

# A Greater Association of Hyperuricemia than of Metabolic Syndrome with the New Incidence of Chronic Kidney Disease

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## Abstract

**Background:** To what extent uric acid (UA) levels and/or metabolic syndrome (Mets) contribute to the onset of chronic kidney disease (CKD) is largely unknown. The present study explores how these two factors have an association with the new incidence of CKD. **Methods:** Study design is a cohort study. A total of 14,485 participants were eligible for the cross-sectional analysis on UA levels and the prevalence of Mets. Among those individuals, 8,223 participants without CKD and 4,839 without Mets were eligible for the longitudinal analysis of the new incidence of CKD. Parameters monitored were body mass index, systolic and diastolic blood pressure, serum creatinine concentration, estimated glomerular filtration rate, lipid profiles, plasma glucose, HbA1c. The primary predictor was the level of UA and Mets to explain the newly-developed CKD. The observation period was 4 years. **Results:** In a cross-sectional analysis, higher UA levels were associated with the greater prevalence of Mets. In addition, UA levels were associated with the numbers of the Mets constituents in both genders. In a longitudinal analysis, higher UA levels were associated with the greater rate of CKD and the greater incidence of Mets. In addition, the incidence of CKD at year 4 was influenced by the presence of hyperuricemia, but not by that of the Mets. The odd ratio (OR) to predict the CKD incidence was 1.42 (95% confidence intervals (CI), 0.52 to 3.78) in the presence of Mets alone, 2.10 (95% CI, 1.36 to 3.23) in the presence of hyperuricemia alone, and 3.56 (95% CI, 1.55 to 8.21) in the presence of both. **Conclusion:** Hyperuricemia has a greater association with the incidence of CKD than Mets does. Hyperuricemia complicated by Mets is additionally detrimental.

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## Keywords

**Uric Acid, Hypertension, CKD, Estimated Glomerular Filtration Rate**

### 1. Introduction

Hyperuricemia plays a pivotal role in the progression of chronic kidney disease (CKD), which includes chronic glomerulonephritis [1], diabetic nephropathy [2] [3], gouty kidney [4] [5], all of which frequently leads to end stage renal failure [6] [7]. Of note is that hyperuricemia not only promotes CKD, but also is involved in its early onset [8]-[10]. These data are suggestive of uric acid (UA) as a strong risk factor renal damage, which could eventually lead to the various major cardiovascular events (MACE).

In the last few decades, the metabolic syndrome (Mets) has been increasing in many countries. It is characterized by comorbid conditions such as hypertension, dyslipidemia and diabetes mellitus. Notably, in the recent clinical guidelines for Mets, hyperuricemia has not been chosen as a constituent of the syndrome [11]. However, physicians are increasingly aware of the strong association of hyperuricemia with the Mets, and both diseases should be clinically intervened in appropriate ways to prevent the upcoming future development of CKD. This context prompted us to investigate to what extent hyperuricemia, in comparison with Mets, contributes to the incident CKD.

In the present trial, we used epidemiological cohorts in a screened population at large to conduct: 1) a cross-sectional analysis on the prevalence of Mets according to UA levels; and 2) a longitudinal survey to observe to what extent Mets and hyperuricemia contribute to the new onset of CKD. We applied strict exclusion criteria in order to choose eligible participants.

### 2. Subjects & Methods

#### 2.1. Study Population and Methods

The study design is a retrospective population-based cohort of Japanese office workers aged 25 to 60 years (average 42  $\pm$  11), the majority of them were living in the vicinity of Tokyo district. The original number of the participants was 14,485 who had an annual medical check-up starting from 2009 to 2013 in our institutions.

The basic exclusion criteria are individuals receiving medications for diabetes, hyperuricemia, hypertension and dyslipidemia; those having insufficient clinical data; those with past history of incident MACE such as cerebral apoplexy or myocardial infarction; those with any disease requiring hospitalization; those with current cancer or other serious diseases judged by the physicians; and those with current pregnancy. These eliminations leave a total number of 14,485 subjects who are eligible for a cross-sectional analysis of the prevalence of Mets.

For a longitudinal analysis of the effect of either Mets or hyperuricemia, or both on the incidence of CKD, individuals with estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73m<sup>2</sup> at entry were also excluded. The present and past history of proteinuria was also another rule out factor. The definition of CKD was a reduction of eGFR less than 60 mL/min/1.73m<sup>2</sup> at any given time of the observation period of 4 years. This exclusion process finally leaves 8,223 CKD-free individuals for the analysis of the new onset of CKD.

