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Serum uric acid as a predictor of future hypertension: Stratified analysis based on body mass index and age

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ABSTRACT

Background. Serum uric acid level is a predictor of future hypertension. However, its dependence on body mass index or age is unclear.

Methods. We examined 26,442 Japanese males aged 18–60 years free from hypertension or diagnosed cardiovascular disease at baseline followed up between 2000 and 2010. Participants were categorized into three groups according to the tertile of serum uric acid levels [mg/dL; 1st (reference): 0.1–5.3; 2nd: 5.4–6.2; 3rd: 6.3–11.6]. Incident hypertension was defined as newly detected blood pressure ≥ 140/90 mm Hg and/or antihypertensive drugs initiation. Body mass index (<25 kg/m^2 vs. ≥25 kg/m^2) and age (<40 years vs. ≥40 years) were stratified into two groups.

Results. During a mean follow-up of 7.2 years, there were 11,361 (43%) hypertension cases. Mean serum uric acid levels (mg/dL) at baseline in each group were 1st tertile, 4.6; 2nd tertile, 5.8; and 3rd tertile, 7.0. The cumulative incident hypertension rate was significantly higher in the 3rd tertile (50.8%) than in the 1st (37.4%). Multiple-adjusted hazard ratios (95% confidence interval) for incident hypertension compared with 1st tertile were 1.01 (0.96–1.05) and 1.15 (1.10–1.21) in the 2nd and 3rd tertile, respectively. There was a significant interaction between age and serum uric acid level (p for interaction = 0.035). In subjects aged ≥40 years, the 3rd serum uric acid group showed higher hazard ratios [1.48 (1.38–1.59)].

Conclusion. High serum uric acid level was associated with future hypertension in young and middle-aged Japanese males. This association was stronger among subjects ≥40 years old.

1. Introduction

Hypertension is one of the most important risk factors of stroke, cardiovascular disease, and renal disease, and the risk of morbidity and death increases as blood pressure exceeds the optimal levels (Fujiyoshi et al., 2012; Imano et al., 2009; Kondo et al., 2013; Okumura et al., 2014; Tozawa et al., 2003). However, approximately 90% hypertension cases are of essential hypertension, and the etiology of its onset is unclear (Anderson et al., 1994; Omura et al., 2004; Rossi et al., 2006).

Uric acid (UA) is the final metabolite of purines in human and increasing serum UA (SUA) levels are known to be associated with incident hypertension (Forman et al., 2009; Grayson et al., 2011; Krishnan et al., 2007; Mellen et al., 2006; Nakanishi et al., 2003; Taniguchi et al., 2001). Some studies have shown that blood pressure is lowered by UA-lowering drugs (Agarwal et al., 2013; Feig et al., 2008; Soletsky and Feig, 2012). However, there is insufficient data regarding whether SUA level is an independent risk factor of incident hypertension and the subgroup that is associated with incident hypertension (Wu et al., 2016).

We conducted a large-scale long-term cohort study to investigate the relationships of SUA levels and incident hypertension and of subgroups associated with incident hypertension in young and middle-aged Japanese males free from hypertension or diagnosed cardiovascular disease at baseline. This study was approved by the ethics committee of the Nagoya University School of Medicine and all subjects gave their informed consent for participation.

2. Methods

2.1. Study population

The subjects were 33,942 Japanese male workers aged 18–60 years, recruited in 2000, who underwent annual medical checkups at their workplaces from

Abbreviations: SUA, serum uric acid; BMI, body mass index; UA, uric acid; HR, hazard ratio; SD, standard deviation; XO, xanthine oxidase; NO, nitric oxide.

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2000 to 2010. The law stipulates annual medical health examinations for all workers in Japan, and none of them refused to participate. All subjects were employed by blue chip manufacturing companies in Aichi Prefecture, in the center of Japan. We excluded subjects with only baseline data (n = 769); with hypertension (≥140/90 mm Hg and/or taking antihypertensive drugs (n = 4223); who were taking drugs for hyperuricemia (n = 953), heart disease (n = 191), renal disease (n = 122), lipid abnormalities (n = 1965), and diabetes mellitus (n = 761). The final sample was 26,442 subjects (Fig. 1).

