ORIGINAL ARTICLE ID: LCEH-2017-0179 Revised

Gender Interaction of Uric Acid in the Development of Hypertension

Shinichiro Nishio[1], Yukio Maruyama[1], Naoki Sugano[1], Tatsuo Hosoya[2], Takashi Yokoo[1], Satoru Kuriyama[1,3]

[1]Division of Hypertension & Nephrology, Department of Internal Medicine, Jikei University, [2]Department of Pathophysiology & Therapy in Chronic Kidney Disease, Jikei University, and [3]Health Management Center of the Tokyo Regional Taxation Bureau Clinic, Tokyo, Japan.

CORRESPONDENCE

Satoru Kuriyama M.D.
Division of Hypertension & Nephrology, Department of Internal Medicine, Jikei University School of Medicine
3-25-8, Nishi-shinbashi, Minato-ku, Tokyo
Japan 105-8461
TEL:03-3433-1111, Ext 3221
FAX: 03-3433-4297
e-mail:kuriyamas218@yahoo.co.jp

Short Title: Gender Interaction of Uric Acid in Hypertension

To Clin Exp Hypertens

ABSTRACT

Aim: The present study explored the gender interaction on the risk of uric acid in the new development of hypertension.

Study Design: A longitudinal retrospective cohort.

Subjects & Methods: A total of 5,807 individuals with an average age of 38 +/− 7 years old were recruited. Individuals whose blood pressure rose more than 140/90mmHg or those who newly commenced antihypertensive treatment were defined as a new onset of hypertension. Cox regression analysis was employed for the analysis.

Results: During the 10−years follow−up, 42.8% of men and 22.2% of women had developed hypertension. Factors to predict the hypertension development were male gender, older age, higher BMI, higher uric acid, and higher mean blood pressure. An association between higher uric acid levels and higher incidence of hypertension remained statistically significant in women in a multivariate model adjusted for various clinical variables (Hazard ration (HR), 1.180; 95%CI, 1.018 to 1.369), whereas such association was not found in men (HR, 1.034; 95%CI, 0.994 to 1.075). The interaction between the two genders reached statistical significance (p for interaction=0.007).

Conclusion: Higher uric acid is associated with the incident hypertension in the both genders. Women are more susceptible to the development of hypertension than men.

Key Words: Uric acid, Risk factor, Hypertension, Gender, Cohort.

Words count:199

INTRODUCTION

Studies have shown that high uric acid (UA) levels are associated with increased prevalence and incidence of hypertension [1–10]. We have also confirmed the link between hyperuricemia and incident hypertension in the latest communications [11,12]. These reports are suggestive that UA is not a mere clinical marker, but can be a risk mediator to develop hypertension independent of the traditional hypertension risk factors.

At all ages, the lifetime risk of hypertension is higher in men than in women, suggesting that the male gender is an independent risk factor. Circulating UA levels are unequivocally higher in men than in women. However, the gender-specific risk of UA for the new development of cardiovascular disorders does not always indicate the incident risk to be male-dominant. For instance, the Hazard ration (HR) for chronic kidney disease (CKD) in female with hyperuricemia was about 3 times higher than that in male, suggesting a greater susceptibility of female to UA in the progression of CKD to end stage renal disease [13]. The similar trait was supported by a recent systemic review and meta-analysis, where the comparison between the two genders revealed that the adjusted HR of incident hypertension in women was substantially higher compared with that in men, suggesting that the association of hyperuricemia to develop hypertension appears more profound in women than in men [14]. These studies provoke the possibilityof a gender-specific role of UA in the development of hypertension and its related cardiovascular diseases. Information on such interaction of UA by gender is of particular interest, but still remains insufficient.

The new concept of this study is, thus, if there is any difference between the two genders, to present a female-dominant gender susceptibility of UA to develop hypertension. These backgrounds prompted us to additionally investigate to what extent and how the gender becomes UA-related risk for the new development of hypertension. The subjects were recruited from relatively younger middle-aged Japanese men and women who had never been diagnosed as having hypertension before.

