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Serum Uric Acid as a Risk Factor for Chronic Kidney Disease in a Japanese Community

– The Hisayama Study –

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Background: Growing evidence suggests that high serum uric acid (SUA) levels are causally related to increased risk of chronic kidney disease (CKD). However, few studies have investigated the influence of elevated SUA levels on the incidence of kidney dysfunction and albuminuria separately in community-based populations.

Methods and Results: A total of 2,059 community-dwelling Japanese subjects aged ≥ 40 years without CKD were followed for 5 years. CKD was defined as kidney dysfunction (estimated glomerular filtration rate < 60 ml/min/1.73 m²) or albuminuria (urine albumin-creatinine ratio ≥ 30 mg/g). The odds ratio (OR) for the development of CKD was estimated according to quartiles of SUA (≤ 4.0 , 4.1–4.9, 5.0–5.8, and ≥ 5.9 mg/dl). During the follow-up, 396 subjects developed CKD, of whom 125 had kidney dysfunction and 312 had albuminuria. The multivariable-adjusted risk of developing CKD increased with higher SUA levels (OR 1.00 [reference] for ≤ 4.0 , 1.21 [95% confidence interval, 0.84–1.74] for 4.1–4.9, 1.47 [1.01–2.17] for 5.0–5.8, and 2.10 [1.37–3.23] for SUA ≥ 5.9 mg/dl, respectively). Similarly, there were positive associations between SUA level and the adjusted risk of developing kidney dysfunction (OR 1.00 [reference], 2.30 [1.10–4.82], 2.81 [1.34–5.88], and 3.73 [1.65–8.44]) and albuminuria (1.00 [reference], 1.12 [0.76–1.65], 1.35 [0.90–2.03], and 1.81 [1.14–2.87], respectively).

Conclusions: Higher SUA levels were a significant risk factor for the development of both kidney dysfunction and albuminuria in a general Japanese population. (*Circ J* 2016; **80**: 1857–1862)

Key Words: Albuminuria; Chronic kidney disease; Epidemiology; Kidney dysfunction; Serum uric acid

Chronic kidney disease (CKD) is increasingly recognized as a global health problem. The prevalence of CKD has been increasing worldwide as well as in Japan.^{1,2} Growing evidence suggests that individuals with CKD are more likely to develop not only endstage kidney disease that requires costly renal replacement therapy,³ but also cardiovascular disease.^{4–7} Kidney dysfunction and albuminuria, which are determinants of CKD, have been acknowledged as mutually independent risk factors for cardiovascular^{6–8} and renal events.⁹ Thus, identification of risk factors for kidney dysfunction and albuminuria will contribute to the establishment of effective healthcare management.

Recently, hyperuricemia has been attracting attention at the clinical level as a risk factor for the progression of kidney dysfunction. Several epidemiological studies have demonstrated an association between higher serum uric acid (SUA) levels and greater risk of CKD incidence.^{10–14} However, there have been few studies investigating the influence of elevated SUA levels on the incidence of kidney dysfunction and albuminuria separately in community-based populations.¹⁵ Community-based studies with a representative sample of the target population enable the extrapolation of findings to external populations, and are of great benefit for establishing the management of patients in the real world. The aim of this study was to assess the influence of high SUA levels on the development of kidney dysfunction and albuminuria and the rate of change in the estimated glomerular filtration rate (eGFR) in a general Japanese population.

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Table 1. Age- and Sex-Adjusted Baseline Characteristics of Subjects According to SUA Level (The Hisayama Study, 2002)