2.2. Examination

Annual medical checkups were performed from 2000 until 2010 or retirement and included physical examination, blood pressure measurement, blood test, dipstick urine test, and structured questionnaire. The questionnaire comprised smoking status, alcohol intake, medical history, and medications. The smoking status was classified into three groups (current smoker, former smoker, and never smoker), and alcohol intake was classified into two groups (habitual and non-habitual). A habitual drinker was defined as a subject who drank alcohol every day. Weight and height were measured while the subject was wearing light clothing and no shoes. The body mass index was computed as the weight in kilograms divided by the square of the height in meters. Blood and urine test samples were collected in the morning after fasting for 1 night. Blood samples were analyzed using autoanalyzer (Dimension RxL MAX; SIEMENS, Munich, Germany) and measured by the uricase ultraviolet method. Urinalysis was performed using a dipstick. Urinalysis for proteinuria was conducted using Uropaper III (Eiken Chemical Co., Ltd., Tokyo, Japan), and the results were measured using a US-2100 Automated Urine Analyzer (Eiken Chemical Co., Ltd., Tokyo, Japan) [trace (±), proteinuria ≥15 mg/dL; 1+, ≥30 mg/dL; 2+, ≥100 mg/dL; 3+, ≥300 mg/dL; 4+, ≥1000 mg/dL].

2.3. Blood pressure measurement

Blood pressure was measured annually with the participant in the sitting position after a 5-min rest using an automated sphygmomanometer (BP-203IIIB; Colin Corporation, Tokyo, Japan). The blood pressure was measured twice on the right arm with intervals of 1 min, and the average value was calculated as the baseline blood pressure. When a subject had frequent premature contractions or atrial fibrillation, trained nurses confirmed the blood pressure using a conventional mercury sphygmomanometer. Incident hypertension was defined as that when the newly detected blood pressure was higher than 140/90 mm Hg and/or when antihypertensive drugs were initiated.

2.4. Statistical analysis

Statistical analyses were performed using the STATA software program version 11 (Stata Corp. College Station, TX, USA). Subjects were classified into tertiles on the basis of the SUA levels at the baseline. In the analyses, we used the lowest tertile of SUA as a reference group. Proteinuria was classified into three groups: negative (−), trace (±), and ≥1+. Baseline characteristics were analyzed using the trend test according to the tertile of SUA level (Table 1). According to the presence of incident hypertension, continuous variables were compared using *t*-test, and categorical variables were compared using a chi-square test (Table 2).

The Kaplan–Meier method was used to create the survival curves for each group and compared using the log-rank test. Cox proportional hazards model was used to calculate adjusted hazard ratio (HR) of incident hypertension according to the tertile of SUA level in five models. Model 1 was crude, model 2 was further adjusted for age, model 3 was further adjusted for BMI, model 4 was further adjusted for systolic blood pressure of baseline, and lastly, model 5 was further adjusted for total cholesterol, triglyceride, fasting blood glucose, creatinine, urine protein, smoking history, and alcohol intake.

In subgroup analysis, we stratified age (≥40 years and <40 years) and BMI (≥25 kg/m^2 and <25 kg/m^2) and also performed the test of interaction using likelihood ratio test. Cut-off value of BMI was decided as per the Japanese definition of obesity (Chin and Miyazaki, 2009). All p values were two tailed, and $p < 0.05$ were considered statistically significant.