A minim requirement of making diagnosis of Mets was defined as individuals with waist circumference  $\geq$  85 cm (if female 90 cm), with two or more additional abnormalities including hypertension (blood pressure (BP);  $\geq$ 130/85 mmHg), fasting plasma glucose (FPG;  $\geq$ 110 mg/dL), triglyceride (TG;  $\geq$ 150 mg/dL) and/or HDL-cholesterol (HDL-C;  $\leq$ 40 mg/dL). Finally, this exclusion criterion leaves 4839 Mets-free individuals for the new onset of Mets in 4 years time. These subjects are all CKD-free at baseline.

#### 2.2. Primary Predictor and Outcome

The primary predictor was the level of UA and Mets to explain the newly-developed CKD. The new incidence of CKD was defined as a decline in eGFR to less than 60 mL/min/1.73m<sup>2</sup> calculated at any given time of 4 observation years [12]. Renal function expressed as eGFR for Japanese was calculated based on the equation;  $eGFR = 194 \times Cr^{-1.094} \times Age^{-0.287}$  (if women  $\times$  0.739), reported elsewhere [13].

### 2.3. Other Clinical Variables

Body mass index (BMI) was calculated based on the equation;  $BMI = \text{Body weight (BW)} \times 1/(\text{Body Height})^2$ . Laboratory tests were carried out after an 8 to 12 hour fasting. Measurements were made on serum creatinine (Cr) concentration, serum uric acid (UA) concentration, blood urea nitrogen (BUN), electrolytes and lipid profiles including total cholesterol (TC), TG, HDLC, LDL-cholesterol (LDLC), hemoglobin A1c (HbA1c) and fasting plasma glucose (FPG). Hyperuricemia was defined as  $UA \geq 7 \text{ mg/dL}$  [14]. Laboratory tests were performed using the Toshiba auto-analyzer (TBA-80 FR neo, Tokyo, Japan). Urinalysis was performed only for qualitative measurement of urinary protein. The value of HbA1c was measured as a unit of JDS (Japan Diabetes Society). Following the worldwide recommendations, all of the HbA1c values was expressed as a unit of NGSP (National glycohemoglobin standardization program) based on the equation;  $NGSP (\%) = JSD \times 1.02 + 0.25 (\%)$ .

### 2.4. Ethical Considerations

The present study was conducted in accordance with “Recommendations on the Establishment of Animal Experimental Guidelines” approved at the 80th General Assembly of the Japanese Science Council in 1980, and the principles set out in the Declaration of Helsinki 1964 as modified by subsequent version revisions.

The present survey was submitted to the Institutional Review Board (IRB)/Ethics Committee of the Jikei University School of Medicine. After the deliberation the protocol was approved in 2014 by the ethics committee of the University with the clinical trial number 25 - 203 (7338).

### 2.5. Statistical Analysis

The database and all statistical outputs were retained by the Jikei University. Statistical analyses were conducted at the University. The access to the database was limited as deemed necessary. The authors assume full responsibility for the completeness and accuracy of the content of the manuscript.

Cross-sectional analysis on the prevalence of Mets was performed as a function of UA levels by dividing the distribution into 4 UA groups. Cross-sectional associations of Mets and UA levels were performed by using Chi-square analysis for discrete variables, analysis of variance (ANOVA) for continuous variables. The prevalence of Mets in reference to different age groups (Age < 29 years old, 30 - 39, 40 - 49, 50 - 59, and 60<) was analyzed by Mann-Whitney test. For the analyses of Mets constituents and UA levels, after obtaining a statistical significance by ANOVA, Turkey’s test was applied to compare the randomly-chosen 2 pair groups.

In the longitudinal analysis, we examined the association of new incident CKD according to UA levels and the presence of Mets. For these outcomes, Cox proportional hazard analysis was used to estimate adjusted odds ratio (OR) and associated 95% CI. Due to the lack of statistical power in the female cohort, analysis was made on only the males in these longitudinal analyses. Variables significant in univariate analysis were considered to be potential confounders of UA in multivariate models.

Statistical analyses were carried out with Stat Flex version 6.0 (Artec Ltd. Co., Osaka, Japan). Data are presented as the mean  $\pm$  standard deviation (SD), unless otherwise indicated.  $P \leq 0.05$  is considered statistically significant. Confidence intervals (CI) are expressed as 95% CI.