Variable	SUA level (mg/dl)				P for trend
	≤4.0 (n=554)	4.1–4.9 (n=515)	5.0–5.8 (n=483)	≥5.9 (n=507)	
Age, years*	58 (0.5)	60 (0.5)	60 (0.5)	58 (0.5)	0.89
Men, %†	13.7	26.5	44.0	83.9	<0.001
Systolic BP, mmHg	124 (0.8)	127 (0.8)	130 (0.8)	132 (0.9)	<0.001
Diastolic BP, mmHg	74 (0.5)	77 (0.5)	78 (0.5)	80 (0.5)	<0.001
Antihypertensive agent, %	10.3	16.6	23.8	23.7	<0.001
Diabetes, %	17.0	14.5	13.7	14.4	0.55
Total cholesterol, mg/dl	198 (1.5)	207 (1.5)	205 (1.5)	209 (1.7)	<0.001
HDL cholesterol, mg/dl	65 (0.7)	64 (0.7)	63 (0.7)	62 (0.8)	0.008
BMI, kg/m ²	21.9 (0.14)	22.8 (0.14)	23.7 (0.14)	24.2 (0.15)	<0.001
Hemoglobin, g/dl	13.3 (0.05)	13.6 (0.05)	13.8 (0.05)	14.0 (0.06)	<0.001
UA-lowering agent, %	0.1	2.3	0.9	2.1	0.08
hs-CRP, mg/L	0.35 (0.32–0.39)	0.44 (0.40–0.48)	0.48 (0.43–0.52)	0.58 (0.52–0.64)	<0.001
eGFR, ml/min/1.73 m ²	83 (0.3)	82 (0.3)	80 (0.3)	79 (0.3)	<0.001
U-ACR, mg/g	7.8 (7.3–8.3)	7.1 (6.6–7.6)	7.3 (6.8–7.8)	7.0 (6.5–7.6)	0.10
Smoking habit, %	23.3	24.2	23.8	21.6	0.26
Alcohol intake, %	32.8	45.1	51.3	53.0	<0.001
Regular exercise, %	9.0	11.4	12.1	13.4	0.45

Data are mean (standard errors), geometric mean (95% CI), or frequency. *Adjusted for sex; †adjusted for age. BMI, body mass index; BP, blood pressure; CI, confidence interval; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; SUA, serum UA; UA, uric acid; U-ACR, urine albumin-creatinine ratio.

Methods

Study Participants

The Hisayama Study is an ongoing population-based prospective cohort study of cardiovascular disease and its risk factors in the town of Hisayama, which is located in a suburb of the Fukuoka metropolitan area on Kyushu Island, Japan. The population of the town in 2010 was approximately 8,400. Full community surveys of the residents have been repeated since 1961.^{16,17} We performed a screening survey for the present study in 2002 and 2003.¹⁸ Briefly, a total of 3,328 residents aged ≥40 years (77.6% of the total population in this age group) underwent examination. After excluding 30 subjects who did not consent to participate in the study, 86 for whom no urine or blood sample was obtained, 250 with an eGFR <60 ml/min/1.73 m², and 538 with a urine albumin-creatinine ratio (U-ACR) ≥30 mg/g, the remaining 2,424 participants (1,042 men and 1,382 women) were enrolled in the baseline examination. Of those, 2,059 subjects (851 men and 1,208 women) who underwent a follow-up examination and had available eGFR and U-ACR data in 2007 were finally selected for analysis in the present study.

Risk Factors

At the baseline examination, blood samples were collected from an antecubital vein after an overnight fast. SUA and serum creatinine (SCr) concentrations were measured using enzymatic methods. Diabetes mellitus was defined as a fasting plasma glucose level ≥126 mg/dl, 2 h post-loaded or casual glucose levels ≥200 mg/dl, or current use of oral glucose-lowering agents or insulin. Total cholesterol and high-density lipoprotein (HDL) cholesterol levels were measured enzymatically. Hemoglobin levels were determined by sodium lauryl sulfate. High-sensitivity C-reactive protein (hs-CRP) level was measured using a modification of the Behring Latex-Enhanced CRP assay on a Behring Nephelometer BN-100 (Behring Diagnostics, Westwood, MA, USA). Fresh voided urine samples were collected at the time of examination, and urine cre-

atinine and albumin levels were measured using the turbidimetric immunoassay method. The U-ACR (mg/g) was calculated by dividing urinary albumin values by the urinary creatinine concentrations.