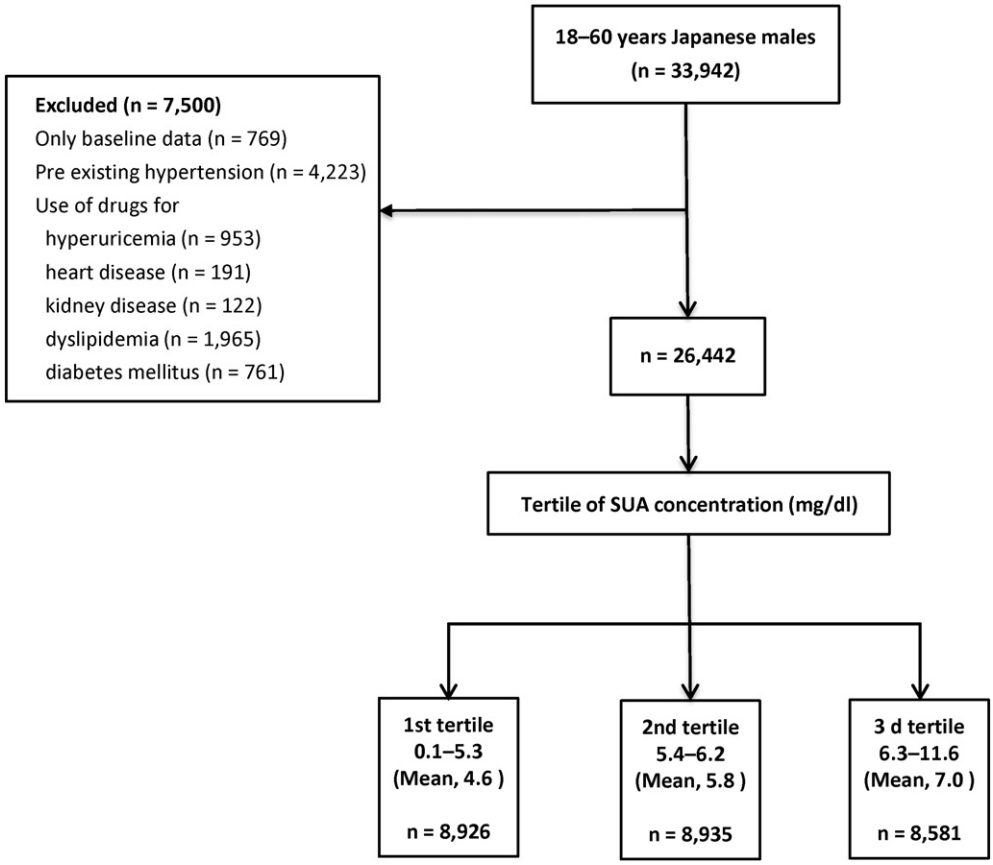


Fig. 1. Flow of study participant selection. Pre existing hypertension was defined as blood pressure ≥ 140/90 mm Hg and/or use of antihypertensive drugs. SUA denotes serum uric acid.

Table 1
Baseline characteristics according to the tertile of SUA concentration.

		Baseline SUA tertile (mg/dL)			
	All	0.1–5.3 (Mean, 4.6)	5.4–6.2 (Mean, 5.8)	6.3–11.6 (Mean, 7.0)	*p* for trend
Number of participants	26,442	8926	8935	8581	
Age (years)	36.8 ± 8.7	36.9 ± 8.9	36.4 ± 8.6	37.1 ± 8.5	0.071
Body mass index (kg/m^2)	22.5 ± 2.8	21.7 ± 2.6	22.3 ± 2.7	23.5 ± 2.9	<0.001
Systolic blood pressure (mm Hg)	113.9 ± 10.3	112.7 ± 10.4	113.8 ± 10.3	115.2 ± 10.1	<0.001
Diastolic blood pressure (mm Hg)	69.1 ± 9.4	68.0 ± 9.3	68.8 ± 9.2	70.6 ± 9.4	<0.001
Total cholesterol (mg/dL)	189.1 ± 31.3	184.1 ± 30.2	187.8 ± 30.9	195.7 ± 31.7	<0.001
HDL cholesterol (mg/dL)	56.9 ± 13.6	58.0 ± 13.5	57.1 ± 13.5	55.5 ± 13.7	<0.001
Triglyceride (mg/dL)	116.2 ± 75.8	103.6 ± 62.4	112.4 ± 73.3	133.2 ± 87.0	<0.001
Creatinine (mg/dL)	0.93 ± 0.11	0.91 ± 0.10	0.93 ± 0.10	0.96 ± 0.11	<0.001
Fasting blood glucose (mg/dL)	90.2 ± 12.5	89.5 ± 13.8	89.8 ± 12.0	91.3 ± 11.6	<0.001
Dipstick proteinuria					
Negative	25,922 (98.0%)	8767 (98.2%)	8770 (98.2%)	8385 (97.7%)	
Trace	177 (0.7%)	65 (0.7%)	55 (0.6%)	57 (0.7%)	
≥1+	343 (1.3%)	94 (1.1%)	110 (1.2%)	139 (1.6%)	0.016
Smoker					
Never	6878 (26.0%)	2199 (24.6%)	2319 (26.0%)	2360 (27.5%)	
Former	4938 (18.7%)	1490 (16.7%)	1631 (18.3%)	1817 (21.2%)	
Current	14,626 (55.3%)	5237 (58.7%)	4985 (55.8%)	4404 (51.3%)	<0.001
Alcohol intake					
Habitual	9538 (36.1%)	2649 (29.7%)	3181 (35.6%)	3708 (43.2%)	
Non-habitual	16,904 (63.9%)	6277 (70.3%)	5754 (64.4%)	4873 (56.8%)	<0.001