## 3. Results

### 3.1. Baseline Characteristics for Cross-Sectional Analysis

After the exclusion at the start for the cross-sectional analysis, the study cohort had an average age of  $42 \pm 11$  years, an eGFR of  $82.0 \pm 14.6 \text{ mL/min/1.73m}^2$ , an overall UA level of  $5.7 \pm 1.4 \text{ mg/dL}$  (Table 1). Greater UA levels were significantly associated with older age, males, greater prevalence of hypertension, BMI, waist circumference, BMI, SBP, DBP, serum Cr concentration, TC, TG, HDLC, LDLC, FPG, HbA1c and lesser eGFR (ANOVA,  $P < 0.001$ ).

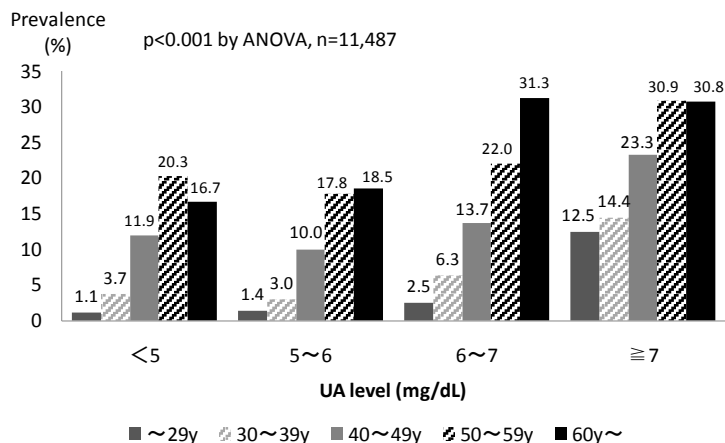
### 3.2. UA Levels and the Prevalence of Mets

The prevalence of Mets in male gender was shown in Figure 1. Higher UA levels were associated with the greater prevalence of Mets; the average of respective UA group was 11.3% (UA < 5 mg/dL), 9.7% (5.0 - 5.9

**Table 1.** Baseline demographics of participants for Mets analyses.

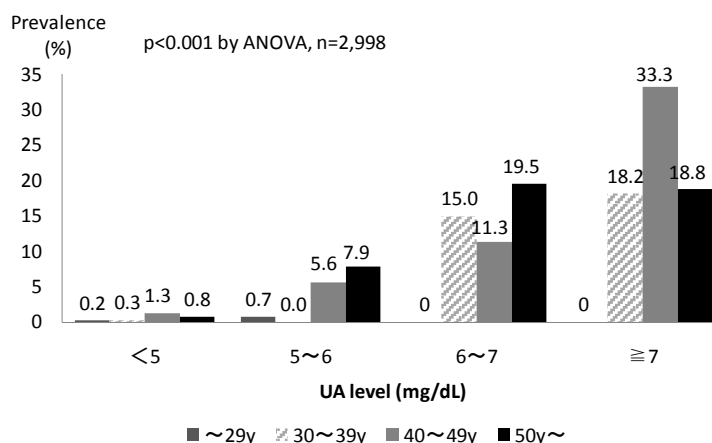
|                                   | UA Groups (mg/dL) |             |             |             |             |           |
|-----------------------------------|-------------------|-------------|-------------|-------------|-------------|-----------|
|                                   | Overall           | <5.0        | 5.0 - 5.9   | 6.0 - 6.9   | ≥7.0        |           |
| N                                 | 14,485            | 4,096       | 4,060       | 3,809       | 2,520       |           |
| Age                               | 42 ± 11           | 40 ± 11     | 42 ± 12     | 43 ± 11     | 44 ± 10     | P < 0.001 |
| Men (%)                           | 79.3              | 44.8        | 86.4        | 96.3        | 98.1        |           |
| BMI (Kg/m <sup>2</sup> )          | 23 ± 4            | 22 ± 3      | 23 ± 3      | 24 ± 3      | 25 ± 4      | P < 0.001 |
| Waist circumference (cm)          | 81.1 ± 10.0       | 76.4 ± 9.3  | 80.4 ± 9.1  | 83.3 ± 9.3  | 86.8 ± 9.7  | P < 0.001 |
| SBP (mmHg)                        | 119 ± 15          | 113 ± 15    | 119 ± 14    | 122 ± 14    | 124 ± 15    | P < 0.001 |
| DBP (mmHg)                        | 75 ± 11           | 71 ± 11     | 75 ± 11     | 77 ± 11     | 80 ± 11     | P < 0.001 |
| Cr (mg/dL)                        | 0.80 ± 0.14       | 0.70 ± 0.13 | 0.80 ± 0.12 | 0.84 ± 0.11 | 0.89 ± 0.14 | P < 0.001 |
| eGFR (mL/min/1.73m <sup>2</sup> ) | 83.0 ± 14.6       | 87.6 ± 15.0 | 83.7 ± 13.9 | 81.0 ± 13.6 | 77.2 ± 13.9 | P < 0.001 |
| TC (mg/dL)                        | 199 ± 107         | 193 ± 31    | 197 ± 31    | 201 ± 32    | 210 ± 33    | P < 0.001 |
| TG (mg/dL)                        | 107 ± 89          | 81 ± 56     | 100 ± 93    | 115 ± 79    | 147 ± 118   | P < 0.001 |
| HDLC (mg/dL)                      | 61 ± 15           | 67 ± 15     | 61 ± 15     | 59 ± 15     | 57 ± 15     | P < 0.001 |
| LDLC (mg/dL)                      | 119 ± 30          | 111 ± 28    | 118 ± 29    | 123 ± 30    | 129 ± 31    | P < 0.001 |
| FPG (mg/dL)                       | 96 ± 18           | 94 ± 20     | 96 ± 17     | 97 ± 17     | 98 ± 15     | P < 0.001 |
| HbA1c (NGSP) (%)                  | 5.43 ± 0.59       | 5.38 ± 0.64 | 5.42 ± 0.58 | 5.46 ± 0.57 | 5.50 ± 0.55 | P < 0.001 |