SUBJECTS &METHODS

Study population and design

The study design is a retrospective population-based cohort of Japanese office workers aged 20 to 65 years old (average 38 +/− 7 at start). The age distribution of men was the followings; < 30 (n=529, 11.0%), 30–40 (n=2,363, 49.1%), 40–50 (n=1,539, 32.0%), 50–60(n=378, 7.9%), 60 ≦ (n=0, 0%), and that of women; < 30 (n=110, 11.0%),

30–40 (n=623, 62.4%), 40–50 (n=231, 23.1%), 50–60(n=34, 3.4%), 60 ≦ (n=0, 0%)

The original number of the participants was15,470 who were scheduled on an annual routine medical check-up every year starting from 2005 to 2015 at the health management center of the Tokyo Regional Taxation Bureau. The basic criteria excludes individuals receiving medications for diabetes, hyperuricemia, hypertension and dyslipidemia; those having insufficient data; those with past history of incident major cardiovascular events such as cerebral apoplexy or myocardial infarction; those with any disease requiring hospitalization; those with current cancer or other life-threatening diseases; and those with current pregnancy. After the application of these exclusion criteria, a total number of 5,807 hypertension-free individuals were eligible for a longitudinal analysis of the development of hypertension for 10 years. The present study is a post-hoc analysis of our previous observations and part of the data have already been reported [11,12].

The definition of hypertension development

The new onset of hypertension was defined as a rise of systolic blood pressure (SBP) to 140 mm Hg or greater, and/or diastolic blood pressure (DBP) of 90 mm Hg or greater evaluated at any allocated time. In addition, the commencement of new antihypertensive drugs was also defined as the development of hypertension. Mean blood pressure (MBP) was calculated based on the following equation; MBP = DBP + (SBP-DBP)/3.

Other variables

Body mass index (BMI) was calculated based on the equation; BMI = Body weight (BW) X 1/(Body Height) squared. Laboratory tests were carried out after an 8- to 12-hour fasting. Measurements were made on serum creatinine (Cr) concentration, serum UA concentration, and lipid profiles including total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDLC), low-density lipoprotein cholesterol (LDLC), HbA1c and plasma glucose (PG). Renal function expressed as eGFR for Japanese was calculated based on the equation; eGFR= 194 x $Cr^{-1.094}$ x $Age^{-0.287}$ (if women x 0.739), reported elsewhere (15). Because the histograms of PG and TG distribute in a non-parametric fashion, logarithmic transformation was performed for these parameters.

Laboratory tests were performed using the Toshiba auto-analyzer (TBA-80 FR neo, Tokyo, Japan). 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 x 1.02 + 0.25 (%).

Ethical considerations

The 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 study protocol design was a retrospective screened cohort. This epidemiological 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 by the ethics committee of the University with the clinical trial number 25-203 (7338).

Statistical analysis

The database and all statistical outputs were retained by 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.

The development rate of hypertension was calculated as a function of gender.

The comparison of the rate of new hypertension was performedby using Chi-square analysis. Cox regresssion hazard analysis was used to estimate adjusted hazard ratio (HR) and associated 95% confidence interval (CI) to estimate hypertension development. The final variables were chosen on the basis of clinical importance and biological plausibility at the investigator's discretion. Forest plots were also applied to detect gender interaction of covariates to explain the development of hypertension, and comparison was made between the two genders.

Statistical analyses were carried out with Stat Flexversion 6.0 (Artec Ltd. Co., Osaka, Japan) and STATA version 11.1 (STATA Cooperation, College Station, TX, USA). Data are presented as the mean +/-standard deviation (SD), unless otherwise indicated. $P \leqq 0.05$ is considered statistically significant. 95% confidence intervals (CI) are expressed as 95%CI.

RESULTS

The rate of hypertension development

After applying exclusion criteria at the start of analysis, the population had an average age of 38+/- 7years, an eGFR of 87.0+/- 13.4mLmin/1.73 m2, SBP and DBP levels of 118+/- 11and 72 +/- 8mmHg (n=5,807, Table 1). All of the parameters indicated significant differences between men and women ($p<0.01$).

The overall rate of hypertension development was 39.3% (n=2,280) in 10 years, accounting for 42.8% in male (n=2,058) and 22.2% in female (n=222) (the Chi square

test, p<0.001) (Fig.1). The rate of the incident hypertension in men is about 2 fold higher than that in women (Fig. 1 left). The Figure 1right depicts the distribution of UA levels in the two genders. As was shown in Table 1, the distributions of serum UA levels are unequivocally greater in men than in women.

Factors to predict hypertension development

Table 2 shows predicting factors to estimate hypertension development in the both genders. Such factors were male gender (Hazard ration (HR) 1.338, 95%CI 1.148 to 1.559), older age (HR 1.007, 95%CI 1.000 to 1.013), greater BMI (HR 1.085, 95%CI 1.069 to 1.100), higher UA (HR 1.040, 95%CI 1.002 to 1.080), and higher MBP (HR 1.043, 95%CI 1.039 to 1.047) (Cox regression analysis).