HDL, high density lipoprotein; SUA, serum uric acid.

3. Result

3.1. Baseline characteristics

The baseline SUA level in this population showed a Gaussian distribution, and the average value [±standard deviation (SD)] was 5.78 (±1.11) mg/dL. The average SUA levels (mg/dL) of each group (±SD) were 4.6 (±0.66), 5.8 (±0.26), and 7.0 (±0.62) at the 1st, 2nd, and 3rd tertiles, respectively. The average age and BMI (±SD) of all participants were 36.8 (±8.7) years and 22.5 (±2.8) kg/m^2, respectively. In comparison, according to the tertile of SUA level, there were statistically significant trends in all parameters, except for age. There was an opposite trend in high-density lipoprotein cholesterol and smoking habit (Fig. 2, Table 1).

As for the baseline characteristics according to the presence of incident hypertension, mean SUA level (±SD) was 5.92 (±1.14) mg/dL in incident hypertension and 5.67 (±1.08) mg/dL in non-hypertension. All parameters showed statistically significant difference (Table 2).

3.2. Serum uric acid and risk for incident hypertension

The mean follow-up period was 7.2 years, and 11,361 (43.0%) subjects developed newly detected hypertension. Newly detected hypertension incidence was 37.4% in the 1st tertile, 41.0% in the 2nd tertile, and 50.8% in the 3rd tertile (log-rank test $p < 0.0001$; Fig. 3).

HR [95% confidence interval (CI)] of incident hypertension of the 3rd tertile in model 1 was 1.51 (1.45–1.58) and remained significant even when adjusting for age in model 2 (adjusted HR: 1.52, 95% CI: 1.45–

Table 2
Baseline characteristics according to the incident hypertension.

	Incident hypertension		
	−	+	*p*
Number of participants (%)	15,081 (57.0%)	11,361 (43.0%)	
Serum uric acid concentration (mg/dL)	5.67 ± 1.08	5.92 ± 1.14	<0.0001
Age (years)	36.4 ± 8.9	37.3 ± 8.3	<0.0001
Body mass index (kg/m^2)	21.9 ± 2.5	23.3 ± 3.0	<0.0001
Systolic blood pressure (mm Hg)	110.6 ± 9.7	118.2 ± 9.5	<0.0001
Diastolic blood pressure (mm Hg)	66.7 ± 8.8	72.3 ± 9.1	<0.0001
Total cholesterol (mg/dL)	186.4 ± 31.2	192.7 ± 31.0	<0.0001
HDL cholesterol (mg/dL)	57.5 ± 13.5	56.1 ± 13.6	<0.0001
Triglyceride (mg/dL)	110.4 ± 70.7	123.9 ± 81.4	<0.0001
Creatinine (mg/dL)	0.93 ± 0.10	0.94 ± 0.11	0.0006
Fasting blood glucose (mg/dL)	89.3 ± 12.4	91.4 ± 12.6	<0.0001
Dipstick proteinuria			
Negative	14,839 (98.4%)	11,083 (97.6%)	
Trace	90 (0.6%)	87 (0.8%)	
≥1+	152 (1.0%)	191 (1.7%)	<0.001
Smoker			
Never	4090 (27.1%)	2788 (24.5%)	
Former	2789 (18.5%)	2149 (18.9%)	
Current	8202 (54.4%)	6424 (56.5%)	<0.001
Alcohol intake			
Habitual	4963 (32.9%)	4575 (40.3%)	
Non-habitual	10,118 (67.1%)	6786 (59.7%)	<0.001

HDL, high density lipoprotein.

