Age-differential association between serum uric acid and incident hypertension

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Age-differential association between serum uric acid and incident hypertension

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ABSTRACT

Age-differential association between serum uric acid and incident hypertension

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Introduction:

Increasing evidence suggests that elevated serum uric acid level is associated with an increased risk of hypertension. Although the positive association between serum uric acid

and incident hypertension has been reported in many previous studies, this association is inconsistent according to age, sex, lipid profiles and adiposity level. Additionally, data on interaction of serum uric acid and other risk factors on incident hypertension in general Korean population are limited. Thus, we aimed to investigate whether there is an independent association between serum uric acid and the risk of hypertension in Korean population, and to assess the interaction between serum uric acid and other risk factors on the risk of developing hypertension.

Methods:

This prospective cohort study included 808 participants aged 40-79 years from the Korean Genome Epidemiology Study (KoGES), which is an ongoing rural community-based cohort study. They were free of hypertension and major cardiovascular disease at baseline. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or using antihypertensive medication. Serial multivariable linear regression models were used to investigate cross-sectional association between serum uric acid and blood pressure. Covariates were sex, age, body mass index, high-density lipoprotein cholesterol and creatinine. A generalized linear model was used to estimate the relative risks for incident hypertension according to serum uric acid level at baseline. In addition to, to examine the consistency of the observed association between serum uric acid and hypertension, we performed subgroup analyses of participants according to sex, age (< 55, ≥ 55 years), body mass index (< 25, ≥ 25 kg/m^2),

triglycerides (< 150, ≥ 150 mg/dL), high-density lipoprotein cholesterol (40 ≤, > 40 mg/dL), low-density lipoprotein cholesterol (130 ≤, > 130 mg/dL) and fasting glucose (100 ≤, > 100 mg/dL) levels. The *p* value for interactions between serum uric acid and other risk factors for incident hypertension were calculated using a Z-test.

Results:

In this study, 314 male and 494 female which is middle-aged adults were included. During the mean follow-up of 3.3 years, cases of incident hypertension were 36 (11.5%) in men and 53 (10.7%) in women. In a cross-sectional analysis, serum uric acid level was positively associated with diastolic blood pressure when adjusting for sex, age, body mass index, high-density lipoprotein cholesterol and creatinine only in men. In a longitudinal analysis, the association between serum uric acid and incident hypertension was different by participant's age (*p* for interaction=0.009). There was no significant association between serum uric acid and incident hypertension in participants of age ≥ 55 years, but we found a significant association between serum uric acid and incident hypertension in participants of age < 55 years (relative risk 1.74 per 1.0 mg/dL increase in serum uric acid, *p*=0.002). However, BMI, triglycerides, fasting glucose, high-density lipoprotein and low-density lipoprotein cholesterol did not affect the association between serum uric acid and incident hypertension.

Conclusion:

We observed that age-differential association between serum uric acid level and incident hypertension among community-dwelling healthy Korean population. Among people who aged < 55 years, increased serum uric acid level was associated with increased risk of developing hypertension. It is recommended to measure and control serum uric acid level for middle-aged population to identify high-risk individuals and prevent future hypertension.

Keywords: hypertension, blood pressure, uric acid, interaction, risk factor, age

Age-differential association between serum uric acid and incident hypertension

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I. Introduction

Hypertension, the most important modifiable risk factor[1,2], is the leading cause of death and a major health burden in the worldwide[3,4]. Hypertension is a common disease among Korean elderly population aged 65 years or older considering that its prevalence

increased between 2007 and 2011 from 49.3% to 58.4% in men and from 61.8% to 68.9% in women[5]. Previous studies have been reported that the reduction of highly or moderately elevated blood pressure levels results in a decrease in stroke and myocardial infarction rates[6,7]. To decrease the rates of mortality and cardiovascular disease effectively, it is important to prevent incident hypertension. It is also important to understand the interrelationships of various risk factors for hypertension to prevent development of hypertension and cardiovascular disease.

Serum uric acid is the metabolic end product of purines in humans and increased serum uric acid levels are known to be associated with an increased risk of hypertension[8-11]. Serum uric acid has been found to be positively related not only to the risk of hypertension but also to the risk of atherosclerosis, cardiovascular diseases and metabolic syndrome[12-14]. Previous studies have reported that blood pressure is lowered by uric acid-lowering drugs[15,16]. The positive association between uric acid and blood pressure has been reported, suggesting that linking mechanism between hyperuricemia and hypertension is renal and metabolic abnormalities[17-19]. Hyperuricemia can also cause systemic inflammation[20] and insulin resistance[21,22].

Although the positive association between serum uric acid and incident hypertension has been reported in many previous studies, this association is inconsistent according to age, sex, lipid profiles and adiposity level. In addition to, there are insufficient data on interaction of serum uric acid and other factors on incident hypertension in general Korean population. Thus, we investigated whether there is independent association

between serum uric acid and incident hypertension among general Korean population, and whether the association is modified by other risk factors of incident hypertension.

II. Materials and Methods

1. Study population

This study analyzed data from the Korean Genome Epidemiology Study (KoGES)-Kangwha Study which is a rural community-based prospective cohort[23]. A total of 4,900 people aged more than 40 years were enrolled between 2006 and 2011. The participants were all independently living in from Kangwha Island, Incheon, South Korea.

For this study, we analyzed baseline and the follow-up data of eligible participants (n=4,210) who had information for serum uric acid levels between 2008 and 2013. We excluded individuals who had a history of stroke, angina pectoris or myocardial infarction at baseline (n=178). We also excluded individuals with high blood pressure (systolic blood pressure ≥ 140; diastolic blood pressure 90 mmHg (n=458)) and/or taking antihypertensive drugs (n=655) at baseline. After further excluding individuals who had no measurement of uric acid (n=1,192) or missing key covariates (n=1) or outlier (n=11), the final sample was 808 individuals (314 men and 494 women) who were aged 55.4 years.

All participants provided written informed consent form and study protocol was approved by the Institutional Review Board of Yonsei University Graduate School of Public Health (2-1040939-AB-N-01-2016-403).

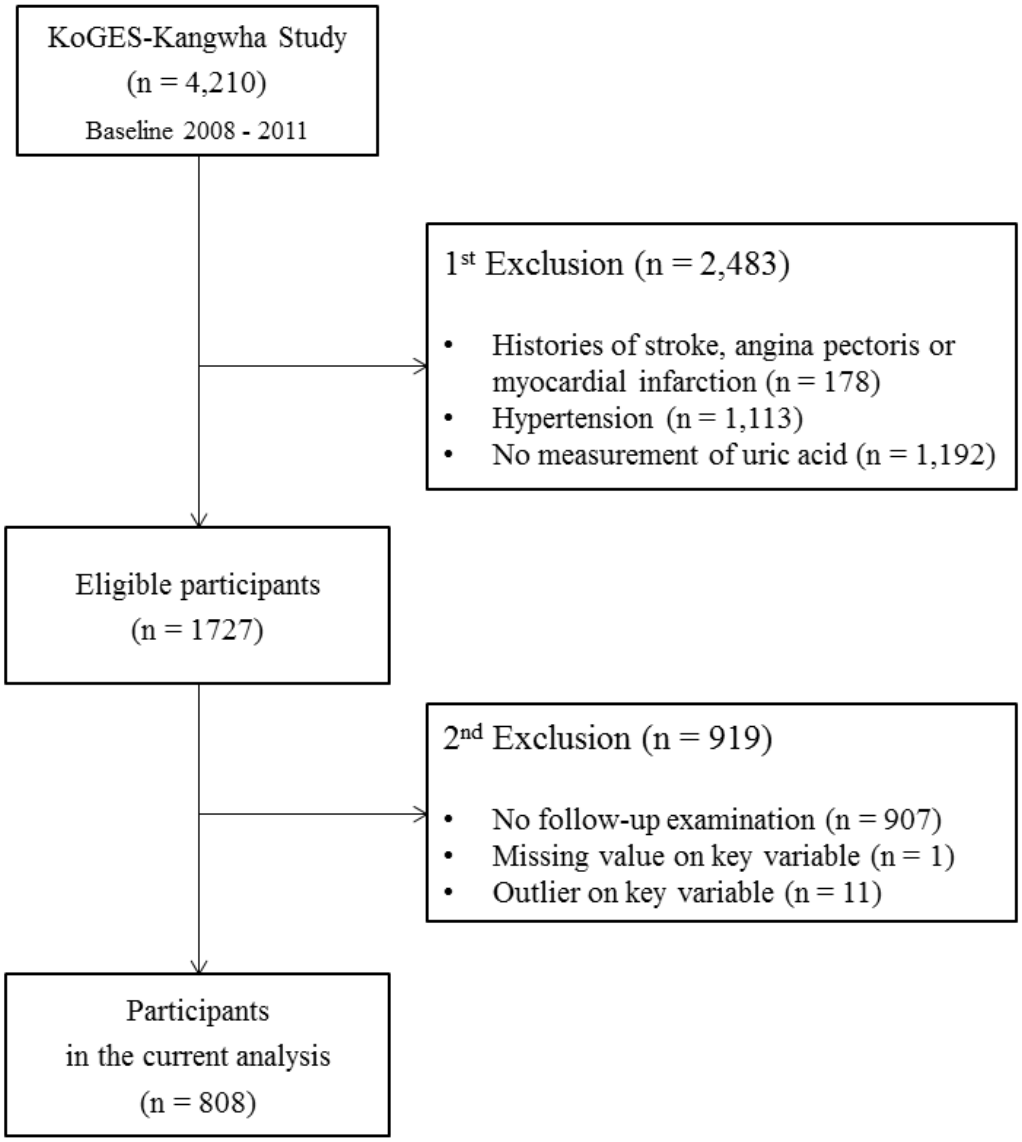

Figure 1. Flow chart of the selection criteria for the final study population

2. Measurements

A. Questionnaire data

All participants had an individual interview using standardized questionnaires to obtain information about their demographics, medical history, and health-related lifestyle. All interviewers were trained and performed questionnaire surveys according to a prescribed procedure. Smoking status was categorized as current smoking group and current nonsmoking group (ex-smokers and non-smokers). Alcohol intake was also classified into two groups: current alcohol drinking or current nondrinking (past alcohol drinking and never drinking).

B. Anthropometrics

Participants were required to refrain from smoking or ingesting caffeine for eight hours preceding the health examination. Prior to blood pressure measurements, participants were asked to sit and rest in a room for at least five minutes. With participants seated, an appropriately sized cuff was applied snugly around the upper right arm at the heart level. Cuff size was chosen for each subject according to mid-arm circumference. Heart rate and blood pressure were measured twice with at least a 5-minute interval between measurements using an automatic sphygmomanometer (Dinamap 1846 SX/P; GE Healthcare, USA). If the difference between the first and second measurements was greater than 10 mmHg, additional measurements were taken. The average of the last two measurements was used for analysis. Hypertension was

defined as average systolic blood pressure ≥ 140mmHg or average diastolic blood pressure ≥ 90mmHg or current blood pressure medication use. Standing height was measured to the nearest 0.1 cm on a stadiometer (SECA763, SECA GMBH, Germany). Body weight was measured to the nearest 0.1 kg on a digital scale (GL-60000-20, Seoul, Korea) with participants wearing underwear and examination gowns. Body mass index (BMI) was calculated as an individual's body weight in kilograms divided by their height in meters squared (Kg/m^2).