Interaction of with other covariates for the incident hypertension

Table 3 shows gender interactions in the development of hypertension. In a multivariable model adjusted for various clinical variables, the association between higher UA levels with higher incidence of hypertension remained statistically significant in women (HR, 1.180; 95%CI,1.018 to 1.369), whereas such association was not observed in men (HR, 1.034; 95%CI, 0.994 to 1.075). The difference in the association between men and women reached statistical significance (p for interaction < 0.001). Similarly, gender interaction was also found in BMI (HR, 1.114; 95%CI, 1.072 to 1.158 for women, and HR, 1.079; 95%CI, 1.063 to 1.095 for men, p for interaction=0.012). However, unlike UA, BMI to develop hypertension was not gender-specific for women. This interaction was depited in Figure 2 using the Forest plots analysis.

For the purpose of taking the difference in UA levels between men and women into account, we reevaluated HR of UA at the same UA levels. We selected 2,802 individuals (512 women and 2,290 men) with UA levels ranging 4.1mg/dL to 5.9mg/dL. Hypertension developed in 38.8 % in men and 25.8 % in women during 10 year follow-up. Among these subjects, Cox regression analysis revealed that UA was no longer chosen as a factor to predict new hypertension development (data not shown).

DISCUSSION

Regarding the influence of hyperuricemia, a recent review on the relationship between hypertension and increase in UA found a significantly increased RR for incident hypertension [14]. Similarly, a recent meta-analysis consisting of 25 studies with a recruitment of 97,824 individuals showed a modest link between hyperuricemia and incident hypertension suggesting that hyperuricemia was associated with a higher risk of incident hypertension [16]. In accordance with these reports, our present study clearly demonstrates the association of higher UA levels with the incident

hypertension. Interestingly, our study presents a female-dominant gender susceptibility of UA to develop hypertension.

As far as a role of gender in UA-associated cardiovascular diseases is concerned, hyperuricemia appears to have a stronger impact among women than among men. This trend has been consistent with gender-specific data from other cardiovascular outcomes. For instance, in a recent meta-analysis of prospective studies has found that hyperuricemia is more strongly associated with the risk of coronary heart disease outcome in women [17]. Moreover, the association between gout and acute myocardial infarction was stronger in women than in men [18]. The gender interaction has also been documented in the incidence of CKD. Namely, Iseki et al. found that the HR for CKD in male with hyperuricemia (UA≧7.0mg/dl) was 2.00 (95%CI: 0.90-4.44), whereas it was 5.77 (95%CI: 2.31-14.42) in female hyperuricemia (UA≧6.0mg/dl), suggesting that hyperuricemia in female can be an independent predictor for end stage renal disease [13]. In human hypertension, Grayson et al. reported that a total of 18 prospective cohort studies representing data from 55,607 participants clearly demonstrate that hyperuricemia was associated with an increased risk for incident hypertension (adjusted HR, 1.41, 95%CI, 1.23-1.58). These effects were significantly larger in younger populations, and tended to be larger in women and among African American individuals, suggesting that the effect of hyperuricemia may be interacted with age, gender and/or ethnicity [14]. All in all, it appears evident that women are more susceptible than men to have cardiovascular diseases, despite the fact that the rate of the development is greater in men than in women. It may imply that relative physiological impact of having certain level of serum UA may be stronger among women than among men.

Why do women have a greater susceptibility to develop hypertension despite relatively lower UA level compared to men? The answer to address this question is crucial, but seems to be difficult. Circulating UA levels in women are clearly lower than that in men. In this context, the female-dominant susceptibility of UA to induce hypertension may be accounted for by other cardiovascular damaging factors presumably existing predominantly in men as the large disease burdens. For instance, if men had more innate risk factors such as obesity, hypertension, diabetes mellitus, dyslipidemia and renal dysfunction than women, and if those factors may overweigh the risk of UA to raise BP, UA may serve as a weaker susceptible risk in men, contributing less to become hypertensive. The present study shows that factors such as age, BP, diabetes mellitus and renal function are not involved in the gender interaction (Table 2). Therefore, such causes for men to be less susceptible to

develop hypertension than women are unknown. It can be assumed that antioxidant action elicited by UA could have been weakened in women than in men, presumably resulting in ill effect on BP regulatory systems. However, there has been absolutely no report on the comparative study of antioxidant effect of UA between the two genders. Given that the statistical potential capability is limited, residual confounding factors such as sex hormones not measured might have been involved in the results.