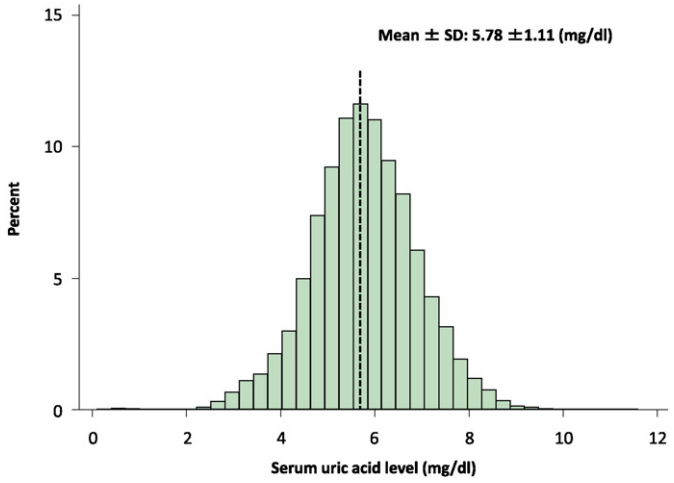


Fig. 2. Histogram of serum uric acid concentration. SUA denotes serum uric acid and SD denotes standard deviation.

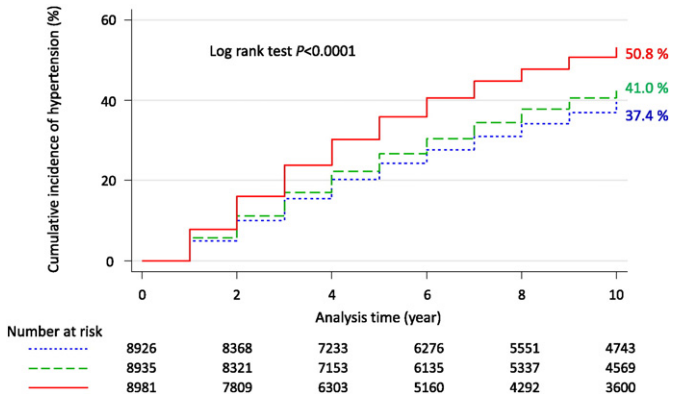


Fig. 3. Cumulative incidence of hypertension according to the tertile of the serum uric acid concentration estimated using the Kaplan–Meier method. Mean follow-up time was 7.2 years. The number of cumulative incident hypertension episodes was 11,361 (43.0%). The blue dotted line indicates the 1st tertile group, green dash indicates the 2nd tertile group, and red solid indicates the 3rd tertile group.

1.59) and remained statistically significant in model 5, although HRs were attenuated as further adjusting for other covariates (adjusted HR: 1.15, 95% CI: 1.10–1.21; Table 3).

3.3. Subgroup analysis

3.3.1. Age

Adjusted HR in model 5 was calculated as a reference for those aged <40 years and the lowest tertile of SUA levels. Adjusted HR was significantly higher in those aged ≥40 years than those aged <40 years (p for interaction = 0.035; Fig. 4).

3.3.2. BMI

As a reference, in those with BMI < 25 kg/m^2 and lowest tertile of SUA, adjusted HR in model 5 was calculated. Adjusted HR was higher in those with BMI ≥ 25 kg/m^2 than those with BMI < 25 kg/m^2 but not significant (p for interaction = 0.080; Fig. 5).

4. Discussion

In this study, we performed a large-scale long-term cohort study and showed that SUA level is an independent predictor of incident hypertension in young and middle-aged Japanese men. Furthermore, the relationship was particularly strong in those aged ≥40 years.