C. Laboratory assays

After at least eight hours of fast, blood samples were collected from the antecubital vein in the morning. Fasting blood glucose levels were determined by a colorimetry method (ADVIA 1800; Siemens Medical Solutions), and fasting insulin levels were determined by a immunoradiometric assay (SR-300; Stratec, Birkenfeld, Germany). Homeostasis model assessment of insulin resistance (HOMA-IR) was used to evaluate insulin resistance: HOMA-IR = fasting glucose (mg/dL) × fasting insulin (μIU/mL)/405[24]. Enzymatic methods were used to measure total cholesterol, high-density cholesterol (HDL), triglyceride and total protein levels (ADVIA 1800; Siemens Medical Solutions, Pleasanton, CA, USA). Low-density-lipoprotein (LDL) cholesterol levels were calculated using the Friedewald formula[25]. Blood urea creatinine was measured by colorimetric methods using automatic analyzers (ADVIA 1650, Bayer Corp, USA). The glomerular filtration rate (GFR) was calculated by Cockcroft and Gault formula[26]. C-reactive protein

(CRP) was measured by turbidimetric immunoassay assay (ADVIA 1800; DenKa Seiken, Japan).

D. Statistical analysis

Gender differences of general characteristics were analyzed using the independent t-test and the Wilcoxon rank-sum test for continuous variables, and the chi-square test for categorical variables. Fasting glucose level, insulin, triglycerides and CRP were log-transformed for parametric testing due to the right-skewed distribution. The relationships between serum uric acid and other variables at baseline were evaluated using Pearson's correlation analysis. We also evaluated linear trend and presented *p* for trend according to quartile range of serum uric acid at baseline which was a major interesting variable. We used a contrast to test for linear trends to calculate *p* values for continuous variables. We also used the Cochran-Armitage test to examine the existence of a linear trend of categorical variables. We made a comparison between baseline characteristics of people who developed hypertension and those who did not. Differences in continuous variable and normally distributed variables were tested by independent t-test and Wilcoxon rank sum test, respectively. Categorical variables were described as numbers with percentage and tested by chi-square tests or Fisher's exact test (for categorical variables with small expected numbers).

To access the cross-sectional associations between serum uric acid and blood pressure, we used serial multivariable linear regression model: model 1 was adjusted for sex (only

in pooled analysis) and age; model 2 was additionally adjusted for BMI; and model 3 was additionally adjusted for HDL cholesterol and creatinine. Potential confounders were evaluated by backward selection method and previous study results. We also presented penalized B-splines to explore the patterns of association between serum uric acid and blood pressure at baseline. Penalized regression methods were used that use a suitable penalty functional to quantify the notion of roughness of a curve, with a necessary compromise between bias and variability in curve fitting[27].

A relative risks of hypertension during follow-up period and associated 95% confidence intervals according to serum uric acid levels were estimated by generalized linear models with log-link-function and a Poisson distribution using robust variance estimator[28,29]. This was done the proportion of the outcome was greater than 10% in which case odd ratios would provide biased estimates of associations[30]. In addition to, restricted cubic spline was used to investigate the possibility of non-linearity association between serum uric acid and incident hypertension[31]. In this method, we selected five serum uric acid values as knots based on serum uric acid percentiles, tested the linear and non-linear associations between knots using a cubic function, and presented the integrated graph smoothly. Since the restricted cubic spline could be affected by outliers, we excluded values lower than the 1st percentile and greater than the 99th percentile. To examine the consistency of the observed association between serum uric acid and hypertension, we performed subgroup analyses of participants according to age (< 55, ≥ 55 years), BMI (< 25, ≥ 25 kg/m^2), triglycerides (< 150, ≥ 150 mg/dL), HDL cholesterol

(40 ≤, > 40 mg/dL) and LDL cholesterol (130 ≤, > 130 mg/dL) which are known risk factors for incident hypertension. The *p* value for interactions between serum uric acid and other risk factors on the incident hypertension were calculated by a Z-test. All analyses were performed using SAS statistical software, version 9.4 (SAS Institute Inc., Cary, NC, USA), and statistical significance was defined as a two-sided *p* value of < 0.05.

III. Results

Baseline characteristics of study population are presented in Table 1. The mean age of the study population was 57.1years in 314 men and 54.3 years in 494 women. The mean level of serum uric acid was 5.7 mg/dL in men and 4.4 mg/dL in women. Age, SBP, DBP, fasting glucose, triglycerides, creatinine, GFR, serum uric acid, smoking and alcohol intake were significantly higher in men than in women. However, fasting insulin level, total cholesterol, HDL cholesterol and LDL cholesterol were higher in women than in men. During follow-up period (mean 3.3 years), 36 men (11.5%) and 53 women (10.7%) developed hypertension.

Table 1. General characteristics of study population

Variables	Total (n=808)	Men (n=314)	Women (n=494)	*p* value
Age, year	55.4 ± 7.2	57.1 ± 6.9	54.3 ± 7.3	<.001
BMI, kg/m^2	24.5 ± 3.1	24.2 ± 2.9	24.6 ± 3.2	0.089
SBP, mmHg	116.1 ± 12.2	117.2 ± 11.6	115.4 ± 12.6	0.035
DBP, mmHg	72.0 ± 8.3	74.7 ± 7.8	70.3 ± 8.2	<.001
Fasting glucose, mg/dL	91.0 [86-98]	93.0 [87-102]	90.0 [85-97]	<.001
Fasting insulin, mg/dL	7.7 [6.0-10.2]	7.0 [5.7-9.8]	8.0 [6.2-10.5]	<.001
HOMA-IR	2.0 ± 1.0	2.0 ± 1.0	2.0 ± 1.0	0.396
Total cholesterol, mg/dL	195.6 ± 34.5	189.1 ± 33.3	199.6 ± 34.6	<.001
HDL cholesterol, mg/dL	45.5 ± 10.8	43.7 ± 10.3	46.6 ± 11.0	<.001
LDL cholesterol, mg/dL	121.7 ± 32.5	115.2 ± 31.9	125.9 ± 32.2	<.001
Triglycerides, mg/dL	122.5 [86-171]	135.5 [92-187]	114.0 [84-163]	0.001
Creatinine, mg/dL	0.9 ± 0.2	1.0 ± 0.1	0.9 ± 0.1	<.001
GFR, mL/min/1.73m^2	69.8 ± 14.9	72.4 ± 15.1	68.1 ± 14.5	<.001
Uric acid, mg/dL	4.9 ± 1.3	5.7 ± 1.3	4.4 ± 1.0	<.001
CRP, mg/L	0.6 [0.3-1.3]	0.7 [0.4-1.3]	0.6 [0.3-1.4]	0.406
Current smoker (n=778)	81 (10.4)	75 (24.8)	6 (1.3)	<.001
Current drinker (n=806)	310 (38.5)	184 (58.6)	126 (25.6)	<.001
Incident hypertension	89 (11.0)	36 (11.5)	53 (10.7)	0.833

Values are presented as mean ± standard deviation, median [interquartile range], or number (%).
P value was derived from the independent t-test, the Wilcoxon rank sum test, or chi-square test.
Abbreviation: BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; GFR, glomerular filtration ratio; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment for insulin resistance; LDL, low-density lipoprotein; SBP, systolic blood pressure

Table 2 shows the baseline characteristics and incident hypertension of study population according to the categories of baseline uric acid levels in quartiles. Men with higher serum uric acid level had significantly higher levels of BMI, fasting insulin, HOMA-IR, creatinine, CRP and triglycerides at baseline. Men with higher blood pressure also had a higher proportion of current drinker. However, men with higher serum uric acid level had significantly lower levels of LDL cholesterol. The cases of incident hypertension during the follow-up period were 7 cases (9.9 %) for the first quartile, 7 cases (8.8 %) for the second quartile, 8 cases (9.9 %) for the third quartile and 17 cases (17.1 %) for the fourth quartile of serum uric acid in men.

On the other hand, women who had a higher level of serum uric acid had significantly older ages and higher levels of BMI, fasting insulin, HOMA-IR, triglycerides, creatinine and CRP. However, women with higher serum uric acid level had significantly lower levels of HDL cholesterol and GFR. The cases of incident hypertension during the follow-up period were 8 cases (6.5%) for the first quartile, 13 cases (10.6%) for the second quartile, 19 cases (15.7%) for the third quartile and 13 cases (10.2%) for the fourth quartile of serum uric acid in women.

Table 2. Characteristics of study participants according to serum uric acid level in quartiles

	Serum uric acid level at baseline				*p*-trend
	Q1	Q2	Q3	Q4	
Men (n=314)	(n=71)	(n=80)	(n=81)	(n=82)	
Uric acid, mg/dL	4.2 ± 0.6	5.3 ± 0.2	6.0 ± 0.3	7.3 ± 0.9	<.001
Age, years	58.2 ± 6.6	57.4 ± 7.0	56.5 ± 6.3	56.6 ± 7.5	0.109
BMI, kg/m^2	23.8 ± 3.2	24.0 ± 2.8	24.4 ± 2.9	24.8 ± 2.9	0.017
SBP, mmHg	116.6 ± 12.3	118.6 ± 11.4	115.3 ± 12.0	118.4 ± 10.9	0.739
DBP, mmHg	73.8 ± 8.6	74.3 ± 7.8	74.9 ± 7.6	75.9 ± 7.1	0.081
Fasting glucose, mg/dL	91.0 [87-105]	93.5 [87-101]	94.0 [87-100]	94.0 [87-102]	0.685
Fasting insulin, mg/dL	6.8 [5.0-9.8]	6.8 [5.5-9.0]	6.9 [6.0-9.8]	8.1 [6.1-10.5]	0.012
HOMA-IR	1.8 ± 0.9	1.8 ± 0.9	2.0 ± 1.1	2.1 ± 1.0	0.045
Total cholesterol, mg/dL	193.3 ± 29.6	184.8 ± 32.7	192.0 ± 37.6	186.9 ± 32.4	0.506
HDL cholesterol,mg/dL	45.3 ± 9.9	44.3 ± 12.1	43.2 ± 9.1	42.3 ± 9.8	0.062
LDL cholesterol,mg/dL	122.2 ± 30.2	112.4 ± 29.3	119.1 ± 34.8	108.1 ± 31.6	0.031
Triglycerides, mg/dL	104.0 [74-156]	126.0 [82-177]	130.0 [94-189]	161.5 [94-189]	0.770
Creatinine, mg/dL	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	1.1 ± 0.2	<.001
GFR, mL/min/1.73m^2	74.9 ± 14.8	75.9 ± 17.4	75.9 ± 15.2	73.0 ± 14.3	0.456
CRP, mg/L	0.5 [0.3-1.0]	0.6 [0.4-1.1]	0.7 [0.4-1.2]	0.8 [0.4-1.2]	<.001
Smoking (n=303)	15 (23.1)	18 (23.4)	20 (25.3)	22 (26.8)	0.550*
Alcohol intake	30 (42.3)	46 (57.5)	53 (65.4)	55 (67.1)	0.001*
Incident hypertension	7 (9.9)	7 (8.8)	8 (9.9)	14 (17.1)	0.147
Women (n=494)	(n=123)	(n=123)	(n=121)	(n=127)	
Uric acid, mg/dL	3.3 ± 0.4	4.0 ± 0.2	4.7 ± 0.2	5.7 ± 0.7	<.001
Age, years	53.3 ± 7.4	53.3 ± 6.8	55.6 ± 6.7	55.3 ± 7.9	0.005
BMI, kg/m^2	23.7 ± 3.0	24.9 ± 3.1	24.5 ± 3.1	25.5 ± 3.3	<.001
SBP, mmHg	115.3 ± 13.5	113.9 ± 12.7	116.2 ± 11.7	116.1 ± 12.4	0.353
DBP, mmHg	69.5 ± 8.4	69.5 ± 8.6	70.7 ± 8.1	71.2 ± 7.8	0.062
Fasting glucose, mg/dL	88.0 [83-92]	91.0 [86-96]	91.0 [85-98]	92.0 [87-98]	0.061
Fasting insulin, mg/dL	7.4 [5.8-9.7]	7.5 [6.1-10.0]	8.6 [6.2-10.9]	9.0 [7.0-11.0]	<.001
HOMA-IR	1.7 ± 0.8	1.9 ± 0.7	2.2 ± 1.3	2.2 ± 0.9	<.001
Total cholesterol, mg/dL	195.1 ± 34.3	199.2 ± 33.0	201.8 ± 34.6	202.5 ± 36.3	0.077
HDL cholesterol,mg/dL	48.2 ± 11.8	46.5 ± 11.4	47.6 ± 10.3	44.2 ± 9.9	0.012
LDL cholesterol,mg/dL	124.1 ± 30.8	128.6 ± 30.6	125.9 ± 32.3	124.9 ± 35.1	0.968
Triglycerides, mg/dL	94.0 [74-136]	108.0 [86-145]	118.0 [86-171]	139.0 [96-206]	<.001
Creatinine, mg/dL	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	0.9 ± 0.1	<.001
GFR, mL/min/1.73m^2	71.9 ± 14.0	72.8 ± 13.2	69.0 ± 16.5	67.7 ± 15.6	0.006
CRP, mg/L	0.5 [0.2-0.9]	0.5 [0.3-1.1]	0.7 [0.3-1.5]	1.1 [0.4-2.1]	<.001
Smoking (n=476)	1 (0.9)	1 (0.8)	2 (1.7)	2 (1.7)	0.466*
Alcohol intake (n=484)	36 (29.5)	29 (23.8)	28 (23.1)	33 (26.0)	0.532*
Incident hypertension	8 (6.5)	13 (10.6)	19 (15.7)	13 (10.2)	0.197

