analyses excluding the 4.3% of the participants with diabetes mellitus did not attenuate the measures of associations between baseline SUA and change in SUA and rapid eGFR decline.

As expected, aging, female sex, hypertension, dyslipidemia were associated with rapid eGFR decline. Iseki et al showed hyperuricemia in female was associated with a stronger risk for kidney diseases than compared to male.[20] Domrongkitchaiporn et al showed systolic hypertension, hyperuricemia (>6.29 mg/dl), elevated body mass index (>24.9 kg/ m^2) were independent risk factor for developing CKD.[21] Furthermore, multiple studies showed that higher level of baseline SUA were independent risk factors for incident CKD.[22–26] A recent study demonstrated that higher SUA levels were associated with developing CKD and experiencing greater eGFR decline over time.[27] Moreover, higher baseline SUA level was related to GFR decline and mortality in female.[28] These results are consistent with the observations of our study, but the novel finding of our study is the independent association between rise in SUA over time and rapid eGFR decline, which appears to be independent of the predicted age-related eGFR decline.

As seen in Table 1, the fastest declining eGFR group (4th quartile) had the lowest baseline SUA levels. However, after multivariable adjustments, higher baseline SUA became a risk factor for rapid eGFR decline. These observations suggested that the increased risk of rapid eGFR decline associated with hyperuricemia may relate to the underlying comorbidities, such as BMI, hypertension, dyslipidemia and baseline eGFR. While our findings support SUA as an important biomarker for rapid eGFR decline, the study is unable to evaluate whether high SUA concentrations play a causal role in the development of CKD. Our longitudinal study (with two measures for each subject) is also subject to random error and therefore our findings could be partially explained by regression to the mean.

Hyperuricemia plays pivotal role in the initiation and progression of kidney disease.[29] One proposed mechanism is the inappropriate renin-angiotensin-aldosterone system (RAAS) activation under hyperuricemic conditions, which was uric acid crystal-independent mechanism.[30] Furthermore, uric acid upregulates the cellular expression of angiotensinogen, angiotensin-converting enzyme and angiotensin II receptors.[31] Activated RAAS leads to glomerular hyper-filtration through an imbalance of vasoconstriction between afferent and efferent arteries, and may lead ultimately to glomerular sclerosis. Another possible contributing pathway is uric-acid mediated inflammation from the course of uric acid production. Hyperuricemia is recognized to cause inflammation of human vascular smooth muscle cells and endothelial cells.[32] A report showed that increased SUA significantly associate with the severity of afferent arteriolar sclerosis.[33] These results implicate inflammation and endothelial dysfunction as pathways in uric-acid mediated development of rapid eGFR decline. Finally, uric acid transporter overexpression in hyperuricemia has been suggested to elicit kidney dysfunction, and uric acid transporter

inhibitors block inflammation of vascular smooth muscle cells and endothelial cells.[32] Only 4.3% of participants in this cohort had diabetes mellitus, and the presence of diabetes mellitus was not an independent risk factor for rapid eGFR decline in the multivariable models. Moreover, excluding participants with diabetes mellitus from the analyses did not attenuate the significance of the measures of association between baseline SUA, change in SUA and rapid eGFR decline.

This study has important limitations worth mentioning. First, this study was a retrospective, single center study, which may introduce selection bias. However, very few subjects were excluded, and an important strength of a single center study is the lack of inter-laboratory variability. Another limitation of this study is that we did not account for medication use for study subjects. Medications and altered renal handling may affect renal function. Of 12,578 subjects without CKD in this study, 3,523 subjects were on medications. We excluded these subjects with medication and analyzed the 9,055 subjects not on any medications. After multivariable adjustments with age, sex, body mass index, smoking habits, hypertension, diabetes, dyslipidemia, baseline eGFR, baseline SUA, and SUA change, higher baseline SUA (OR per 1 mg/dL increase: 1.25, 95% CI: 1.13–1.37) and increase in change in SUA (OR per 1 mg/dL increase: 3.84, 95% CI: 3.31–4.45) became independent risk factors of rapid eGFR decline, and those results were similar to the models presented in Table 2. Moreover, we conducted sub-group analyses of 4,336 subjects with 90–120 mL/min/1.73m², and 328 subjects with eGFR $\geq$ 120 mL/min/1.73m². There were very few subjects taking medications in these sub-groups, and the results were similar in the 90–120 mL/min/1.73m² and $\geq$ 120 mL/min/1.73m² subgroups. The rapid decline in eGFR could be due to a chronic or acute glomerulonephritis, but we were not able to exclude these patients. In this study, we estimated rather than measured GFR, by the Japanese GFR equation. There is the possibility that eGFR could introduce inaccuracy at higher eGFR ranges. For that reason, we also stratified our analyses by baseline eGFR ranges, and all sub-analyses yielded similar measures of associations between baseline SUA, change in SUA and rapid eGFR decline.