The mechanism by which elevated SUA levels induce hypertension remains elusive. Oxidative stress, inflammation, nitric oxide (NO) production impairment, vascular endothelial dysfunction, vascular smooth muscle proliferation, and renin angiotensin system enhancement have been reported as mechanisms for developing hypertension by hyperuricemia (Corry et al., 2008; Glantzounis et al., 2005; Kang et al., 2005a, 2005b; Khosla et al., 2005; Kono et al., 2010).

Crystallization of UA itself has also been reported to cause inflammation, gouty kidney, and urinary tract calculi, and progression to renal failure (Chonchol et al., 2007; Iseki et al., 2004; Low and Stoller, 1997; Weiner et al., 2008). Vascular disorders are important as a mechanism of incident hypertension by hyperuricemia, and there have been two reported pathways in previous studies (Battelli et al., 2014; Kang et al., 2005a, 2005b; Neogi et al., 2012; Price et al., 2006).

Vascular disorders can be caused by active oxygen produced by xanthine oxidase (XO). Hypoxanthine is a UA precursor and is metabolized to UA by XO present in the vascular endothelium where the active oxygen generated in the process inactivates NO in the vascular endothelium and proliferates vascular smooth muscle thus promoting arteriosclerosis (Battelli et al., 2014; Neogi et al., 2012).

Another pathway causing vascular disorders is the mechanism by UA itself flowing into the cells via a UA transporter present in the vascular endothelial cells and vascular smooth muscle cells. The UA transporter is mainly present in the proximal tubule in addition to the vascular smooth muscle cells (Price et al., 2006). UA causes vascular smooth muscle cell proliferation through urate transporters (Kang et al., 2005a, 2005b).

The vasorelaxant effect of acetylcholine was reported to attenuate as UA concentration increased in *in vitro* experiments using rat aorta (Nakagawa et al., 2006).

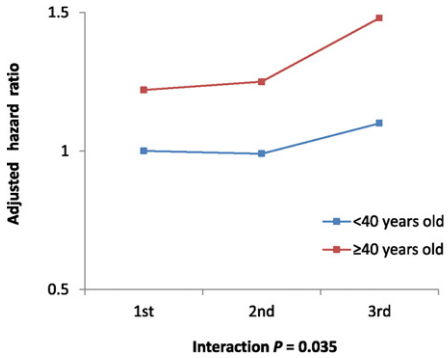
In developing hypertension by hyperuricemia, two phases would be conceived. In the first phase, inhibition of NO production and activation of the renin–angiotensin system by hyperuricemia causes excessive vasoconstriction, resulting in hypertension. This process is reversible and is a UA-dependent reaction where blood pressure can be reduced by lowering UA (Feig, 2012; Mazzali et al., 2001; Mazzali et al., 2002).

In the second phase, when hyperuricemia persists, the proliferation of vascular smooth muscle cells thickens vessel wall and increases blood pressure because of changes in the vascular structure. This step is UA independent and blood pressure does not return to the original level anymore by lowering UA as in the first phase (Feig, 2012; Kang et al., 2005a, 2005b). In this study, a stronger relationship between SUA level and hypertension developed in subjects aged ≥40 years. Long-term exposure

Table 3
Hazard ratios for incident hypertension.

SUA tertile (mg/dL)	Hazard ratio (95% CI)				
	Model 1	Model 2	Model 3	Model 4	Model 5
1st 0.1–5.3	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
2nd 5.4–6.2	1.12 (1.06–1.17)	1.13 (1.08–1.18)	1.04 (1.00–1.09)	1.01 (0.96–1.06)	1.01 (0.96–1.05)
3rd 6.3–11.6	1.51 (1.45–1.58)	1.52 (1.45–1.59)	1.22 (1.16–1.27)	1.16 (1.11–1.22)	1.15 (1.10–1.21)

Model 1, crude; Model 2, age; Model 3: Model 2 + BMI; Model 4: Model 3 + baseline BP; Model 5: Model 4 + total cholesterol, triglyceride, creatinine, proteinuria, fasting blood sugar, smoking, alcohol intake. CI, confidence interval; SUA, serum uric acid.