Data was expressed as mean ± standard deviation or number (percent).
**P*-trend was derived from the Cochran-Armitage trend test.
Abbreviation: BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; GFR, glomerular filtration ratio; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment for insulin resistance; LDL, low-density lipoprotein; SBP, systolic blood pressure

Table 3 presents the correlations between serum uric acid and other variables using the Pearson's correlation coefficient. In men, serum uric acid had positive correlations with BMI, SBP, fasting glucose, HDL cholesterol, creatinine, GFR and CRP in age-adjusted model. On the other hand, serum uric acid had negative correlations HOMA-IR, total cholesterol and LDL cholesterol in men.

In women, serum uric acid had positive correlations with BMI, fasting glucose, HDL cholesterol, creatinine, GFR and CRP in age-adjusted model. On the other hand, serum uric acid had a negative correlation with HOMA-IR in women. The correlations between blood pressure and other characteristics in baseline were presented in Table A1.

Table 3. Correlation between serum uric acid level and other characteristics in baseline

	Simple correlation*		Partial correlation†	
	Pearson's coefficients	*p*-value	Pearson's coefficients	*p*-value
Total (n=808)				
Age	0.04	0.207	NA	NA
BMI	0.18	<.001	0.18	<.001
SBP	0.10	0.006	0.10	0.005
DBP	0.03	0.350	0.02	0.488
Fasting glucose (logarithmic)	0.16	<.001	0.16	<.001
Fasting Insulin (logarithmic)	0.04	0.313	0.04	0.304
HOMA-IR	- 0.12	0.001	- 0.12	0.001
Total cholesterol	- 0.05	0.130	- 0.05	0.137
HDL cholesterol	0.37	<.001	0.37	<.001
LDL cholesterol	- 0.10	0.005	- 0.09	0.011
Triglycerides (logarithmic)	0.02	0.590	0.02	0.607
Creatinine	0.19	<.001	0.19	<.001
GFR	0.28	<.001	0.28	<.001
CRP (logarithmic)	0.21	<.001	0.21	<.001
Men (n=314)				
Age	- 0.07	0.211	NA	NA
BMI	0.17	0.002	0.16	0.004
SBP	0.15	0.008	0.14	0.014
DBP	0.02	0.716	0.03	0.619
Fasting glucose (logarithmic)	0.15	0.008	0.14	0.013
Fasting Insulin (logarithmic)	- 0.03	0.582	- 0.04	0.484
HOMA-IR	- 0.12	0.037	- 0.12	0.040
Total cholesterol	- 0.13	0.026	- 0.13	0.021
HDL cholesterol	0.33	<.001	0.33	<.001
LDL cholesterol	- 0.05	0.338	- 0.12	0.033
Triglycerides (logarithmic)	- 0.05	0.358	- 0.06	0.284
Creatinine	0.20	<.001	0.19	0.001
GFR	0.29	<.001	0.28	<.001
CRP (logarithmic)	0.11	0.052	0.12	0.040
Women (n=494)				
Age	0.13	0.004	NA	NA
BMI	0.19	<.001	0.19	<.001
SBP	0.06	0.199	0.05	0.238
DBP	0.04	0.344	0.01	0.837
Fasting glucose (logarithmic)	0.16	<.001	0.15	0.001
Fasting Insulin (logarithmic)	0.09	0.053	0.08	0.068
HOMA-IR	- 0.13	0.005	- 0.12	0.009
Total cholesterol	<.01	0.958	<.01	0.965
HDL cholesterol	0.41	<.001	0.40	<.001
LDL cholesterol	- 0.14	0.002	- 0.08	0.075
Triglycerides (logarithmic)	0.09	0.059	0.07	0.116
Creatinine	0.18	<.001	0.18	<.001
GFR	0.28	<.001	0.26	<.001
CRP (logarithmic)	0.29	<.001	0.27	<.001

*Adjusted for sex; †Adjusted for sex and age

Abbreviation: BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; GFR, glomerular filtration ratio; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment for insulin resistance; LDL, low-density lipoprotein; SBP, systolic blood pressure

Table 4 presents baseline characteristics of the study population according to the incident hypertension during follow-up period. In men, BMI, SBP, DBP, fasting insulin and triglycerides were significantly higher in those who developed hypertension than in those who did not. In women, age, BMI, SBP and DBP were significantly higher in those who developed hypertension than in those who did not. On the contrary, HDL cholesterol was significantly lower in those who developed hypertension than in those who did not in women. Total cholesterol was higher in those who developed hypertension compared with those who did not, but the association was of borderline significance. In both sexes, serum uric acid level was higher in those who developed hypertension compared with those who did not, but the difference between these groups was not statistically significant.

Table 4. Baseline characteristics of study participants according to incident hypertension during the follow-up period

Variables	Men (n=314)			Women (n=494)		
	Non-hypertension at f/u (n=278)	Hypertension at f/u (n=36)	*p*-value	Non-hypertension at f/u (n=441)	Hypertension at f/u (n=53)	*p*-value
Age, years	57.0 ± 6.9	58.4 ± 6.9	0.243	54.0 ± 7.2	57.5 ± 7.5	0.001
BMI, kg/m^2	24.1 ± 3.0	25.6 ± 2.3	0.003	24.5 ± 3.1	25.6 ± 3.5	0.015
SBP, mmHg	116.4 ± 11.7	123.4 ± 8.8	<.001	114.1 ± 12.4	125.9 ± 9.1	<.001
DBP, mmHg	74.3 ± 7.8	77.9 ± 6.6	0.010	69.6 ± 8.1	75.7 ± 7.2	<.001
HOMA-IR	1.9 ± 1.0	2.1 ± 0.7	0.243	2.0 ± 0.9	2.2 ± 1.5	0.402
Fasting glucose, mg/dL	93.0 [87.0-101.0]	95.5 [90.0-105.0]	0.202	90.0 [85.0-96.0]	8.0 [85.0-97.0]	0.944
Fasting insulin, mg/dL	6.9 [5.4-9.8]	8.0 [7.0-10.25]	0.018	8.0 [6.3-10.5]	7.9 [6.2-10.7]	0.922
Total cholesterol, mg/dL	189.9 ± 33.4	183.0 ± 32.7	0.239	200.3 ± 34.5	194.4 ± 34.9	0.244
HDL cholesterol,mg/dL	44.0 ± 10.3	41.8 ± 10.0	0.231	46.9 ± 10.8	43.9 ± 12.3	0.056
LDL cholesterol,mg/dL	116.1 ± 32.4	108.8 ± 27.0	0.198	126.4 ± 32.1	121.9 ± 33.5	0.047
Uric acid, mg/dL	5.7 ± 1.2	6.1 ± 1.5	0.181	4.4 ± 1.0	4.7 ± 1.2	0.332
Triglycerides, mg/dL	130.0 [89.0-188.0]	157.5 [132.5-187.0]	0.044	113.0 [84.0-162.0]	113.0 [88.0-175.0]	0.250
Creatinine, mg/dL	1.0 ± 0.1	1.0 ± 0.1	0.955	0.9 ± 0.1	0.8 ± 0.1	0.844
GFR, mL/min/1.73m^2	74.5 ± 15.2	78.0 ± 16.7	0.198	70.5 ± 15.0	69.1 ± 14.7	0.513
CRP, mg/L	0.6 [0.4-1.3]	0.7 [0.4-1.3]	0.574	0.6 [0.3-1.4]	0.8 [0.4-1.6]	0.190
Current smoker	65 (24.3)	10 (28.6)	0.728	6 (1.4)	0 (0.0)	0.838
Current drinker	161 (57.9)	23 (63.9)	0.614	118 (26.9)	8 (15.1)	0.090

p-value was derived from the independent t-test, the Wilcoxon rank sum test, chi-square test or Fisher's exact test.
Abbreviation: BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; GFR, glomerular filtration ratio; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment for insulin resistance; LDL, low-density lipoprotein; SBP, systolic blood pressure

Tables 5 present a cross-sectional association between serum uric acid and blood pressure at baseline using multivariable linear regression model.

Serum uric acid was not associated with SBP before and after adjusting for covariates in both sexes. But serum uric acid was positively associated with DBP in men before and after adjusting for age, BMI, HDL cholesterol and creatinine ($\beta = 0.85$, $p = 0.014$ for unadjusted model; $\beta = 0.86$, $p = 0.017$ for fully adjusted model).