Mets: metabolic syndrome; UA: serum uric acid concentration; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; Cr: serum creatinine concentration; eGFR: estimated glomerular filtration rate; TC: total cholesterol; TG: triglycerides; HDLC: high-density lipoprotein cholesterol; LDLC: low-density lipoprotein cholesterol; FPG: fasting plasma glucose concentration; HbA1c: hemoglobin A1c.

**Figure 1.** UA levels and the prevalence of Mets (Male only).

mg/dL), 13.9% (6.0 - 6.9 mg/dL) and 23.0% (≥7 mg/dL), respectively (by the Chi-square test, P < 0.001). In each UA group, there was a statistical difference in the prevalence according to age (P < 0.01, by Mann-Whitney test). This increasing trend of the Mets prevalence was prominent in the individual groups with older age.

**Figure 2** showed the prevalence of Mets in female gender. Although the magnitude is smaller than male (**Figure 1**), higher UA levels were also associated with the greater prevalence of Mets; the average value was 0.8% (UA < 5 mg/dL), 3.6% (5.0 - 5.9 mg/dL), 12.9% (6.0 - 6.9 mg/dL) and 23.0% (≥7 mg/dL), respectively (by the Chi-square test, P < 0.001). In each UA groups, there was a statistical difference in the prevalence ac-



**Figure 2.** UA levels and the prevalence of Mets (Female only).

according to age ( $P < 0.01$ , by Mann-Whitney test). The increasing trend of the Mets prevalence was prominent in the individual groups with older age.

### 3.3. UA Levels and the Mets Constituents

**Figure 3** showed relationship between UA levels and the numbers of Mets constituents, consisting of BP ( $\geq 130/85$  mmHg), FPG ( $\geq 110$  mg/dL), TG ( $\geq 150$  mg/dL) and/or HDLC ( $\leq 40$  mg/dL) with the minimum requirement of waist circumference (WC) of  $\geq 85$  cm (if female 90 cm). There was a significant difference among the 5 groups ( $P < 0.01$  by ANOVA). Further analyses by Turkey's test showed a strong association between UA levels and the number of the constituents ( $P < 0.01$ , except for 2 vs 3 constituents, 2 vs 4 constituents and 3 vs 4 constituents).

### 3.4. UA Levels and the New Incidence of CKD

A total of 124 individuals had a decrease in eGFR less than  $60$  mL/min/ $1.73\text{m}^2$  at year 4 (124/6, 542 individuals = 2.0%). Among them, the rate of proteinuria appearance at year 4 was 1.6% (2/124 individuals). In 124 individuals with CKD at year 4, mean eGFR at baseline and closeout were  $67.8 \pm 7.2$  and  $56.2 \pm 2.5$  mL/min/ $1.73\text{m}^2$ , respectively. In contrast, mean eGFR of individuals without CKD at baseline and closeout were  $91.2 \pm 17.5$  and  $83.4 \pm 13.6$  mL/min/ $1.73\text{m}^2$  ( $n = 6262$ ), respectively.