Noteworthy is that UA even within a normal range or neighboring the high normal may become a risk factor for hypertension in women (Fig 1 and Table 1). This may suggest that even high normal UA in female could be a substantial risk for the development of hypertension, because UA *per see* is regarded as a cardiovascular risk element or mediators to induce UA-mediated hypertension (19-23). A prospective cohort study recruiting 49,413 Japanese workers with a 7-years follow-up showed increase in UA or hyperuricemia has a strong association with the risks of death in all causes, CHD, stroke, liver disease and CKD suggesting that high UA appears to be a considerable risk factor for reduced life expectancy [24]. In this context, the present study has evoked several concerns. First, in women having high normal UA level, could UA be really a risk for hypertension? Second, do we have to therapeutically treat women having high normal UA levels? And, is it still validated that men and women share the same normal UA range in our daily medical practice? Of note is that chronic hyperuricemia may induce salt sensitive hypertension as a consequence of preglomerular arterioler disease [25]. If this holds true, lowering of elevated UA can be therapeutically essential to prevent UA-associated hypertension. Correction of hyperuricemia with xanthine oxidase inhibitor, allopurinol, improves the primary cardiovascular outcomes in a human prospective study [26]. However, at this point there are few studies that lowering levels of UA may slow the progression of hypertension induced cardiovascular complications. Whether correction of the elevated UA is beneficial or not remains to be elucidated in the future study and by then it is still a matter for debate [27].

Despite the large scale of the data setting, the present study has several limitations. This is a retrospective epidemiological study in which "Cause & Effect" is not always rightly proven. And, we studied a relatively younger healthy general population, which may make it difficult to extrapolate the results to other ill populations.

In summary, UA can be a risk for the development of hypertension in the both genders. Although the rate of the development is greater in men than in women, women are more susceptible to be hypertensive than men even without apparent hyperuricemia.

References

1. Sundstrom J, Sullivan L, D'Agostino RB, Levy D, Kannel WB, Vasan RS. Relations of serum uric acid to longitudinal blood pressure tracking and hypertension incidence. Hypertension 2005; 45(1):28–33.

2. Mellen PB, Bleyer AJ, Erlinger TP, Evans GW, Nieto FJ, Wagenknecht LE, Wofford MR, Herrington DM. Serum uric acid predicts incident hypertension in a biethnic cohort: the atherosclerosis risk in communities study. Hypertension 2006; 48(6):1037–1042.

3. Perlstein TS, Gumieniak O, Williams GH, Sparrow D, Vokonas PS, Gaziano M, Weiss ST, Litonja AA. Uric acid and the development of hypertension: the normative aging study. Hypertension 2006; 48(6):1031– 1036.

4. Shankar A, Klein R, Klein BEK, Nieto FJ. The association between serum uric acid level and long term incidence of hypertension: Population–based cohort study. Journal of Human Hypertension 2006; 20(12):937–945.

5. Forman JP, Choi H, Curhan GC. Plasma uric acid level and risk for incident hypertension among men. J Am Soc Nephrol 2007; 18(1):287–292.

6. Krishnan E, Kwoh CK, Schumacher HR, Kuller L. Hyperuricemia and incidence of hypertension among men without metabolic syndrome. Hypertension 2007; 49(2):298–303.

7. Taniguchi Y, Hayashi T, Tsumura K, Endo G, Fujii S, Okada K. Serum uric acid and the risk for hypertension and Type 2 diabetes in Japanese men: The Osaka Health Survey. J Hypertens 2001; 19(7):1209–1215.

8. Kawai T, Ohishi M, Takeya Y, Onishi M, Ito N, Yamamoto K, Kamide K, Rakugi H. Serum uric acid is an independent risk factor for cardiovascular disease and mortality in hypertensive patients. Hypertens Res 2012; 35(11):1087–92.

9. Krishnan E, Kwoh CK, Schumacher HR, Kuller L .Hyperuricemia and incidence of hypertension among men without metabolic syndrome. Hypertension2007;49(2):298–303.

10. Mellen PB, Bleyer AJ, Erlinger TP, Evans GW, Nieto FJ, Wagenknecht LE, Wofford MR, Herrington DM. Serum uric acid predicts incident hypertension in a biethnic cohort: the atherosclerosis risk in communities study. Hypertension 2006 48(6):1037–42.