In summary, this epidemiology study demonstrated that a rise SUA over time in addition to baseline SUA were strong risk factors for rapid eGFR decline. Further research is needed to evaluate whether strategies to reduce SUA over time can abate CKD development in high risk individuals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Flow diagram of study enrollment

Of 13,201 subjects who underwent annual medical examination both in 2004 and in 2009, we enrolled 12,578 subjects between 30 and 85 years old without chronic kidney disease (eGFR <60 mL/min/1.73m²) in 2004 in the analyses of this study.

Serum uric acid change and eGFR change

Figure 2. The correlations between serum uric acid change and eGFR change over 5 years
 There was significant inverse correlations between serum uric acid change and eGFR change for 5 years ($r=0.305$, $p<0.001$) by Pearson's correlation analysis.

Table 1

Study subjects' demographic data among quartile of eGFR change.

eGFR	60 mL/min/1.73m ²	Total	1 st quartile	2 nd quartile	3 rd quartile	4 th quartile	p
Number		12,578	3,145	3,144	3,145	3,144	
Sex (male)		47.7%	57.0%	52.5%	45.9%	35.4%	<0.001
Weight (kg)		60.3±11.9	61.8±12.0	61.0±12.0	60.1±11.7	58.2±11.7	<0.001
Body mass index (kg/m ²)		22.5±3.2	22.7±3.1	22.5±3.2	22.4±3.1	22.1±3.3	<0.001
Smoking habit		38.6%	41.6%	39.4%	37.6%	35.9%	<0.001
Hypertension		18.8%	19.3%	19.6%	18.7%	17.7%	0.245
Diabetes		4.3%	4.1%	3.3%	4.1%	5.6%	<0.001
Dyslipidemia		38.4%	39.8%	41.5%	38.5%	33.8%	<0.001
Systolic BP (mmHg)		118.8±17.9	119.1±17.7	119.4±18.1	118.8±18.0	118.0±17.9	0.013
Diastolic BP (mmHg)		74.0±11.5	74.4±11.3	74.4±11.5	74.0±11.5	73.3±11.5	0.001
Fasting blood glucose (mg/dL)		100.3±15.7	100.9±15.0	99.8±12.7	99.8±13.8	100.7±20.1	0.005
HbA1c (%)		5.07±0.59	5.08±0.53	5.06±0.51	5.05±0.55	5.08±0.75	0.189
Baseline serum uric acid (mg/dL)		5.30±1.38	5.64±1.39	5.47±1.38	5.21±1.33	4.87±1.32	<0.001
- Male,		6.21±1.22,	6.36±1.22,	6.26±1.20,	6.11±1.19,	6.00±1.25,	
Female		4.47±0.93	4.69±0.95	4.59±0.96	4.45±0.89	4.26±0.88	
Follow-up serum uric acid (mg/dL)		5.24±1.32	5.26±1.30	5.34±1.31	5.28±1.33	5.11±1.32	<0.001
- Male,		6.06±1.19,	5.89±1.16,	6.07±1.16,	6.15±1.21,	6.19±1.24,	
Female		4.50±0.95	4.43±0.95	4.53±0.96	4.54±0.93	4.51±0.96	
Serum uric acid change (mg/dL)		-0.05±0.77	-0.38±0.78	-0.13±0.71	0.06±0.71	0.23±0.76	<0.001
Baseline eGFR(mL/min/1.73m ²)		86.7±14.8	77.8±11.1	81.3±11.2	87.4±11.1	100.2±14.6	<0.001
- Male,		84.3±14.1,	76.6±10.5,	80.4±10.8,	86.9±10.9,	98.7±15.5,	