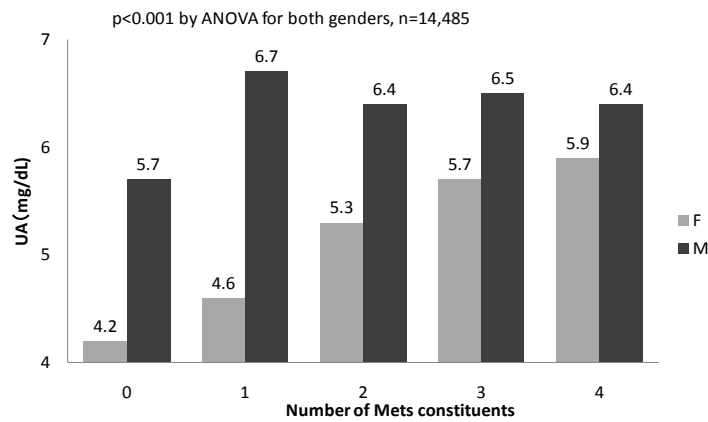
**Table 2** showed demographic findings of CKD free subjects for the CKD incidence. These subjects were followed for 4 years. **Figure 4** showed the incident rates of newly developed CKD. Higher UA levels had a close association with new CKD; 1.1% (UA  $< 5$  mg/dL), 1.5% (5.0 - 5.9 mg/dL), 1.7% (6.0 - 6.9 mg/dL), and 3.4% ( $\geq 7$  mg/dL), respectively ( $P < 0.001$  by the Chi-square test).

### 3.5. UA Levels and the Newly Developed Mets

**Table 3** showed Mets free subjects to look into the CKD incidence. Among 4,839 Mets free individuals, 400 individuals (8% = 400/4,839) developed Mets during 4 years time. **Figure 5** showed the rates of newly developed Mets, showing that higher UA levels had a close association with the new development of Mets; 3.3% (UA  $< 5$  mg/dL), 6.2% (5.0 - 5.9 mg/dL), 11.6% (6.0 - 6.9 mg/dL), and 17.1% ( $\geq 7$  mg/dL), respectively ( $P < 0.001$  by the Chi-square test).

### 3.6. The Association of Hyperuricemia and Mets on the CKD Incidence

After adjustment for age, sex, BMI, waist circumference, systolic BP (SBP), diastolic BP (DBP), TC, TG, HDLC, LDLC, FPG and HbA1c, the multivariate adjusted OR for new-onset of CKD (a decrease in eGFR  $< 60$  mL/min/ $1.73\text{m}^2$  at year 4) in conjunction with hyperuricemia and Mets were calculated in **Figure 6**. The OR were 1.00 (reference), 1.42 (95% confidence intervals (CI), 0.52 to 3.78) in the presence of Mets only, 2.10 (95% CI, 1.36 to 3.23) in the presence of hyperuricemia only, and 3.56 (95% CI, 1.55 to 8.21) in the presence of