Table 5. Cross-sectional association between serum uric acid level and blood pressure at baseline by multivariable linear regression model

	Association between serum uric acid (mg/dL) and SBP (mmHg)			Association between serum uric acid (mg/dL) and DBP (mmHg)		
	β	R^2	p value	β	R^2	p value
Total (n=808)						
Model 1	0.27	0.043	0.488	0.71	0.076	0.005
Model 2	- 0.11	0.076	0.774	0.49	0.100	0.057
Model 3	0.13	0.077	0.754	0.58	0.100	0.035
Men (n=314)						
Model 1	0.26	0.005	0.619	0.85	0.044	0.014
Model 2	- 0.09	0.056	0.858	0.68	0.069	0.049
Model 3	0.31	0.068	0.565	0.86	0.074	0.017
Women (n=494)						
Model 1	0.11	0.062	0.837	0.44	<.001	0.238
Model 2	- 0.25	0.083	0.659	0.19	0.023	0.605
Model 3	- 0.21	0.081	0.733	0.15	0.019	0.710

Model 1: adjusted for sex and age
Model 2: adjusted for sex, age and BMI
Model 3: adjusted for sex, age, BMI, HDL cholesterol and creatinine
Abbreviation: BMI, body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; SBP, systolic blood pressure

Figures 2-5 present penalized B-splines to explore the patterns of the association between serum uric acid and blood pressure by sex. Solid lines, gray shadows and blue dash lines represent the estimated blood pressure, 95% confidence intervals and 95% prediction intervals according to serum uric acid level. The estimated blood pressure was calculated by using the penalized regression method. The 95% confidence interval means that the possibility of blood pressure lying within these bands (shades) is 95%, while the 95% prediction interval means that the possibility of a specific observation lying within these bands (dashed lines) is 95% when we are interested in a specific observation (i.e. independent variable: serum uric acid). In men, serum uric acid level shows a linear association with DBP. However, in women, there was no significant association between serum uric acid level and DBP. On the other hand, SBP had no significant association with serum uric acid levels in both sexes.

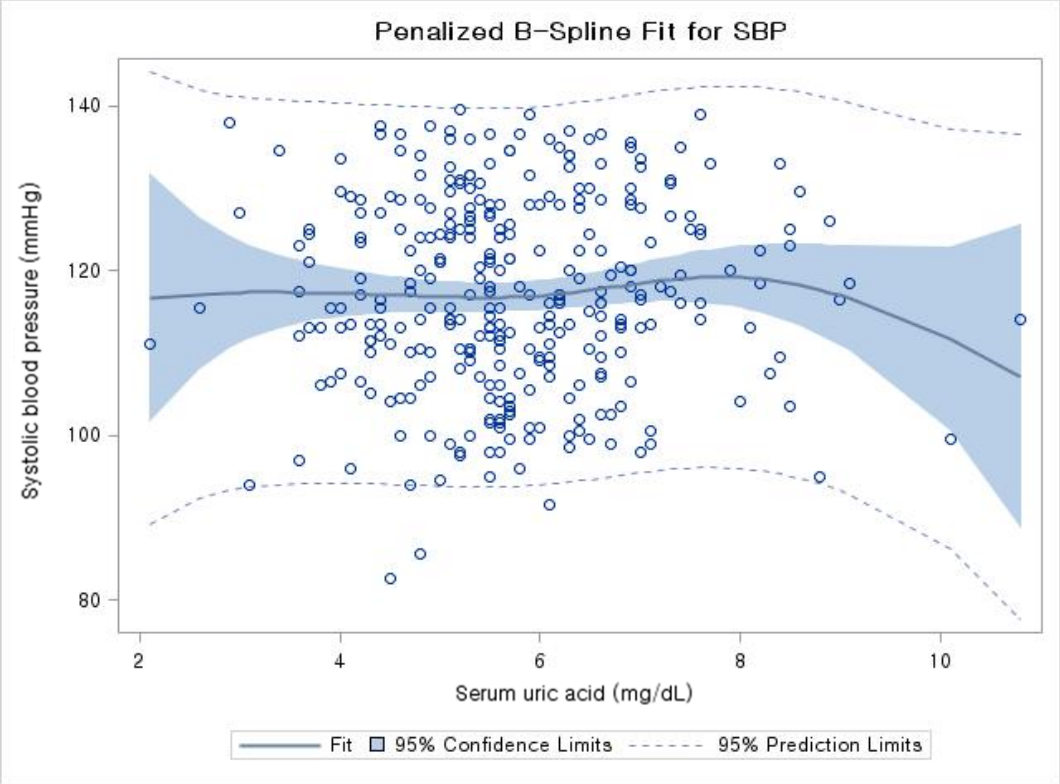

Figure 2. The association between serum uric acid and systolic blood pressure at baseline in men fitted by B-spline methods

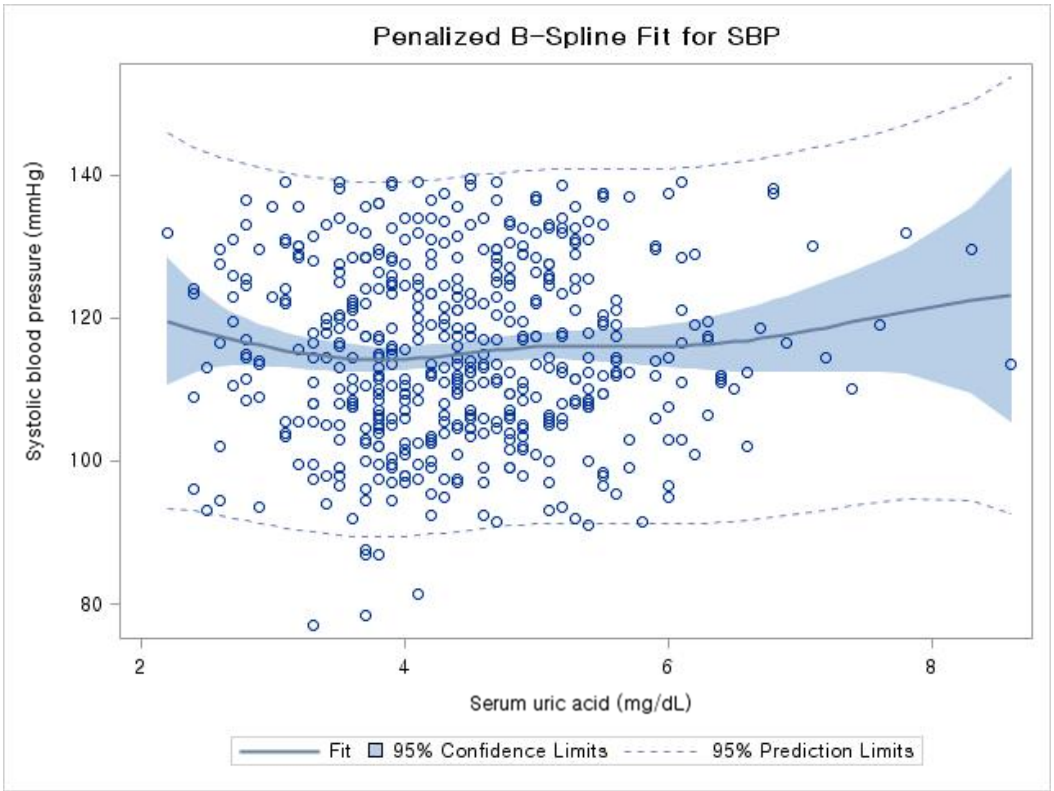

Figure 3. The association between serum uric acid and systolic blood pressure at baseline in women fitted by B-spline methods

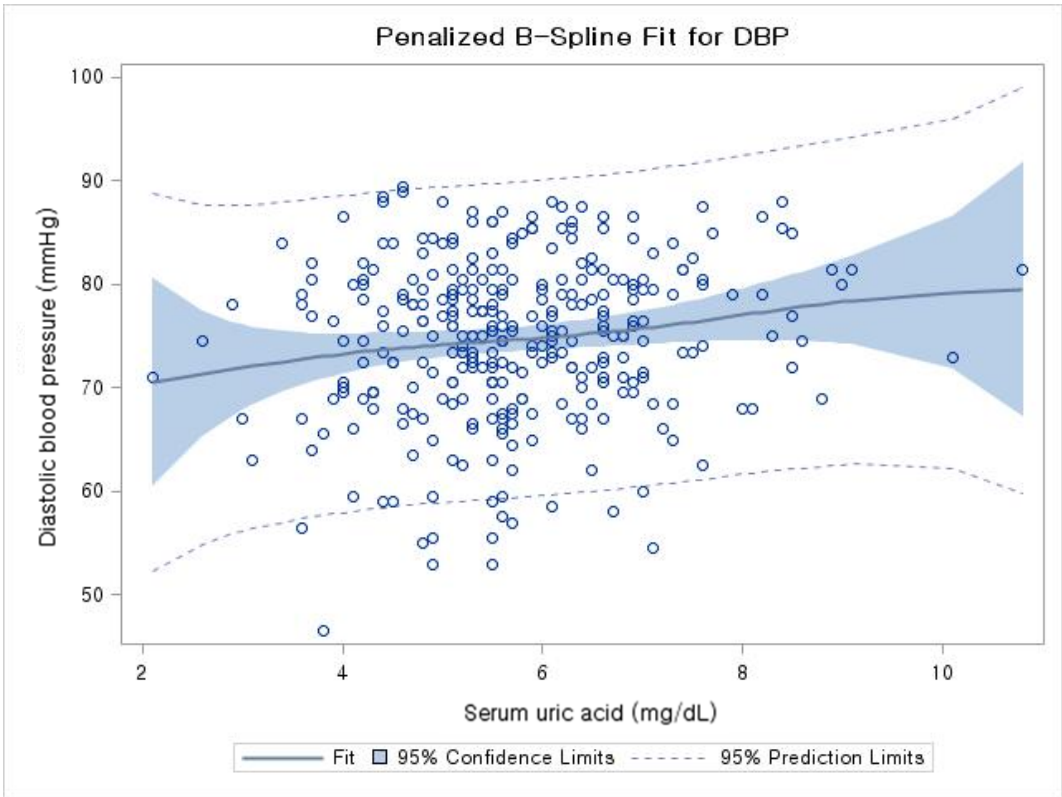

Figure 4. The association between serum uric acid and diastolic blood pressure at baseline in men fitted by B-spline methods