eGFR	60 mL/min/1.73m ²	Total	1 st quartile	2 nd quartile	3 rd quartile	4 th quartile	p
Female		89.0±15.0	79.4±11.8	82.4±11.5	87.9±11.3	101.0±14.1	
Follow-up eGFR (mL/min/1.73m ²)		71.2±11.6	72.8±11.8	69.1±11.1	69.9±10.9	72.9±12.2	<0.001
- Male,		70.1±11.4,	71.5±11.0,	68.2±10.7,	69.4±10.8,	71.8±13.1,	
Female		72.1±11.8	74.6±12.6	70.1±11.5	70.3±11.0	73.4±11.6	

GFR, glomerular filtration rate; BP, blood pressure; p, probability

Data are presented as mean ± standard deviation.

Comparisons among four groups were performed by one-way analysis of variance (ANOVA) with Tukey's post hoc method.

Table 2

Risk factors for rapid eGFR decline: comparing the highest (4th) quartile with the lowest (1st) quartile of eGFR change

		Adjusted*		
		Odds ratio	95% C.I.	p
Age	per 1 year increase	1.035	1.027–1.043	<0.001
Sex (male)	male vs female	0.443	0.358–0.550	<0.001
Body mass index	per 1 kg/m ² increase	1.010	0.982–1.038	0.488
Smoking habits	positive vs negative	0.895	0.749–1.068	0.217
Hypertension	positive vs negative	1.508	1.212–1.875	<0.001
Diabetes	positive vs negative	1.324	0.900–1.947	0.154
Dyslipidemia	positive vs negative	1.294	1.089–1.538	0.003
Baseline eGFR	per 1 mL/min/1.73m ² increase	1.174	1.164–1.183	<0.001
Baseline serum uric acid	per 1 mg/dL increase	1.273	1.174–1.381	<0.001
Serum uric acid change	per 1 mg/dL increase	3.774	3.348–4.255	<0.001

GFR, glomerular filtration rate; C.I., confidence interval; p, probability

* Data adjusted for age, sex, body mass index, smoking habits, hypertension, diabetes, dyslipidemia, baseline eGFR, baseline serum uric acid level, and serum uric acid change.

Table 3

Odds of rapid eGFR decline for quartile of baseline serum uric acid level and serum uric acid change by sex

Total	Range	Number	Odds ratio	95% C.I.	P
Quantile 1	-4.2	1,630	Reference		
Quantile 2	4.3 – 5.1	1,617	1.060	0.857–1.311	0.592
Quantile 3	5.2 – 6.2	1,502	1.182	0.923–1.513	0.186
Quantile 4	6.3 -	1,540	2.238	1.656–3.023	<0.001
Serum uric acid change per 1 mg/dL increase					
Male	Range	Number	Odds ratio	95% C.I.	p
Quantile 1	-5.4	735	Reference		
Quantile 2	5.5 – 6.2	747	1.096	0.805–1.494	0.560
Quantile 3	6.3 – 7.0	701	1.467	1.057–2.035	0.022
Quantile 4	7.1 -	722	2.309	1.616–3.299	<0.001
Serum uric acid change per 1 mg/dL increase					
Female	Range	Number	Odds ratio	95% C.I.	p
Quantile 1	-3.8	884	Reference		
Quantile 2	3.9 – 4.4	911	1.266	0.943–1.699	0.116
Quantile 3	4.5 – 5.0	822	1.360	0.997–1.856	0.052
Quantile 4	5.1 -	767	1.809	1.283–2.549	0.001
Serum uric acid change per 1 mg/dL increase					
			5.502	4.532–6.681	<0.001

Data adjusted for age, sex, body mass index, smoking habits, hypertension, diabetes, dyslipidemia, and baseline eGFR.