**Figure 3.** UA levels and the number of Mets constituents.

**Table 2.** CKD free subjects for the CKD incidence.

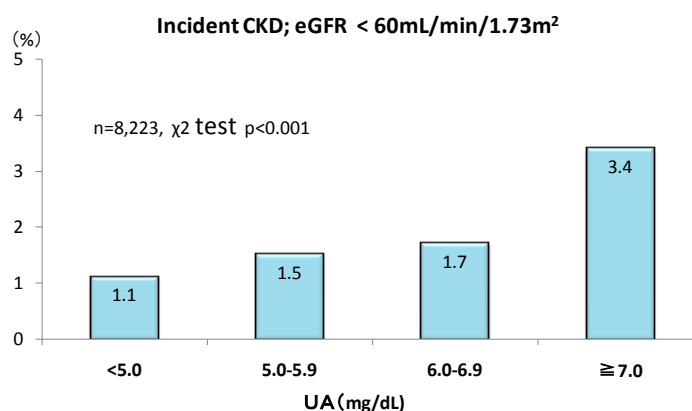
|                                   | UA Groups (mg/dL) |             |             |             |             |        |
|-----------------------------------|-------------------|-------------|-------------|-------------|-------------|--------|
|                                   | Overall           | <5.0        | 5.0 - 5.9   | 6.0 - 6.9   | ≥7.0        |        |
| N                                 | 8,223             | 2,631       | 2,418       | 2,118       | 1,056       |        |
| Age (y)                           | 39 ± 10           | 37 ± 9      | 39 ± 10     | 40 ± 10     | 41 ± 9      | <0.001 |
| Men (%)                           | 77.7              | 42.2        | 89.6        | 97.9        | 98.8        | <0.001 |
| Hypertension (%)                  | 7.7               | 3.8         | 7.1         | 10.6        | 15.1        | <0.001 |
| BMI (Kg/m <sup>2</sup> )          | 22 ± 3            | 21 ± 3      | 22 ± 3      | 23 ± 3      | 24 ± 3      | <0.001 |
| Waist circumference (cm)          | 78.6 ± 8.8        | 74.1 ± 8.2  | 78.6 ± 7.9  | 81.1 ± 7.9  | 84.2 ± 8.6  | <0.001 |
| SBP (mmHg)                        | 118 ± 13          | 113 ± 12    | 118 ± 12    | 120 ± 13    | 123 ± 14    | <0.001 |
| DBP (mmHg)                        | 74 ± 9            | 70 ± 9      | 74 ± 9      | 75 ± 9      | 77 ± 9      | <0.001 |
| Cr (mg/dL)                        | 0.75 ± 0.14       | 0.65 ± 0.13 | 0.77 ± 0.11 | 0.80 ± 0.11 | 0.83 ± 0.11 | <0.001 |
| eGFR (mL/min/1.73m <sup>2</sup> ) | 91.2 ± 17.6       | 96.5 ± 19.5 | 91.1 ± 16.6 | 88.1 ± 15.4 | 84.3 ± 15.0 | <0.001 |
| TC (mg/dL)                        | 192 ± 29          | 187 ± 29    | 192 ± 29    | 194 ± 28    | 201 ± 28    | <0.001 |
| TG (mg/dL)                        | 94 ± 59           | 72 ± 42     | 91 ± 51     | 106 ± 65    | 126 ± 76    | <0.001 |
| HDLC (mg/dL)                      | 64 ± 15           | 69 ± 15     | 64 ± 15     | 61 ± 14     | 59 ± 16     | <0.001 |
| LDLC (mg/dL)                      | 113 ± 26          | 106 ± 25    | 113 ± 26    | 117 ± 26    | 122 ± 27    | <0.001 |
| FPG (mg/dL)                       | 93 ± 10           | 91 ± 9      | 93 ± 10     | 94 ± 10     | 96 ± 11     | <0.001 |
| HbA1c (NGSP) (%)                  | 5.23 ± 0.34       | 5.21 ± 0.33 | 5.23 ± 0.33 | 5.25 ± 0.34 | 5.29 ± 0.37 | <0.001 |

CKD: chronic kidney disease; UA: serum uric acid concentration; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; Cr: serum creatinine concentration; eGFR: estimated glomerular filtration rate; TC: total cholesterol; TG: triglycerides; HDLC: high-density lipoprotein cholesterol; LDLC: low-density lipoprotein cholesterol; FPG: fasting plasma glucose concentration; HbA1c: hemoglobin A1c.

both Mets and hyperuricemia. The association of hyperuricemia with the incidence of CKD appeared to be greater than that of the Mets. Moreover, the presence of both has a substantial additive effect on Mets or hyperuricemia alone.

#### 4. Discussion

The present study demonstrates that: 1) In a cross-sectional analysis, higher UA levels are associated with the



**Figure 4.** UA levels and the incident CKD at year 4.

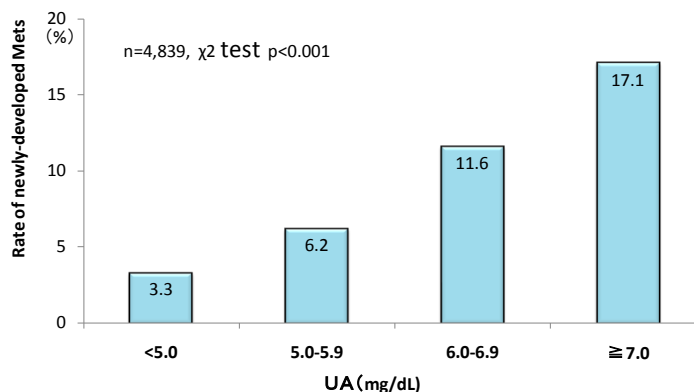
**Table 3.** Mets free subjects for the CKD incidence.