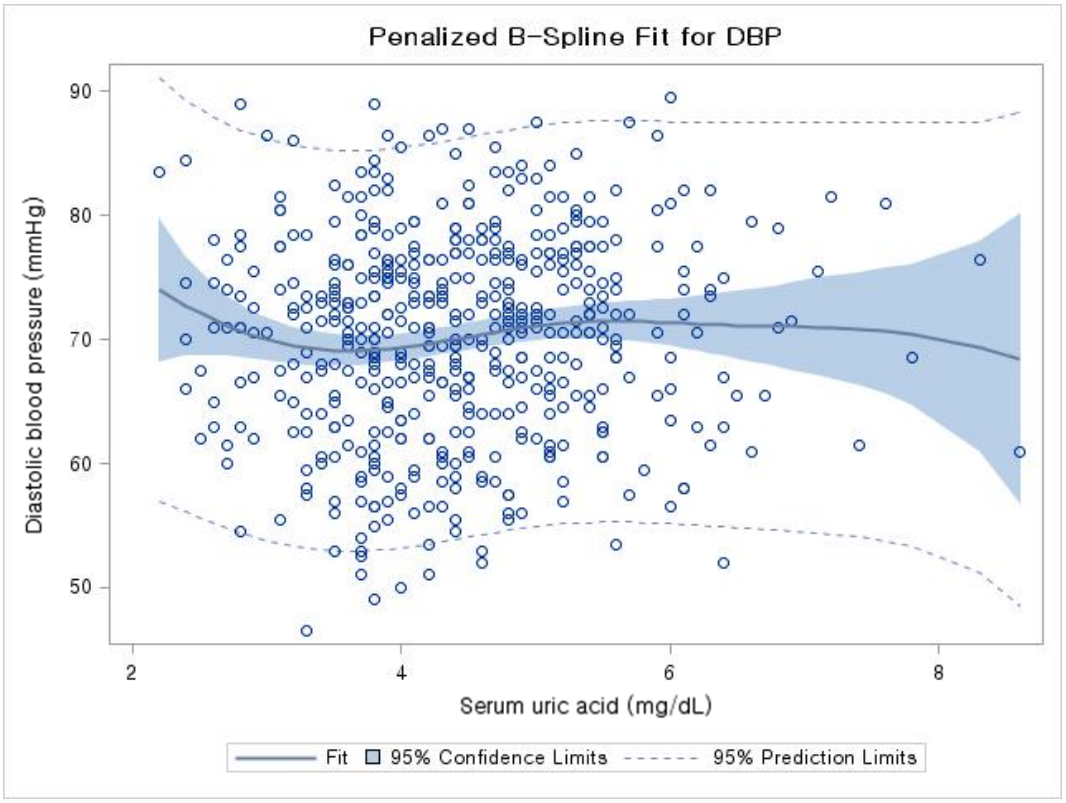

Figure 5. The association between serum uric acid and diastolic blood pressure at baseline in women fitted by B-spline methods

Table 6 shows the prospective association between serum uric acid level and incident hypertension using a generalized linear model. The unadjusted relative risk (95% CI) for incident hypertension in total participants was 1.18 (1.01-1.37) per 1.0 mg/dL increase in baseline serum uric acid (p=0.034). When adjusting for sex, age, BMI, SBP, DBP, HDL cholesterol and creatinine, relative risk (95% CI) was 1.19 per 1.0 mg/dL increase in baseline serum uric acid (p = 0.087). Stratified according to sex, relative risk (95% CI) were 1.20 (0.91-1.57) in men and 1.25 (0.93-1.69) in women after adjusting for age, BMI, SBP, DBP, HDL cholesterol and creatinine.

Table 6. Relative risk and associated 95% confidence interval of hypertension according to serum uric acid levels during follow-up period

Models	Relative risk (95% CI) for incident hypertension per serum uric acid 1.0 mg/dL	*p* value
Total (n=808)		
Unadjusted	1.18 (1.01 - 1.37)	0.034
Model 1	1.23 (0.94 - 1.33)	0.190
Model 2	1.14 (0.96 - 1.36)	0.137
Model 3	1.19 (0.98 - 1.44)	0.087
Men (n=314)		
Unadjusted	1.21 (0.95 - 1.54)	0.126
Model 1	1.13 (0.90 - 1.42)	0.297
Model 2	1.15 (0.90 - 1.46)	0.255
Model 3	1.20 (0.91 - 1.57)	0.194
Women (n=494)		
Unadjusted	1.24 (0.96 - 1.59)	0.093
Model 1	1.10 (0.85 - 1.43)	0.457
Model 2	1.12 (0.88 - 1.44)	0.360
Model 3	1.25 (0.93 - 1.69)	0.139

Model 1: adjusted for sex, age and BMI
Model 2: adjusted for sex, age, BMI, SBP and DBP
Model 3: adjusted for sex, age, BMI, SBP, DBP, HDL cholesterol and creatinine
Abbreviation: BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; HDL, high-density lipoprotein; SBP, systolic blood pressure

Figure 6 presents relative risks for incident hypertension according to serum uric acid levels by restricted cubic spline. The relative risks were adjusted for age, BMI, baseline SBP, baseline DBP, HDL cholesterol and creatinine. Knots were set at the 5th, 25th, 75th, and 95th percentiles, and the plot was truncated at the 1st and 99th percentiles. The median to serum uric acid level was used as the reference. There was no significant association between serum uric acid and incident hypertension (*p*-value for the non-linear relation of 0.075; *p*-value for the linear relation of 0.120).

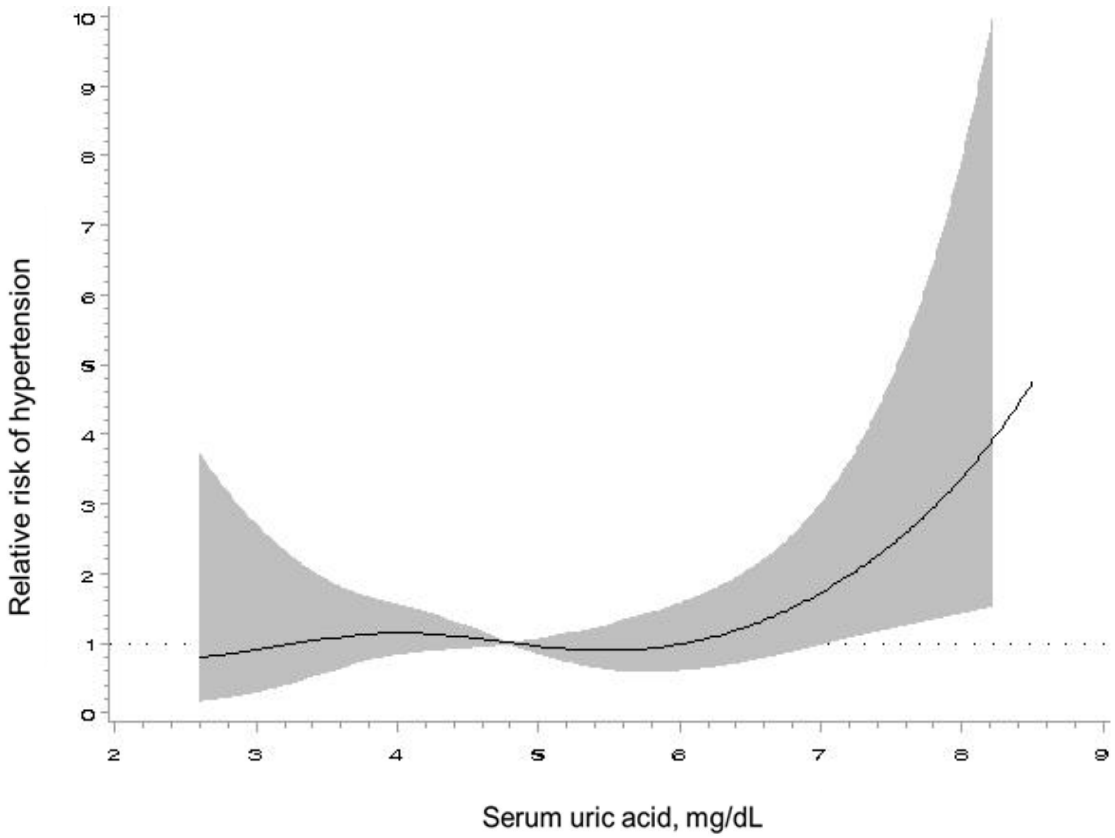

Figure 6. The association of serum uric acid levels with relative risks for incident hypertension, restricted cubic splines

Table 7 shows associations between serum uric acid level and incident hypertension among subgroups categorized by known risk factors for hypertension including sex, age, BMI, triglycerides, HDL cholesterol, LDL cholesterol and fasting glucose. The interaction test for sex was not significant (p interaction with sex = 0.936).

We found that an association between serum uric acid level and incident hypertension was significant in participants of age < 55 years (relative risk 1.74 per 1 mg/dL increase in serum uric acid, $p = 0.002$), but the association was not significant in participants of age ≥ 55 years ($p = 0.894$). In addition to, when analyzed people age ≥ 55 years divided into people who aged 55-64 years and ≥ 65 years, the associations between uric acid and incident diabetes among them were not different from people's age ≥ 55 years (data not shown). The interaction test for age was significant (p interaction with age = 0.009). However, the p for interaction tests of BMI, triglycerides, HDL cholesterol, LDL cholesterol and fasting glucose was not significant.

Additionally, we examined whether smoking status modifies the association between serum uric acid level and incident hypertension (Table A2). Smoking status did not modify the association between serum uric acid level and incident hypertension, but reliability of the result is low due to the small number of samples.

Table 7. Associations between serum uric acid and incident hypertension according to sex, age, body mass index, lipid profiles and fasting glucose using a generalized linear model*

Subgroup	No. of participants	No. of incident case	Relative risk (95% CI)	*p* value	*p* interaction†
Sex					
Men	314	36	1.18 (0.90 - 1.55)	0.221	0.936
Women	494	53	1.20 (0.91 - 1.59)	0.196	
Age					
< 55 year	374	29	1.74 (1.22 - 2.47)	0.002	0.009
≥ 55 year	434	60	0.98 (0.77 - 1.25)	0.894	
BMI					
< 25 kg/m^2	476	40	1.10 (0.78 - 1.53)	0.591	0.575
≥ 25 kg/m^2	332	49	1.24 (0.97 - 1.58)	0.089	
Triglycerides					
< 150 mg/dL	524	48	1.20 (0.90 - 1.59)	0.215	0.826
≥ 150 mg/dL	284	41	1.14 (0.86 - 1.53)	0.366	
HDL cholesterol					
≤ 40 mg/dL	272	46	1.12 (0.86 - 1.45)	0.391	0.395
> 40 mg/dL	536	43	1.33 (0.98 - 1.82)	0.067	
LDL cholesterol					
< 130 mg/dL	501	58	1.17 (0.93 - 1.46)	0.181	0.960
≥ 130 mg/dL	307	31	1.15 (0.76 - 1.74)	0.495	
Fasting glucose					
< 100 mg/dL	628	63	1.04 (0.82 - 1.33)	0.727	0.099
≥ 100 mg/dL	180	26	1.50 (1.05 - 2.13)	0.025	

*Adjusted for sex, age, BMI, SBP, DBP, HDL cholesterol and creatinine
†The p value for interactions between serum uric acid and known risk factors on the risk of developing hypertension were calculated by a Z-test.
Abbreviation: BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure

Figure 7 shows relative risks for incident hypertension according to serum uric acid levels by participant's age using restricted cubic spline. The relative risks were adjusted for age, BMI, baseline SBP, baseline DBP, HDL cholesterol and creatinine. Knots were set at the 5th, 25th, 75th, and 95th percentiles, and the plot was truncated at the 1st and 99th percentiles. The median to serum uric acid level was used as the reference. In people who aged < 55 years, there was a significant linear association between serum uric acid and incident hypertension (*p*-value for the non-linear relation of 0.196; *p*-value for the linear relation of 0.002). Thus, we show the linear model. However, among people who aged ≥ 55 years, there was no significant linear association between serum uric acid and incident hypertension (*p*-value for the non-linear relation of 0.282; *p*-value for the linear relation of 0.909).