11. Kuriyama S, Maruyama Y, Nishio S, Takahashi Y, Kidoguchi S, Kobayashi C, Takahashi D, Sugano N, Hosoya T, Yokoo T. Serum uric acid and the incidence of CKD and hypertension. Clin Exp Nephrol 2015;19(6):1127–34.

12. Nishio S, Kuriyama S, Hosoya T, Yokoo T. Hyperuricemia as a risk factor for the development of hypertension and chronic kidney disease –A 8-year follow-up study–. Gout and Nucleic Acid Metabolism 2016;40(1):33-46. (in Japanese)

13. Iseki K, Ikemiya Y, Inoue T, Iseki C, Kinjo K, Takishita S. Significance of hyperuricemia as a risk factor for developing ESRD in a screened cohort. Am J Kidney Dis 2004;44:642-50.

14. Grayson PC, Kim SY, LaValley M, Choi HK. Hyperuricemia and incident hypertension: a systematic review and meta-analysis. Arthritis Care Res 2011; 63(1):102-10.

15. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, Hishida A, on behalf of the collaborators developing the Japanese equation for estimated GFR. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis 2009;53:982-92.

16. Wang J, Qin T, Chen J, Li Y, Wang L, Huang H, Li J. Hyperuricemia and risk of incident hypertension: A systematic review and meta-analysis of observational studies. PLoS One. 2014 Dec 1;9(12):e114259. doi: 10.1371/journal.pone.0114259. eCollection 2014.

17. Kim SY, Guevara JP, Kim KM, Choi HK, Heitjan DF, Albert DA. Hyperuricemia and coronary heart disease: A systematic review and meta-analysis. Arthritis Care Res (Hoboken). 2010,62(2):170-180. [PubMed: 20191515]

18. De Vera MA, Rahman MM, Bhole V, Kopec JA, Choi HK. Independent impact of gout on the risk of acute myocardial infarction among elderly women: a population-based study. Ann Rheum Dis 2010 Jun;69(6):1162-4. doi: 10.1136/ard.2009.122770. Epub 2010 Feb 2.

19. Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. N Engl J Med 2008;359(17):1811-21.

20. Johnson RJ, Feig DI, Kang DH, Herrera-Acosta J. Resurrection of uric acid as a causal risk factor for essential hypertension. Hypertension 2005;45:18-20.

21. Nakagawa T, Kang DH, Feig D, Sanchez-Lozada LG, Srinivas TR, Sautin Y, Ejaz AA, Segal M, Johnson RJ. Unearthing uricacid: An ancient factor with recently found significance in renal and cardiovascular disease. Kidney Int 2006;69(10):1722-5.

22. Feig DI, Mazzali M, Kang DH, Nakagawa T, Price K, Kannelis J, Johnson RJ.: Serum uric acid: A risk factor and a target for treatment? J Am SocNephrol 2006;17:S69-S73 (suppl 2).

23. Johnson RJ, Segal MS, Srinivas T, Ejaz A, Mu W, Roncal C, Sánchez-Lozada LG, Gersch M, Rodriguez-Iturbe B, Kang DH, Acosta JH. Essentia lhypertension, progressive renal disease, and uric acid: Apathogenetic link? J Am Soc Nephrol 2005;16:1909-19.

24. Tomita M, Mizuno S, Yamanaka H, Hosoda Y, Sakuma K, Matsuoka Y, Okada M, Yamaguchi M, Yosida H, Morisawa, Murayama T. Does hyperuricemia affect mortality? A prospective cohort study of Japanese male workers. J Epidemiol 2000;10:403-9.

25. Johnson RJ, Herrera-Acosta J, Schreiner GF, Rodríguez-Iturbe B. Subtle acquired renal injury as a mechanism of salt-sensitive hypertension. N Engl J Med 2002; 346: 913-923.

26. Goicoechea M, de Vinuesa SG, Verdalles U, Ruiz-Caro C, Ampuero J, Rincón A, Arroyo D, Luño J. Effect of allopurinol in chronic kidney disease progression and cardiovascular risk. Clin J Am Soc Nephrol 2010 Aug;5(8):1388-93. doi: 10.2215/CJN.01580210. Epub 2010 Jun 10.

27. Watanabe S, Kang DH, Feng L, Nakagawa T, Kanellis J, Lan H, Mazzali M, Johnson RJ. Uric acid, hominoid evolution, and the pathogenesis of salt-sensitivity. Hypertension 2002; 40(3):355-360. [PubMed: 12215479]

ACKNOWLEDGEMENT

We are grateful to Ms. Tomoko Tanabe and Dr. Tomoko Nakano for their excellent technical expertise. A part of this study was presented at the annual scientific meeting of the Japanese Society of Gout and Nucleic Acid Metabolism held in Tokyo, Feb 2017.