Blood pressure was measured 3 times using an automated sphygmomanometer with subjects seated after at least 5 min of rest. The mean value of the 3 measurements was used for the present analysis. Hypertension was defined as a systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or current use of antihypertensive agents. Body height and weight were measured in light clothing without shoes, and body mass index (BMI) was calculated as body weight in kilograms divided by height in meters squared. A self-administered questionnaire covering information on medical treatment including the use of uric acid-lowering agents (allopurinol, benzbromarone, and probenecid), smoking habits, alcohol intake, and regular exercise was completed by each participant and checked by trained interviewers. Smoking habit and alcohol intake were classified as being either habitual or not. Subjects engaging in sports or other forms of exercise ≥3 times per week during their leisure time were defined as having regular exercise.

Definition of CKD, Kidney Dysfunction, Albuminuria, and Decline in eGFR

eGFR was calculated using the following Chronic Kidney Disease Epidemiology Collaboration (CKD) equation with a Japanese coefficient¹⁹ of 0.813, where SCr is serum creatinine, κ , is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min (SCr/ κ , 1) indicates the minimum of SCr/ κ or 1, and max (SCr/ κ , 1) indicates the maximum of SCr/ κ or 1:

$$\text{eGFR (ml/min/1.73 m}^2\text{)} = 0.813 \times 141 \times \text{min (SCr}/\kappa, 1\text{)}^\alpha \times \text{max (SCr}/\kappa, 1\text{)}^{-1.209} \times 0.993^{\text{Age}} \text{ (if female, } \times 1.018\text{)}.$$

Kidney dysfunction was defined as reduced eGFR (eGFR <60 ml/min/1.73 m²), and albuminuria was defined as increased U-ACR (U-ACR ≥30 mg/g) according to the Kidney Disease:

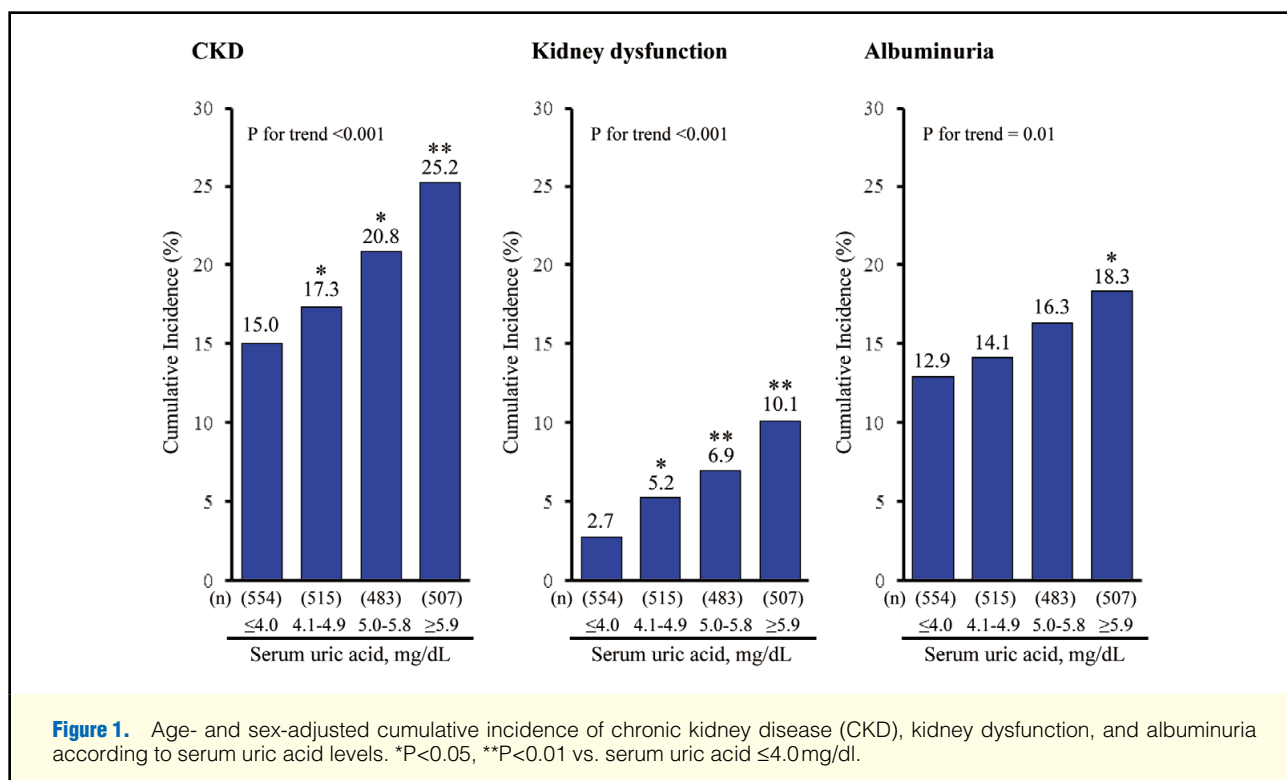


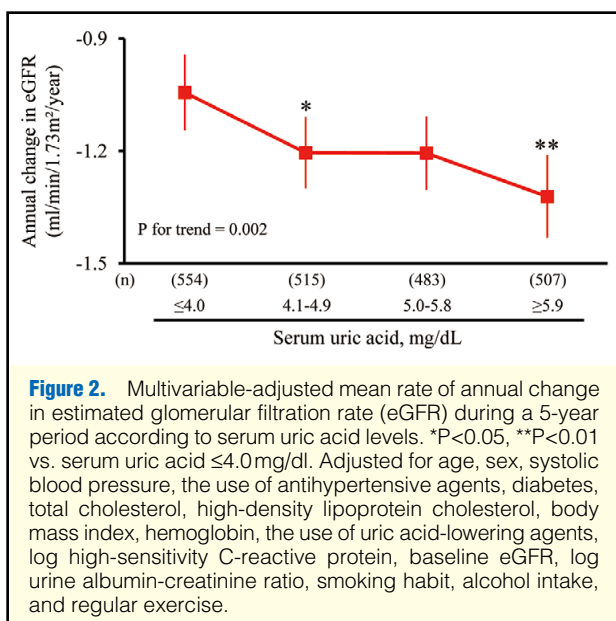
Table 2. Age- and Sex-Adjusted and Multivariable-Adjusted OR for the Development of CKD, Kidney Dysfunction, and Albuminuria According to SUA Levels and Per 1 mg/dl Increase

SUA, mg/dl	Age- and sex-adjusted			P for trend	Multivariable-adjusted†			P for trend
	OR	95% CI	P value		OR	95% CI	P value	
CKD								
≤4.0	1.00	(Reference)	} <0.001	1.00	(Reference)	} <0.001		
4.1–4.9	1.22	(0.87–1.72)		0.26	1.21		(0.84–1.74)	0.32
5.0–5.8	1.57	(1.11–2.22)		0.01	1.47		(1.01–2.17)	0.04
≥5.9	2.18	(1.49–3.18)		<0.001	2.10		(1.37–3.23)	<0.001
Per 1 mg/dl increment	1.21	(1.10–1.34)	<0.001	1.18	(1.05–1.32)	0.005		
Kidney dysfunction								
≤4.0	1.00	(Reference)	} <0.001	1.00	(Reference)	} 0.002		
4.1–4.9	2.40	(1.21–4.78)		0.01	2.30		(1.10–4.82)	0.03
5.0–5.8	3.58	(1.81–7.03)		<0.001	2.81		(1.34–5.88)	0.006
≥5.9	5.98	(2.91–12.26)		<0.001	3.73		(1.65–8.44)	0.002
Per 1 mg/dl increment	1.50	(1.27–1.76)	<0.001	1.24	(1.03–1.49)	0.03		
Albuminuria								
≤4.0	1.00	(Reference)	} 0.01	1.00	(Reference)	} 0.01		
4.1–4.9	1.13	(0.79–1.62)		0.52	1.12		(0.76–1.65)	0.64
5.0–5.8	1.33	(0.93–1.92)		0.12	1.35		(0.90–2.03)	0.15
≥5.9	1.63	(1.09–2.44)		0.02	1.81		(1.14–2.87)	0.01
Per 1 mg/dl increment	1.12	(1.01–1.25)	0.03	1.15	(1.02–1.30)	0.02		