	Hazards ratio (95% confidence interval)	
SUA tertile (mg/dl)	Age < 40 years (n = 17,596)	Age ≥40 years (n = 8,846)
1st (0.1–5.3)	1 (reference)	1.22 (1.14–1.32)
2nd (5.4–6.2)	0.99 (0.93–1.05)	1.25 (1.17–1.34)
3rd (6.3–11.6)	1.10 (1.03–1.16)	1.48 (1.38–1.59)

Fig. 4. Adjusted hazard ratios stratified by age (<40 years vs. ≥40 years). Adjusted hazard ratios were calculated in Model 5. The lowest tertile of serum uric acid and age ≤ 40 years group was used as reference. Covariates included age, body mass index, baseline blood pressure, total cholesterol, triglyceride, creatinine, proteinuria, fasting blood sugar, smoking, and alcohol intake in Model 5.

to hyperuricemia may progress to irreversible arteriosclerosis of blood vessels, which could be related to higher HR in ≥40-year-old subjects and existence of interaction between age and SUA.

On the other hand, there was no significant interaction between SUA and BMI in this study. SUA and obesity may resonate each other by activating the renin-angiotensin system (Corry et al., 2008; Goossens et al., 2003; Reaven, 2011). In fact, the Tromsø Study in Norway, in contrast to our present study, demonstrated that higher baseline SUA was associated with higher odds of developing elevated blood pressure in overweight subjects (BMI ≥ 25 kg/m^2), but not in normal-weight subjects (BMI < 25 kg/m^2) (Norvik et al., 2016). The subjects in the present study were relatively thin and the average of BMI was 22.5 kg/m^2. Therefore, the significant interaction between SUA and BMI (<25 kg/m^2 vs. ≥25 kg/m^2) would not be observed. Further research of more overweight/obese samples is needed to verify the interaction.

5. Limitations

There were some limitations to this study. Only Japanese men were used as subjects because there was not long-term enough data for female workers; the number of female workers was limited and most female workers took one to three years maternity leave, during which blood pressures were not followed. Blood pressure was measured only once a year; in addition, blood pressure was not monitored at home. Data on abdominal circumference, daily exercise, diet, stress, and family history were not collected.

6. Conclusion

High SUA levels increases the risk of incident hypertension in young and middle-aged Japanese males without hypertension, hyperuricemia, heart disease, renal disease, lipid abnormalities, and diabetes mellitus. This association was stronger among subjects ≥40 years old.

Conflicts of interest

We declare no conflicts of interests.

Transparency document

The Transparency document associated to this article can be found, in online version.

Acknowledgments

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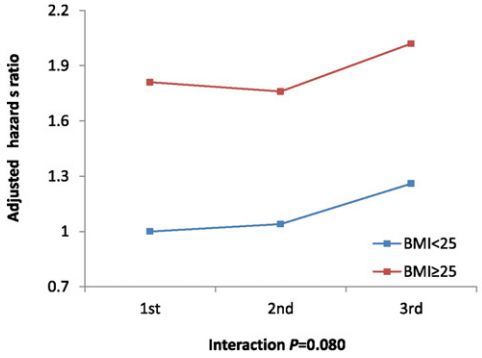

	Hazards ratio (95% confidence interval)	
SUA tertile (mg/dl)	BMI < 25 (n = 21,871)	BMI ≥ 25 (n = 4,571)
1st (0.1–5.3)	1 (reference)	1.81 (1.66–1.99)
2nd (5.4–6.2)	1.04 (0.99–1.10)	1.76 (1.63–1.91)
3rd (6.3–11.6)	1.26 (1.19–1.33)	2.02 (1.89–2.15)

Fig. 5. Adjusted hazard ratios stratified by body mass index (BMI; <25 kg/m^2 vs. ≥25 kg/m^2). Adjusted hazard ratios were calculated in Model 5. The lowest tertile of serum uric acid and BMI < 25 kg/m^2 group was used as reference. Covariates included age, body mass index, baseline blood pressure, total cholesterol, triglyceride, creatinine, proteinuria, fasting blood sugar, smoking, and alcohol intake in Model 5.

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