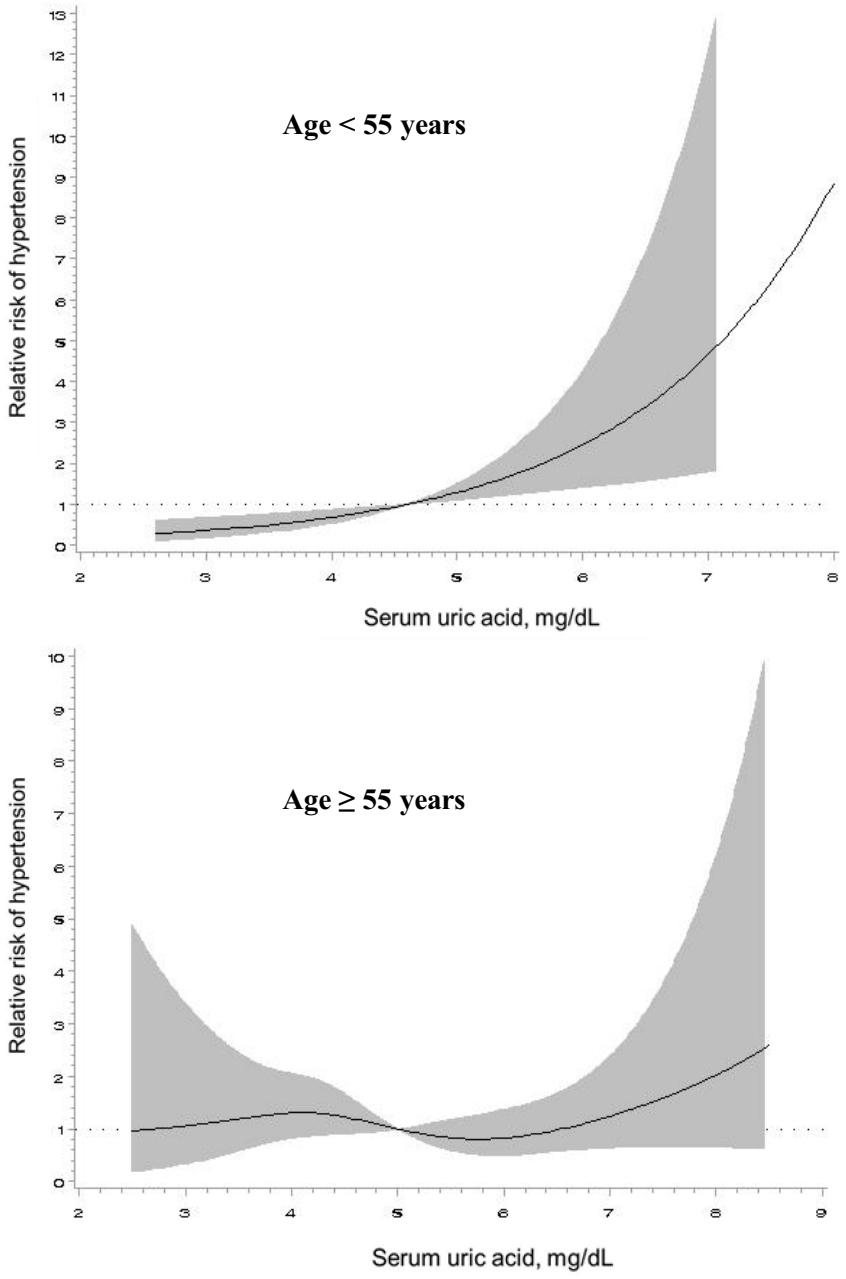

Figure 7. The association of serum uric acid levels with relative risks for incident hypertension by participant's age, restricted cubic splines

IV. Discussion

We examined whether there is an independent association between serum uric acid and incident hypertension and assessed the interaction between serum uric acid and other risk factors for progression of blood pressure and incident hypertension. We observed that age-differential association between serum uric acid level and incident hypertension. The association between serum uric acid level and incident hypertension was positively significant among people who aged < 55 years, but there was no significant association among people who aged ≥ 55 years (p for interaction=0.009).

1. Associations of serum uric acid and other risk factors with incident hypertension in previous studies

A previous longitudinal study with a mean follow-up 5.41 years in a Taiwanese population suggested that serum uric acid level was an independent predictor of incident hypertension[32]. The Beaver Dam Eye Study, which is a population-based cohort study with older Americans in Wisconsin, also observed that increasing quartiles of serum uric acid was associated with 10-year incidence of hypertension independent of smoking, alcohol intake and baseline kidney function[33]. Another longitudinal study over 8 years with Americans reported that higher baseline SBP and lower HDL cholesterol were significant independent predictors for incident hypertension in a multivariate Cox regression model[34]

In previous cross-sectional study in which investigate interaction of blood pressure and other risk factors on hypertension, the interaction between serum uric acid and triglyceride was significant for SBP, but not for DBP after adjusting for sex and age [35]. Higher serum uric acid level was significantly associated with prehypertension in a group with triglycerides level of < 150 mg/dL, but not in a group with triglycerides level of ≥ 150 mg/dL. Another study reported that there was an independent and positive association between serum acid and hypertension suggesting HDL cholesterol may modify the association between serum uric acid and hypertension[36]. In that study, the associations between uric acid and hypertension were most prominent in those with highest quintiles of HDL cholesterol. In the Physicians' Health Study among men without diabetes and obesity, there was an independent association between baseline lipids (total cholesterol, HDL cholesterol and total cholesterol/HDL cholesterol ratio) and hypertension[37]. This previous study suggested that dyslipidemia may lead to the subsequent development of hypertension. The Women's Health Study was also reported that dyslipidemia was independently associated with the subsequent development of hypertension among healthy women[38]. The Tehran Lipid and Glucose Study from a population-based cohort in the Middle East, suggested that dyslipidemia measured by serum triglycerides and triglycerides/HDL cholesterol ratio may be useful in identification of women at risk of hypertension[39]. However, the interactions of serum uric acid with lipid profiles on the blood pressure were not significant in the current study.

Another previous longitudinal study with young and middle-aged Japanese male

reported that high serum uric acid level was also associated with future hypertension and this association was stronger in participants aged 40-60 years than that of those who aged 18-40 years (p for interaction = 0.035)[11]. We observed that age-differential association between serum uric acid level and incident hypertension. The positive association was significant in participants of age < 55 years, but there was no significant association in participants of age ≥ 55 years. Considering these results, elevated serum uric acid level can be a trigger for hypertension in middle aged population.

2. Potential mechanisms linking the association of serum uric acid and other risk factors for incident hypertension

The mechanism linking the association between increased serum uric acid level and incident hypertension is not completely understood. Previous studies reported that oxidative stress, inflammation, nitric oxide production impairment, vascular endothelial dysfunction, vascular smooth muscle proliferation, and renin angiotensin system enhancement were mechanisms for incident hypertension by hyperuricemia[40-46]. Crystallization of uric acid itself has also been reported to cause inflammation, gouty kidney, and urinary tract, and progression to renal failure[47-50]. High serum uric acid level may lead to decreasing of endothelial nitric oxide, which is well known as a mediator of insulin action and increases blood flow to skeletal muscle and enhance glucose uptake[40]. High serum uric acid can cause renal vasoconstriction and alters the proliferation/migration on endothelial and vascular smooth muscle cells through

inhibition of the nitric oxide and stimulation of the renin-angiotensin system, and then may lead to endothelial dysfunction[41-43,51,52]. Thus, hyperuricemia may lead to raised blood pressure. In addition to, serum uric acid is an indicator of systematic inflammation[53] and associated with cardiovascular risk factors such as insulin resistance[54], BMI, total cholesterol, HDL cholesterol, triglycerides and fasting glucose[54-56].

In additional analyses, we considered blood lipids as covariates for incident hypertension, although these variables including total cholesterol, LDL cholesterol and triglycerides were not influential in a generalized linear model (data not shown). Dyslipidemia may lead to impairment in endothelial function and resulting in defective vasoregulation[57], increasing arterial stiffness[58], decreasing compliance and renal microvascular disease. It has been reported that high triglyceride level may cause endothelial dysfunction[59], the loss of vasomotor reactivity[60] and arterial stiffness[61]. Previous reported that high triglyceride level is significantly associated with insulin resistance[41] which may lead to incident hypertension by promoting renal tubular sodium reabsorption, stimulating sympathetic nervous system reactivity and the renin-angiotensin system[36]. Previous study with postmenopausal women in Japan reported that reductions of triglycerides and serum uric acid are synergistic factors of reduction in insulin resistance[62].

High levels of cholesterol and low levels of HDL cholesterol are also toxic for endothelial cells and impair the nitric oxide production, release and later activity[57], and these status can cause incident hypertension. Especially, high level of HDL cholesterol

stimulates nitric oxide production and has antithrombotic and antioxidant function[63-65]. Normal functional HDL cholesterol has high levels of anti-oxidants and active anti-oxidant proteins and enzymes with high anti-oxidant potential and has anti-inflammatory activity[64]. Several studies have reported its atheroprotective role as a key player in reverse cholesterol transport. HDL cholesterol carries cholesterol in the circulation and delivers it to the liver so that it can be either reutilized for assembly of very low-density lipoprotein or excreted as free cholesterol or bile acids[64,66]. However, when antioxidant and anti-inflammatory functions of HDL cholesterol are overwhelmed by pathological processes, such as inflammation, HDL cholesterol is converted into a dysfunctional pro-inflammatory particle[67,68]. Elevated serum uric acid level may promote cardio-protective role of HDL cholesterol and the conversion process of HDL cholesterol to pro-inflammatory factor through endothelial dysfunction and systematic inflammation, which may promote the progression of blood pressure.

Previous studies reported that both of serum uric acid and lipids can cause incident hypertension through endothelial dysfunction and systematic inflammation[13,35,36,39,62]. According to our analysis, blood lipids at baseline were not independent predictors for future hypertension, but serum uric acid, BMI, SBP and DBP were independent predictors for future hypertension when fully adjusted (Table A3). The results suggested that such unfavorable pathophysiological process induced by serum uric acid might be greater than that of blood lipids.

A previous prospective study examined the association of serum uric acid with

development of hypertension and impaired fasting glucose or type 2 diabetes mellitus[21]. In this previous study, elevated serum uric acid level was significantly associated future hypertension and impaired fasting glucose or type 2 diabetes mellitus. In our study, fasting glucose level was not independent predictor for hypertension in generalized linear model (data not shown), but serum uric acid level was significantly associated with incident hypertension in a group with fasting glucose level of ≥ 100 mg/dL, (relative risk 1.50 per 1 mg/dL, p=0.025) although the interaction with fasting glucose group was not significant (p for interaction with fasting glucose=0.099). It is suggesting that elevated serum uric acid might increase fasting glucose level through mechanisms linking decreasing of endothelial nitric oxide, which is above mentioned as a mediator of insulin action and increases blood flow to skeletal muscle and enhance glucose uptake[40].

In our study, the association between serum uric acid and incident hypertension is inconsistent according to subgroups which were categorized by age. We cannot explain how age modifies the effects of uric acid on the development of hypertension. One of the possible explanations can be pathophysiological change with aging. If serum uric acid can affect premature vascular degeneration, serum uric acid could not affect elderly people whose pathophysiological changes including premature vascular degeneration and endothelial dysfunction may have already been done with aging. The potential underlying mechanisms between uric acid and hypertension was very similar to a process of progression in blood pressure[69]. Thus, increased serum uric acid level can be a trigger for hypertension through early vascular change in middle aged population, but it cannot be

among people aged ≥ 55 years. A previous study suggested that uric acid level might have a role in the early pathogenesis of primary hypertension[70,71]. Furthermore, previous study reported that the strength of the relationship between uric acid and hypertension decreases with increasing patient age and duration of hypertension, suggesting that uric acid may be most important in younger people with early-onset hypertension[72].