†Adjusted for age, sex, systolic BP, the use of antihypertensive agents, diabetes, total cholesterol, HDL cholesterol, BMI, hemoglobin, use of UA-lowering agents, log hs-CRP, baseline estimated glomerular filtration rate, log U-ACR, smoking habit, alcohol intake, and regular exercise. CKD, chronic kidney disease; OR, odds ratios. Other abbreviations as in Table 1.

Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease.²⁰ CKD was defined as kidney dysfunction or albuminuria. The rate of annual change in eGFR was calculated by the following equation:

annual change in eGFR (ml/min/1.73 m²/year)=[eGFR in 2007 (ml/min/1.73 m²)-eGFR in 2002 (ml/min/1.73 m²)]/ follow-up period (years).



Statistical Analysis

Baseline SUA levels were divided into quartiles: ≤4.0, 4.1–4.9, 5.0–5.8, and ≥5.9 mg/dL. The age- and sex-adjusted linear trends in the means and frequencies of risk factors across SUA levels were tested using a linear regression analysis and a logistic regression analysis, respectively. U-ACR and hs-CRP were logarithmically transformed, because their distributions were skewed. The age- and sex-adjusted cumulative incidence of CKD, kidney dysfunction, and albuminuria were calculated using the direct method with the age and sex distributions of the overall study group. A logistic regression analysis was used to estimate odds ratios (ORs) with 95% confidence intervals (CIs) for the development of CKD, kidney dysfunction, and albuminuria according to the SUA levels. The heterogeneity in the association between the sexes was assessed by adding an interaction term in the relevant logistic model. The multivariable-adjusted mean rate of annual change in the eGFR according to the SUA levels was calculated by analysis of covariance, and the difference in the values among SUA levels were tested using a Dunnett t-test. All data analyses were done with SAS version 9.3 (SAS Institute, Cary, NC, USA) for statistical computing. A 2-tailed value of P<0.05 was considered statistically significant in all analyses.

Results

The age- and sex-adjusted baseline characteristics of the study subjects according to SUA levels are listed in [Table 1](#). Subjects with higher SUA levels were likely to be male. The mean values of systolic and diastolic blood pressures, total cholesterol, BMI, hemoglobin, and hs-CRP and the frequency of alcohol intake increased with higher SUA levels, while the mean values of eGFR and HDL cholesterol decreased.

During the 5-year follow-up, 396 subjects developed CKD, of whom 125 had kidney dysfunction, and 312 had albuminuria. [Figure 1](#) shows the age- and sex-adjusted cumulative incidence of CKD according to the SUA levels. The incidence of CKD increased significantly with higher SUA levels (P for trend <0.001). Similar findings were observed for kidney dysfunction and albuminuria (P for trend <0.001 and =0.01, respec-