CONFLICT OF INTEREST

The authors have declared that no conflict of interest exists.

FIGURE LEGENDS

Figure 1: The rate of hypertension development during 10 years follow-up.
The rate is greater in men than in women ($p<0.01$). The distribution of UA level is greater in men than in women ($p<0.01$).

Figure2: Forest plot on the interaction of gender in the incidenct hypertension.

FOOTNOTE FOR TABLES

Table 1: Baseline characteristics of analyzed subjects.

Abbreviations and Acronyms: UA; serum uric acid concentration, BMI; body mass index, SBP; systolic blood pressure, DBP; diastolic blood pressure, MBP; mean 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, PG; plasma glucose concentration, HbA1c; glycated hemoglobin. TG and PG were expressed as median with IQR(interquartile range) (in blacket), as their values were distributed in a non-parametric fashion. Comparison was made between men and women by the Chi square analysis.

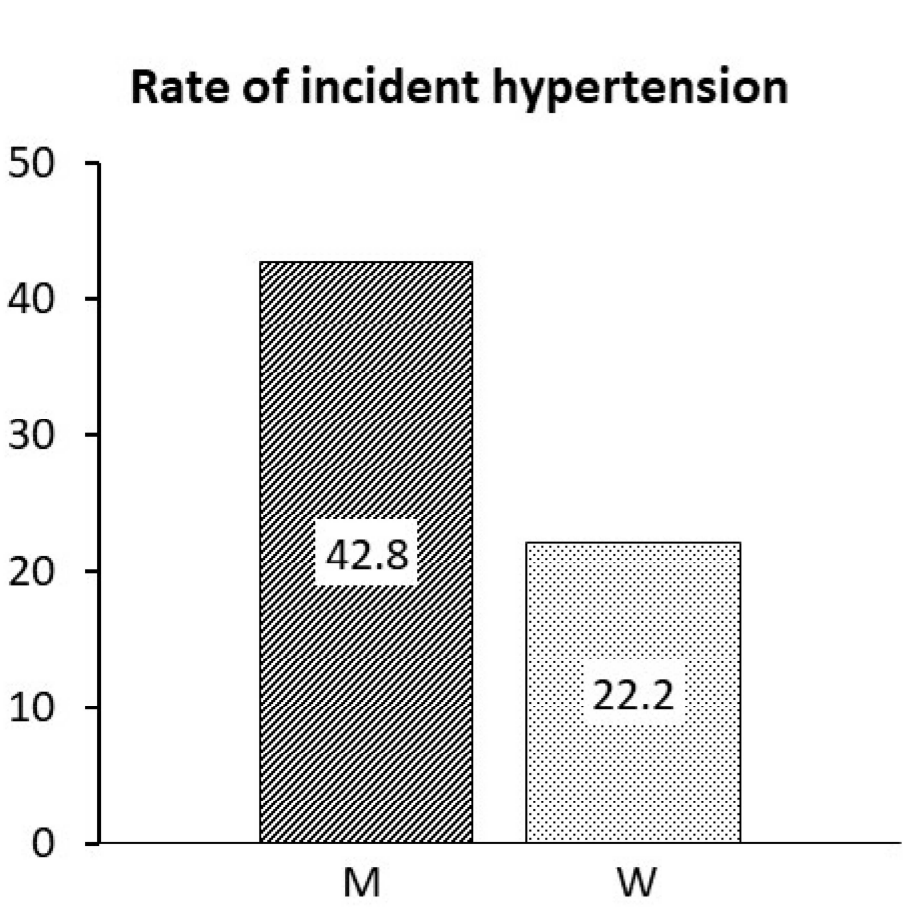
Table 2: Predicting factors to explain the development of hypertension.

UA; serum uric acid concentration, BMI; body mass index, eGFR; estimated glomerular filtration rate, MBP; mean blood pressure, HbA1c; glycated hemoglobin.

Table 3: Gender interaction in the development of hypertension.

UA; serum uric acid concentration, BMI; body mass index, eGFR; estimated glomerular filtration rate, MBP; mean blood pressure, HbA1c; glycated hemoglobin.