Another possible explanation is that serum uric acid is associated with an increase of DBP rather than SBP. Previous studies have reported that the prevalence of isolated systolic hypertension (SBP ≥ 160 and DBP < 95 or 90 mmHg) rise with age[73-76]. In these previous studies, SBP was increases with age at least until more than 80 years old, but DBP rises only until 50-60 years of age, and thereafter either levels off, or even slightly decreases. A study with Korean adults also reported similar results[77]. In this previous study, mean SBP increased progressively across entire age range. In contrast, mean DBP increased slightly before the age of 55 years, since then DBP plateaued or decreased. In the 2011 Korean National Health and Nutrition Examination Survey, SBP steadily increase with age more than 60 years whereas DBP decrease, resulting in an increase in the pulse pressure[78]. In our secondary analysis, serum uric acid level was not associated with an increase of SBP, but positively associated with an increase of DBP (Table A5). It is likely that higher serum uric acid is associated with an increase of DBP rather than SBP, but higher serum uric acid level could not affect participants aged ≥ 55 years as DBP level get closer to maximum in the age of ≥ 55 years. Therefore, the age-differential association between serum uric acid and incident hypertension in our study can be partly

explained that isolated systolic hypertension, which is predominates after the age of 50 years as SBP continues to rise and DBP tends to fall, and results of our secondary analysis that serum uric acid level was significantly associated with only DBP. Further studies are needed to clarify interrelationships between serum uric acid and age for incident hypertension and which group is most vulnerable to incident hypertension. It is also needed to assess whether treatment strategies need to be targeted differentially according to each individual's comorbid risk factor.

3. Limitations of the current study

The current study has some limitations. First, it may not be appropriate to generalize it to another ethnic group because this study was conducted among Korean adults from a single rural community. Second, we could not take into account day-to-day variation of blood pressure because blood pressure level was decided in a single visit, although we conducted blood pressure measurement multiple times. These may have led to a misclassification of incident hypertension. However, the effects of non-differential misclassification would have resulted in bias toward the null. Third, we did not consider medications for diabetes and dyslipidemia as covariates. Fasting glucose levels and blood lipids can be influenced these medications. Fourth, although even though we took into consideration a large number of potential confounders, the possibility remains that unmeasured factors such as specific dietary patterns could account for the association of serum uric acid with incident hypertension.

V. **Conclusions**

We observed that age-differential association between serum uric acid level and incident hypertension among community-dwelling healthy Korean population. The positive association was significant among middle-aged population (< 55 years). Our study suggests that, to prevent future hypertension and cardiovascular disease effectively, active intervention to avoid increasing serum uric acid level may be required, especially in middle-aged healthy population.

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Appendix

Table A1. Correlation between blood pressure and other characteristics in baseline

	SBP				DBP			
	Pearson coefficients*	*p*-value	Pearson coefficients†	*p*-value	Pearson coefficients*	*p*-value	Pearson coefficients†	*p*-value
Total (n=808)								
Age	0.20	<.001	NA	NA	- 0.04	0.261	NA	NA
BMI	0.17	<.001	0.19	<.001	0.18	<.001	0.18	<.001
SBP	NA	NA	NA	NA	0.64	<.001	0.66	<.001
DBP	0.64	<.001	0.66	<.001	NA	NA	NA	NA
Fasting glucose	0.09	0.009	0.09	0.011	0.03	0.330	0.04	0.319
Fasting insulin	0.13	<.001	0.14	<.001	0.15	<.001	0.15	<.001
HOMA-IR	0.13	<.001	0.14	<.001	0.12	0.001	0.12	0.001
Total cholesterol	0.08	0.018	0.09	0.012	0.07	0.046	0.07	0.048
HDL cholesterol	- 0.05	0.159	- 0.04	0.219	- 0.03	0.413	- 0.03	0.390
LDL cholesterol	<.01	0.958	0.01	0.852	- 0.03	0.371	- 0.03	0.357
Triglycerides	0.22	<.001	0.22	<.001	0.23	<.001	0.24	<.001
Creatinine	- 0.02	0.621	- 0.04	0.318	0.01	0.726	0.02	0.655
GFR	0.01	0.824	0.15	<.001	0.11	0.001	0.11	0.002
Uric acid	0.03	0.350	0.02	0.488	0.10	0.006	0.10	0.005
CRP	0.13	<.001	0.10	0.004	0.10	0.004	0.11	0.002
Men (n=314)								
Age	0.10	0.064	NA	NA	- 0.18	0.002	NA	NA
BMI	0.20	<.001	0.23	<.001	0.22	<.001	0.19	0.001
SBP	NA	NA	NA	NA	0.63	<.001	0.66	<.001
DBP	0.63	<.001	0.66	<.001	NA	NA	NA	NA
Fasting glucose	0.04	0.428	0.06	0.309	0.06	0.257	0.04	0.431
Fasting insulin	0.20	<.001	0.22	<.001	0.21	<.001	0.18	0.001
HOMA-IR	0.15	0.007	0.17	0.002	0.15	0.007	0.13	0.024
Total cholesterol	0.09	0.101	0.11	0.061	0.12	0.040	0.10	0.084
HDL cholesterol	<.01	1.000	<.01	0.956	0.01	0.855	0.02	0.780
LDL cholesterol	0.01	0.822	0.02	0.727	- 0.02	0.772	-0.03	0.613
Triglycerides	0.17	0.002	0.19	0.001	0.28	<.001	0.27	<.001
Creatinine	- 0.07	0.230	- 0.07	0.190	- 0.02	0.787	-0.01	0.926
GFR	0.10	0.065	0.21	0.000	0.22	<.001	0.14	0.012
Uric acid	0.02	0.716	0.03	0.619	0.15	0.008	0.14	0.014
CRP (L)	0.12	0.028	0.12	0.040	0.19	0.001	0.21	<.001
Women (n=494)								
Age	0.26	<.001	NA	NA	0.04	0.388	NA	NA
BMI	0.15	0.001	0.15	0.001	0.16	<.001	0.16	<.001
SBP	NA	NA	NA	NA	0.64	<.001	0.65	<.001
DBP	0.64	<.001	0.65	<.001	NA	NA	NA	NA
Fasting glucose	0.13	0.005	0.10	0.027	0.01	0.762	0.01	0.837
Fasting insulin	0.08	0.080	0.08	0.075	0.11	0.017	0.11	0.017
HOMA-IR	0.12	0.006	0.11	0.018	0.10	0.034	0.09	0.040
Total cholesterol	0.08	0.082	0.07	0.123	0.04	0.332	0.04	0.351
HDL cholesterol	- 0.08	0.088	- 0.06	0.179	-0.05	0.258	-0.05	0.284
LDL cholesterol	<.01	0.921	- 0.01	0.904	-0.04	0.369	-0.04	0.368
Triglycerides	0.25	<.001	0.22	<.001	0.20	<.001	0.20	<.001
Creatinine	0.02	0.670	- 0.01	0.857	0.03	0.461	0.03	0.515
GFR	- 0.05	0.264	0.10	0.023	0.05	0.296	0.08	0.079
Uric acid	0.04	0.344	0.01	0.837	0.06	0.199	0.05	0.238
CRP	0.13	0.004	0.09	0.046	0.05	0.248	0.05	0.306

*Adjusted for sex; †Adjusted for sex and age

Abbreviation: BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; GFR, glomerular filtration ratio; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment for insulin resistance; LDL, low-density lipoprotein; SBP, systolic blood pressure

Table A2. Associations between serum uric acid and incident hypertension by smoking status

	No. of people	No. of incident case	RR (95% CI)	*p* value	*p* interaction
Smoking status					
Current smoker	81	10	1.53 (0.86 - 2.74)	0.150	0.363
Non-smoker	697	77	1.15 (0.92 - 1.43)	0.220	

*Adjusted for sex, age, BMI, SBP, DBP, HDL cholesterol and creatinine
Abbreviation: BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; HDL, high-density lipoprotein; SBP, systolic blood pressure; RR, relative risk

Table A3. Adjusted relative risk and associated 95% confidential interval for indent hypertension using a generalized linear model*

Variables	Relative risk (95% CI)	*p* value
Total (n=808)		
Uric acid, mg/dL	1.19 (0.98 - 1.44)	0.087
Sex, men	1.27 (0.72 - 2.23)	0.405
Age, year	1.04 (1.01 - 1.08)	0.008
BMI, kg/m^2	1.07 (1.00 - 1.14)	0.043
SBP, mmHg	1.04 (1.02 - 1.07)	<.001
DBP, mmHg	1.04 (1.00 - 1.08)	0.035
HDL cholesterol, mg/dL	0.98 (0.96 - 1.01)	0.162
Creatinine, mg/dL	0.32 (0.05 - 2.17)	0.243
Men (n=314)		
Uric acid, mg/dL	1.20 (0.91 - 1.59)	0.196
Age, year	1.05 (1.01 - 1.09)	0.021
BMI, kg/m^2	1.05 (0.96 - 1.14)	0.285
SBP, mmHg	1.05 (1.02 - 1.09)	0.001
DBP, mmHg	1.05 (1.00 - 1.10)	0.044
HDL cholesterol, mg/dL	0.98 (0.96 - 1.01)	0.259
Creatinine, mg/dL	0.22 (0.02 - 3.02)	0.258
Women (n=494)		
Uric acid, mg/dL	1.18 (0.90 - 1.55)	0.221
Age, year	1.04 (0.98 - 1.10)	0.163
BMI, kg/m^2	1.12 (1.00 - 1.25)	0.046
SBP, mmHg	1.03 (0.99 - 1.07)	0.147
DBP, mmHg	1.03 (0.96 - 1.09)	0.409
HDL cholesterol, mg/dL	0.99 (0.95 - 1.02)	0.476
Creatinine, mg/dL	0.36 (0.02 - 6.12)	0.482

*Adjusted for all variables in the tables
Abbreviation: BMI, body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; SBP, systolic blood pressure