|                                   | UA Groups (mg/dL) |             |             |             |             |        |
|-----------------------------------|-------------------|-------------|-------------|-------------|-------------|--------|
|                                   | Overall           | <5.0        | 5.0 - 5.9   | 6.0 - 6.9   | ≥7.0        |        |
| N                                 | 4,839             | 1,440       | 1,446       | 1,297       | 656         |        |
| Age (y)                           | 41 ± 8            | 41 ± 8      | 42 ± 8      | 42 ± 7      | 42 ± 7      | <0.001 |
| Men (%)                           | 81.3              | 48.1        | 91.1        | 98.5        | 98.6        | <0.001 |
| BMI (Kg/m <sup>2</sup> )          | 22 ± 3            | 21 ± 3      | 22 ± 3      | 23 ± 3      | 24 ± 3      | <0.001 |
| Waist circumference (cm)          | 79.0 ± 8.3        | 75.1 ± 8.0  | 78.9 ± 7.7  | 81.0 ± 7.4  | 83.6 ± 7.8  | <0.001 |
| SBP (mmHg)                        | 117 ± 13          | 113 ± 12    | 117 ± 12    | 119 ± 13    | 121 ± 13    | <0.001 |
| DBP (mmHg)                        | 74 ± 9            | 71 ± 9      | 74 ± 9      | 75 ± 9      | 76 ± 9      | <0.001 |
| Cr (mg/dL)                        | 0.76 ± 0.13       | 0.68 ± 0.13 | 0.78 ± 0.11 | 0.81 ± 0.11 | 0.83 ± 0.11 | <0.001 |
| eGFR (mL/min/1.73m <sup>2</sup> ) | 87.6 ± 14.9       | 91.2 ± 16.1 | 87.9 ± 14.5 | 85.8 ± 13.7 | 82.8 ± 13.1 | <0.001 |
| TC (mg/dL)                        | 194 ± 29          | 190 ± 29    | 194 ± 29    | 196 ± 28    | 202 ± 29    | <0.001 |
| TG (mg/dL)                        | 95 ± 59           | 75 ± 44     | 93 ± 50     | 106 ± 64    | 123 ± 77    | <0.001 |
| HDLC (mg/dL)                      | 64 ± 16           | 69 ± 16     | 64 ± 15     | 61 ± 14     | 60 ± 16     | <0.001 |
| LDLC (mg/dL)                      | 115 ± 26          | 109 ± 25    | 115 ± 26    | 118 ± 25    | 123 ± 27    | <0.001 |
| FPG (mg/dL)                       | 94 ± 9            | 92 ± 9      | 94 ± 9      | 95 ± 9      | 96 ± 10     | <0.001 |
| HbA1c (NGSP) (%)                  | 5.26 ± 0.3        | 5.24 ± 0.30 | 5.25 ± 0.30 | 5.27 ± 0.29 | 5.28 ± 0.33 | <0.01  |

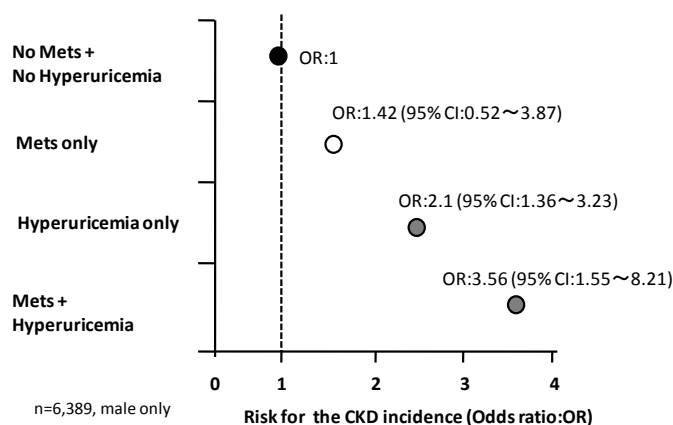
Mets: metabolic syndrome; UA: serum uric acid concentration; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; Cr: serum creatinine concentration; eGFR: estimated glomerular filtration rate; TC: total cholesterol; TG: triglycerides; HDLC: high-density lipoprotein cholesterol; LDLC: low-density lipoprotein cholesterol; FPG: fasting plasma glucose concentration; HbA1c: hemoglobin A1c.

greater prevalence of CKD and Mets; and 2) In a longitudinal analysis, hyperuricemia and Mets are associated with the new incidence of CKD in which the association of the former appears to be substantially greater than that of the latter.

The strengths of this study are the large number of individuals who did not have CKD at the entry, the complete nature of the data set, and the ability to link demographic and clinical factors with CKD. Other advantages include the ability to adjust for multiple factors that may affect initiation of CKD. We must also emphasize that



**Figure 5.** UA levels and newly-developed Mets at year 4.



**Figure 6.** A greater association of hyperuricemia than of Mets with the new incidence of CKD.

we controlled for the currently treated diabetes, hypertension, hyperuricemia, dyslipidemia and MACE etc., all known as well-established predictors of CKD.