Figure. 1: The rate of hypertension development during 10 years follow-up



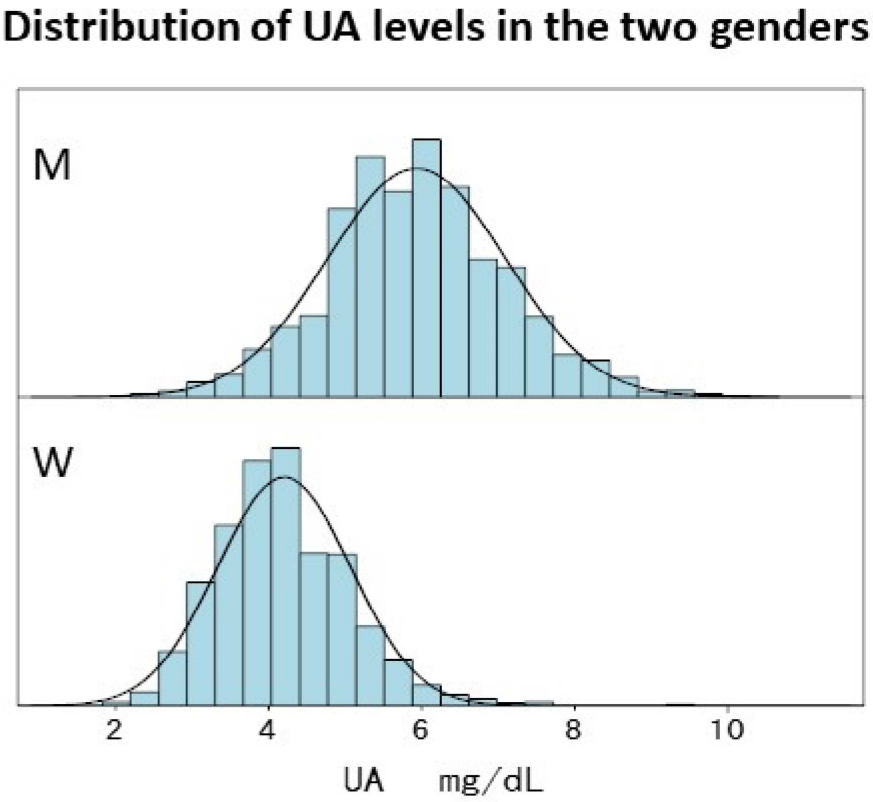


Figure 2: Forest plots on the interaction of gender in the incident hypertension

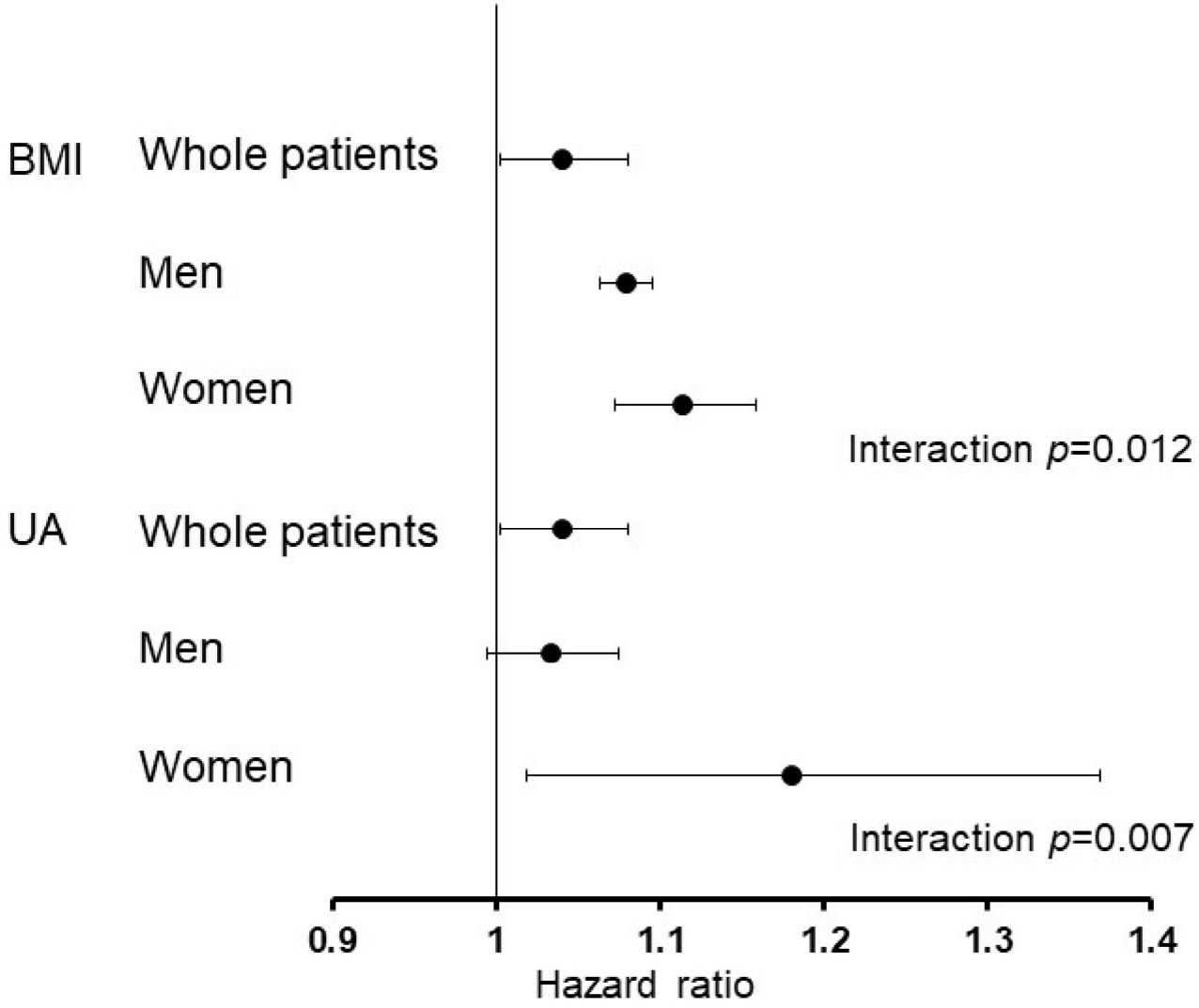


Table 1: Baseline characteristic of analyzed subjects

(n)	Overall（5,807）	Men（4,809）	Women（998）	P
Incident Rate (%)	39.3	42.8	22.2	<0.01
Age (y)	38±7	38±7	36±7	<0.01
BMI (Kg/m2)	23±3	22±3	21±3	<0.01
SBP (mmHg)	118±11	119±11	112±11	<0.01
DBP (mmHg)	72±8	73±8	68±8	<0.01
MBP(mmHg)	88±8	89±8	83±8	<0.01
Cr (mg/dL)	0.79±0.13	0.82±0.10	0.62±0.08	<0.01
eGFR (mL/min/1.73m2)	87.0±13.4	86.6±13.1	88.9±15.0	<0.01
UA (mg/dL)	5.6±1.3	5.9±1.2	4.2±0.9	<0.01
TC (mg/dL)	194±33	195±33	186±30	<0.01
TG (mg/dL)	80（68）	88（72）	53（31）	<0.01
HDLC (mg/dL)	61±15	59±14	71±14	<0.01
LDLC (mg/dL)	113±31	115±31	103±28	<0.01
PG (mg/dL)	90（11）	91（10）	87（9）	<0.01
HbA1c (NGSP)(%)	5.11±0.52	5.12±0.54	5.04±0.40	<0.01