tively). The age- and sex-adjusted OR for developing CKD increased gradually with higher SUA levels (P for trend <0.001; [Table 2](#)). This association remained unchanged after adjusting for potential confounding factors; namely, age, sex, systolic blood pressure, use of antihypertensive agents, diabetes, total cholesterol, HDL cholesterol, BMI, hemoglobin, use of UA-lowering agents, hs-CRP, baseline eGFR, U-ACR, smoking habit, alcohol intake, and regular exercise (P for trend <0.001). Compared with those with SUA ≤4.0 mg/dL, the multivariable-adjusted OR for the development of CKD was 1.21 (95% CI, 0.84–1.74), 1.47 (1.01–2.17), and 2.10 (1.37–3.23) in subjects with SUA of 4.1–4.9 mg/dL, 5.0–5.8 mg/dL, and ≥5.9 mg/dL, respectively. With regard to the component of CKD, similar linear associations were observed for the development of kidney dysfunction (OR 2.30 [95% CI 1.10–4.82] for SUA 4.1–4.9 mg/dL, 2.81 [1.34–5.88] for SUA 5.0–5.8 mg/dL, and 3.73 [1.65–8.44] for SUA ≥5.9 mg/dL) and albuminuria (1.12 [0.76–1.65] for SUA 4.1–4.9 mg/dL, 1.35 [0.90–2.03] for SUA 5.0–5.8 mg/dL, and 1.81 [1.14–2.87] for SUA ≥5.9 mg/dL). In the analysis using a continuous variable of SUA, the OR of each event increased significantly per every 1 mg/dL increment in SUA level by 18% (95% CI 5–32%) for CKD, 24% (3–49%) for kidney dysfunction, and 15% (2–30%) for albuminuria. In the subgroup analysis stratified by sex, similar associations of SUA levels with the risk of developing CKD, kidney dysfunction, and albuminuria were observed in both sexes ([Table S1](#)), and there was no evidence of heterogeneity in these associations between the sexes (all P for heterogeneity >0.41). The sensitivity analysis excluding the subjects using the UA-lowering agents (n=36) did not make any material difference to the findings ([Table S2](#)).

Next, we investigated the association between SUA levels and the rate of annual change in eGFR ([Figure 2](#)). This analysis showed that higher SUA levels were significantly associated with a greater decline in eGFR after adjusting for the potential confounding factors: SUA ≤4.0 mg/dL, −1.05 (95% CI −1.15 to −0.94); SUA 4.1–4.9 mg/dL, −1.21 (−1.31 to −1.12); SUA 5.0–5.8 mg/dL, −1.21 (−1.31 to −1.11); and SUA ≥5.9 mg/dL, −1.33 (−1.44 to −1.22). The difference in the multivariable-adjusted mean values of the decline in eGFR was more significant in the 2nd and 4th lowest quartile groups than in the lowest (1st) quartile group. The amount of annual change in eGFR was −0.07 (95% CI −0.12 to −0.03) ml/min/1.73 m²/year per every 1 mg/dL increment in serum SUA levels.

Discussion

The present results clearly showed that the risk for the development of CKD dose-dependently and significantly increased with higher SUA levels after adjustment for other risk factors, and this association was observed even in the normal range of SUA levels. In addition, subjects with higher SUA levels had a greater decline in eGFR. Importantly, higher SUA levels were a significant risk factor not only for the development of kidney dysfunction, but also for albuminuria. To the best of our knowledge, this is the first study to clarify prospectively the association between SUA levels and future risk of both kidney dysfunction and albuminuria in a community-based Asian population.

Several epidemiological studies have examined the association between SUA and the development of kidney dysfunction.^{10–14} The Okinawa General Health Maintenance Association analyzed data from 6,403 Japanese participants in a community-based screening, and found that those with SUA ≥8.0 mg/dL had a significantly higher risk of developing kidney dysfunction.

tion (defined as SCr level ≥ 1.4 mg/dl in men and ≥ 1.2 mg/dl in women) over the 2-year study period.¹⁰ In the Atherosclerosis Risks in Communities and the Cardiovascular Health Study conducted in 13,338 Americans with intact kidney function, higher SUA levels were associated with the development of kidney dysfunction (defined as eGFR < 60 ml/min/1.73 m²).¹¹ In other prospective cohort studies, both the risk for moderate to severe kidney dysfunction as assessed by eGFR^{12,13} and the risk for endstage kidney disease¹⁴ increased with SUA levels. These findings are in accordance with ours. Moreover, a small randomized controlled trial conducted in 54 patients with mild to moderate CKD showed that urate-lowering therapy almost halved the risk of developing kidney failure.²¹ These findings suggest a causal association between high SUA levels and deterioration of kidney function. Further large-scale clinical trials are warranted to elucidate this issue.