To date, a large body of epidemiological trials demonstrates that increased UA is associated with increased risk for future hypertension, diabetic nephropathy and CKD, and that hyperuricemia, per se, could be an independent risk factor for poor cardiovascular prognosis [1]-[10]. In addition, animal experiments demonstrate that increased serum UA causes hypertension that is reversible at the early stage but becomes irreversible at the later stage [15]. Based on these studies, it appears that increased UA represents a possible new and intriguing target for the reduction of morbidity and mortality in CKD-associated MACE.

#### 4.1. UA Levels and the Prevalence of Mets

Previous reports showed that hyperuricemia is closely related with visceral fat volume and that changes in UA levels are also strongly correlated with changes in the visceral fat volume [16]. Recent clinical trials disclosed that individuals with Mets have a greater UA levels than those without it [17] [18]. Moreover, higher UA levels were closely related with the number of Mets constituents [16] [19] [20]. Taking all of these studies into consideration, the increased UA levels should have been regarded as one of the adjacent factors to the Mets components despite that hyperuricemia’s not being included in one of the constituents of Mets according to many guidelines in the world [11].

#### 4.2. UA Levels with CKD Incidence

Advanced CKD is a high risk condition, since it frequently induces fatal cardiovascular complications such as MACE [22]. There are mixed literatures on the role of UA level on progression of CKD, with both positive and



negative results. UA level is an independent risk factor for the progression of kidney disease in a variety of kidney diseases [1]-[10]. Weiner *et al.* recruited 13,338 participants with intact kidney function in two community-based cohorts and concluded that elevated UA level is a modest, independent risk factor for incident CKD in the general population [23]. In contrast, Choncol *et al.* reported that UA level has a minor association with progression of kidney disease and does not appear to be an important risk factor for incident CKD [24]. The present study demonstrates that even without kidney dysfunction, high UA acts as a trigger for new incidence of CKD, suggesting that UA, *per se*, independent of renal dysfunction has some contribution to declining kidney function.

### 4.3. A greater Association of Hyperuricemia than Mets with the CKD Incidence

Choi *et al.* reported that the prevalence of the Mets increases substantially with increasing levels of serum UA, suggesting that physicians should recognize the Mets as a frequent comorbidity of hyperuricemia and the treatment of hyperuricemia to prevent serious complications could be crucial [19].

The association of serum UA and Mets with CKD remains controversial. See and associates using data from 81,799 adults with or without Mets (45,148 men and 36,651 women) suggested that hyperuricemia is strongly associated with CKD, independent of the presence of Mets [21]. On the other hand, Hjortnaes *et al.* showed that although elevated serum UA levels are strongly associated with the Mets, they are as yet not an independent risk factor for vascular disease in patients with the Mets. In patients without Mets, elevated serum UA levels are associated with increased risk for vascular disease [20].

### 4.4. Putative Mechanisms of UA Induced CKD

Although it is beyond the scope of the present study, presuming the mechanism of UA-induced kidney dysfunction is of great interest. Although the entire pathogenesis is largely unknown, the mechanisms by which UA exerts a BP raising effect have been described as a UA-mediated hypertension, which can be highlighted that increase in circulating UA induces vasoconstrictive-hypertension in the early stage and salt sensitive volume-expanded hypertension in the late stage. This is, presumably, via an activation of intra renal renin-angiotensin system, an increased reactive oxygen species, and a decreased nitric oxide production [25]. Studies of humans also found that UA level was an important predictor of both hyperinsulinemia and weight gain [26] [27]. Due to the lack of information, future study must be carried out focusing on whether or not hyperuricemia, *per se*, affects patients' mortality [28].

### 4.5. Limitation of the Study

Despite the large scale of the data setting, the present study has several limitations. First, the definition of CKD incidence is merely based on changes in eGFR, rather than more precise measures of endogenous Cr clearance. Second, this is a retrospective study in which "Cause & Effect" is not always appropriately proven. Third, we studied a relatively younger healthy population, which may make it difficult to extrapolate the results to other ill populations. Fourth, residual confounding, by unmeasured factors or by kidney function, could have been present in this analysis. Finally, we did not have information on urine protein excretion, which could have either strengthened or attenuated the results.

## 5. Conclusion

The present study shows that both hyperuricemia and Mets have an impact on the new incidence of CKD. The former appears to be more influential than the latter.

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## Conflict of Interest

The authors have declared that no conflict of interest exists.

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