Table 2: Predicting factors to explain the development of hypertension

	Unadjusted	Adjusted	P
Male gender	2.192 (1.908 to 2.517)	1.338 (1.148 to 1.559)	<0.001
Age	1.005 (0.999 to 1.010)	1.007 (1.0002 to 1.013)	0.04
BMI	1.139 (1.125 to 1.153)	1.085 (1.069 to 1.100)	<0.001
UA	1.242 (1.203 to 1.282)	1.040 (1.002 to 1.080)	0.041
eGFR	0.999 (0.997 to 1.003)	1.002 (0.999 to 1.006)	0.165
MBP	1.050 (1.046 to 1.053)	1.043 (1.039 to 1.047)	<0.001
HbA1c	1.230 (1.149 to 1.317)	1.061 (0.982 to 1.147)	0.134

Table 3: Gender Interactions in the development of hypertension

	Men	Women	Interaction p
Age	1.005 (0.998 to 1.012)	1.019 (0.997 to 1.041)	0.086
BMI	1.079 (1.063 to 1.095)	1.114 (1.072 to 1.158)	0.012
UA	1.034 (0.994 to 1.075)	1.180 (1.018 to 1.369)	0.007
eGFR	1.003 (0.999 to 1.006)	1.000 (0.991 to 1.010)	0.234
MBP	1.042 (1.038 to 1.046)	1.050 (1.039 to 1.062)	0.092
HbA1c	1.073 (0.990 to 1.162)	0.991 (0.715 to 1.374)	0.775