Hyperuricemia associated with hyperuricosuria has been postulated to cause kidney disease by depositing intraluminal crystals in the collecting duct of the nephron.²² UA crystals induce an acute inflammatory response, which leads to tubulointerstitial damage and reduction of kidney function.²² On the other hand, experimental studies have indicated that hyperuricemia progressed to kidney disease rapidly despite an absence of crystals in the kidney.²³ In support of this finding, there was no evidence of a significant association between filtered loads of UA and the development of CKD, kidney dysfunction, and albuminuria in the present study (Table S3). It has been reported that hyperuricemia activates the renin-angiotensin-aldosterone system by a crystal-independent mechanism,²⁴ and subsequently deteriorates kidney function through afferent renal arteriopathy²⁵ and tubulointerstitial fibrosis.²⁴ Thus, subjects with higher SUA levels are likely to develop kidney dysfunction.

The present study demonstrated that higher SUA levels were significantly associated with the development of albuminuria. However, there have been very few studies addressing this association in community-based populations. Chang et al found that each 1 mg/dl increase of SUA was associated with a 1.42-fold increased risk of microalbuminuria (defined as U-ACR ≥ 30 mg/g) during a 4-year follow-up in a southern Taiwanese community-based population.²⁶ The Takahata Study of Japanese community-dwellers also demonstrated that higher SUA levels at baseline were an independent risk factor for an increase in U-ACR over 1 year.²⁷

Several possible underlying mechanisms have been proposed. Experimental studies have suggested that UA itself can promote endothelial dysfunction by several biological processes, including glomerular hypertension,²⁸ inflammatory action,²⁹ oxidative stress,³⁰ and inhibition of angiogenesis.³¹ It has also been acknowledged that albuminuria reflects systemic endothelial dysfunction.³² The pathophysiology of the influence of SUA on albuminuria requires further exploration.

It is commonly recognized that subjects with higher SUA levels at baseline are likely to have lower eGFR levels, so our findings could have reflected nothing more than the faster development of kidney dysfunction in subjects with lower eGFR at baseline. Therefore, to rule out this potential association, we also compared the rate of change in eGFR across SUA levels. Even when accounting for this parameter, however, we found that higher SUA levels were a significant risk factor for the decline in eGFR.

Study Limitations

First, SUA levels were based on a single measurement at baseline. This may cause a misclassification of SUA level, which could have weakened the association found in this study, bias-

ing the results toward the null hypothesis. Second, a selection bias may have arisen by the exclusion of 317 subjects who did not return to the follow-up examination. However, we believe that such a bias, if present, had little influence on our findings, because the mean values of SUA, eGFR, and albuminuria were similar between the included and excluded participants. Third, the association between SUA levels and proteinuria could not be estimated in this study, because the 5-year incidence of proteinuria was low (3.6%). Finally, we had no information about the cause of underlying kidney disease or family history of kidney disease. Accurate kidney disease information should be obtained by renal biopsy and ultrasonography, but these diagnostic procedures are not feasible for a cohort study with subjects recruited from a community-based population.

Conclusions

Higher SUA levels were a significant risk factor for the development of not only kidney dysfunction but also albuminuria in a general Japanese population. Our findings suggested that subjects with higher SUA levels should be considered a high-risk population for albuminuria as well as kidney dysfunction and should be recommended for more careful observation for the potential development of these conditions in clinical practice. At the present stage, to what extent reducing SUA levels can attenuate the risk of albuminuria and kidney disease is unknown. A clinical trial reducing SUA levels is needed to clarify whether lower SUA levels will reduce the risk of developing kidney disease.

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Conflicts of Interest

The authors report no conflicts of interest.

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Supplementary Files

Supplementary File 1

Table S1. Age- and sex-adjusted and multivariable-adjusted OR for the development of CKD, kidney dysfunction, and albuminuria according to SUA levels and per 1 mg/dl increase stratified by sex

Table S2. Age- and sex-adjusted and multivariable-adjusted OR for the development of CKD, kidney dysfunction, and albuminuria according to SUA quartile excluding subjects using UA-lowering agents

Table S3. Multivariable-adjusted OR for the development of CKD, kidney dysfunction, and albuminuria according to SUA load quartile

Please find supplementary file(s);
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