Table A4. Baseline characteristics of study participants according to age

Variables	Participants of age < 55 years (n=374)	Participants of age ≥ 55 years (n=434)	*p*-value
Sex, men	107 (28.6)	207 (47.7)	<.001
Age, years	48.9 ± 3.6	61.0 ± 4.3	<.001
BMI, kg/m^2	24.7 ± 3.1	24.3 ± 3.1	0.038
SBP, mmHg	113.5 ± 11.8	118.3 ± 12.2	<.001
DBP, mmHg	71.6 ± 8.9	72.3 ± 7.9	0.234
Fasting glucose, mg/dL	91.0 [85.0-97.0]	92.0 [86.0-99.0]	0.194
Fasting insulin, mg/dL	7.8 [6.1-10.6]	7.5 [5.9-10.0]	0.054
HOMA-IR	2.0 ± 0.9	2.0 ± 1.1	0.794
Total cholesterol, mg/dL	196.8 ± 33.5	194.5 ± 35.3	0.348
HDL cholesterol,mg/dL	46.2 ± 10.8	44.9 ± 10.7	0.089
LDL cholesterol,mg/dL	123.2 ± 31.2	120.5 ± 33.6	0.230
Triglycerides, mg/dL	118.5 [84.0-164.0]	126.5 [88.0-178.0]	0.049
Uric acid, mg/dL	4.8 ± 1.2	5.1 ± 1.3	<.001
Creatinine, mg/dL	0.9 ± 0.1	0.9 ± 0.2	<.001
GFR, mL/min/1.73m^2	78.8 ± 14.2	66.4 ± 13.9	<.001
C-reactive protein, mg/L	0.6 [0.3-1.2]	0.7 [0.4-1.5]	<.001
Current smoker	37 (10.3)	44 (10.5)	1.000
Current drinker	153 (41.1)	157 (36.2)	0.171

p-value was derived from the independent t-test, the Wilcoxon rank sum test or chi-square test
Abbreviation: BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; GFR, glomerular filtration ratio; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment for insulin resistance; L, logarithmic; LDL, low-density lipoprotein; SBP, systolic blood pressure

Table A5. Adjusted relative risk and associated 95% confidential interval for indent hypertension according to age using a generalized linear model*

Variables	Relative risk (95% CI)	*p* value
Age < 55		
Serum uric acid, mg/dL	1.74 (1.22 - 2.47)	0.002
Sex, men	2.19 (0.71 - 6.75)	0.174
Age, year	1.05 (0.94 - 1.18)	0.376
BMI, kg/m^2	1.03 (0.92 - 1.15)	0.597
SBP, mmHg	1.05 (1.00 - 1.11)	0.041
DBP, mmHg	1.08 (1.00 - 1.16)	0.045
HDL cholesterol, mg/dL	0.98 (0.94 - 1.03)	0.444
Creatinine, mg/dL	0.22 (0.01 - 7.25)	0.397
Age ≥ 55		
Serum uric acid, mg/dL	0.98 (0.77 - 1.25)	0.894
Sex, men	1.03 (0.53 - 2.01)	0.932
Age, year	1.06 (1.00 - 1.13)	0.064
BMI, kg/m^2	1.08 (1.00 - 1.17)	0.065
SBP, mmHg	1.04 (1.01 - 1.07)	0.005
DBP, mmHg	1.02 (0.98 - 1.06)	0.396
HDL cholesterol, mg/dL	0.98 (0.96 - 1.01)	0.253
Creatinine, mg/dL	0.40 (0.04 - 4.17)	0.445

Abbreviation: BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; DBP, diastolic blood pressure; HOMA-IR, homeostatic model assessment for insulin resistance; SBP, systolic blood pressure

Table A6. Relative risk and 95% confidence interval of increasing systolic and diastolic blood pressure according to serum uric acid levels during follow-up period

Models	20mmHg increase of SBP per serum uric acid 1.0 mg/dL			10mmHg increase of DBP per serum uric acid 1.0 mg/dL		
	No. of case	Relative risk (95% CI)	*p* value	No. of case	Relative risk (95% CI)	*p* value
Total (n=808)	37			123		
Unadjusted		1.23 (0.98 - 1.55)	0.071		1.18 (1.04 - 1.34)	0.011
Adjusted		1.22 (0.90 - 1.64)	0.196		1.29 (1.09 - 1.53)	0.003
Men (n=314)	16			48		
Unadjusted		1.18 (0.81 - 1.70)	0.385		1.11 (0.89 - 1.38)	0.360
Adjusted		1.12 (0.74 - 1.68)	0.598		1.08 (0.85 - 1.38)	0.507
Women (n=494)	21			75		
Unadjusted		1.38 (0.94 - 2.02)	0.101		1.39 (1.14 - 1.71)	0.001
Adjusted		1.24 (0.79 - 1.94)	0.359		1.51 (1.19 - 1.91)	0.001

*Adjusted for sex, age, BMI, SBP, DBP, HDL cholesterol and creatinine
Abbreviation: BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; HDL, high-density lipoprotein; SBP, systolic blood pressure

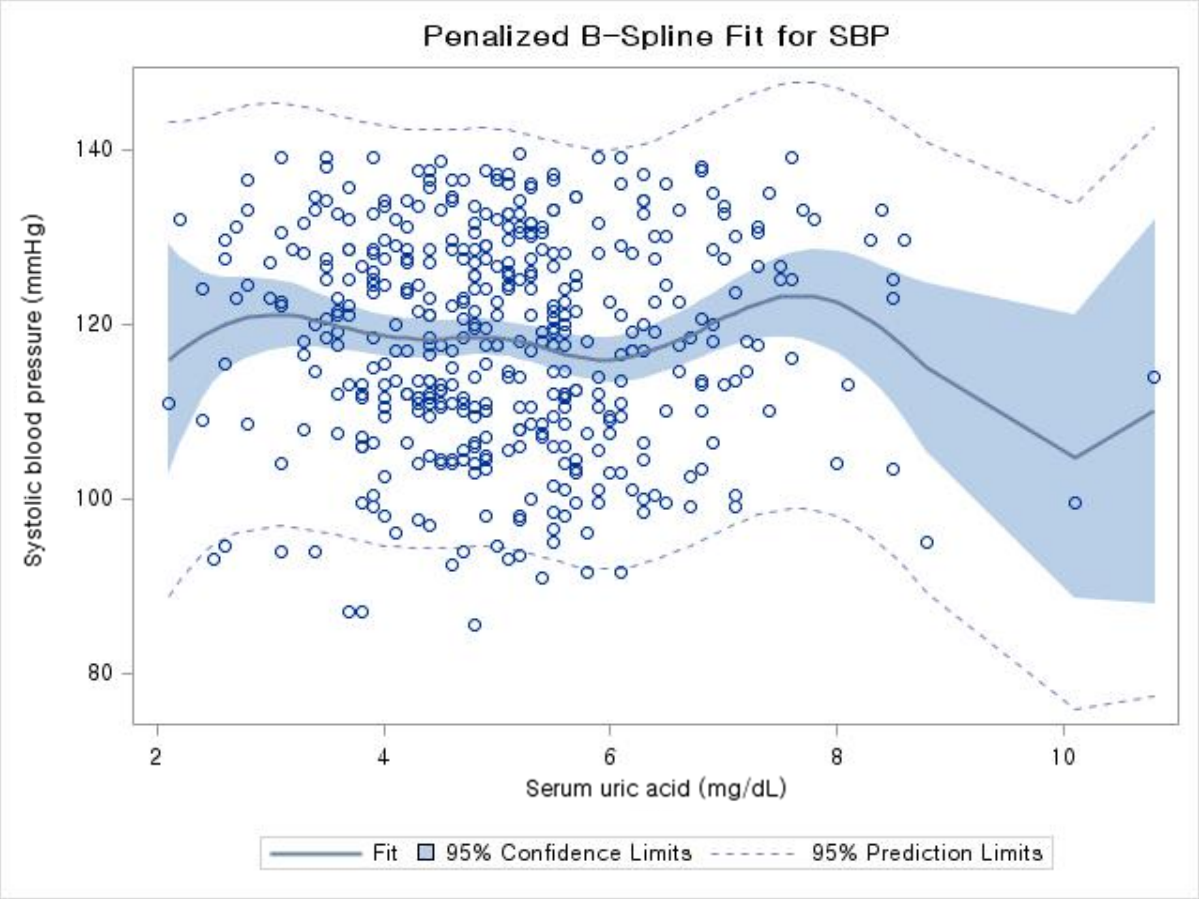

Figure A1. The association between serum uric acid and systolic blood pressure at baseline among people < 55 years old fitted by B-spline methods

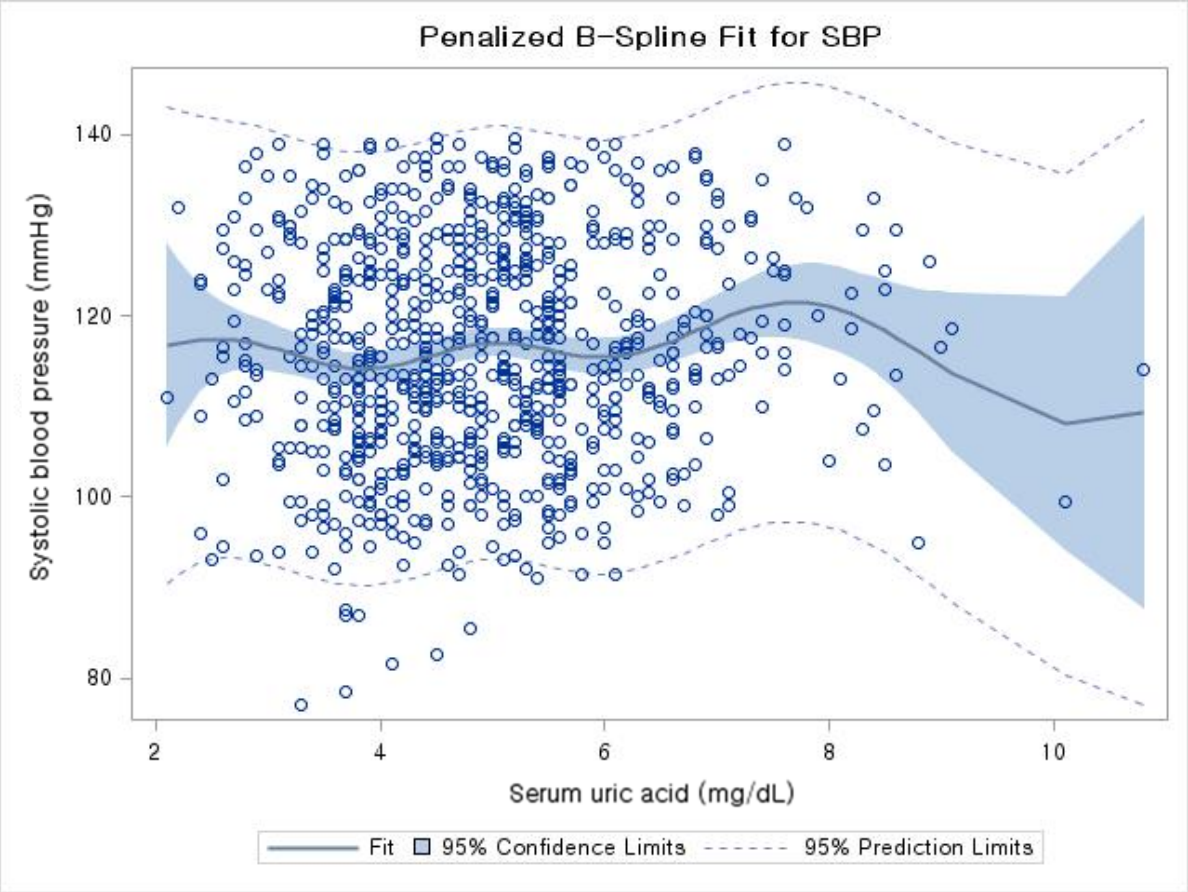

Figure A2. The association between serum uric acid and systolic blood pressure at baseline among people ≥ 55 years old fitted by B-spline methods

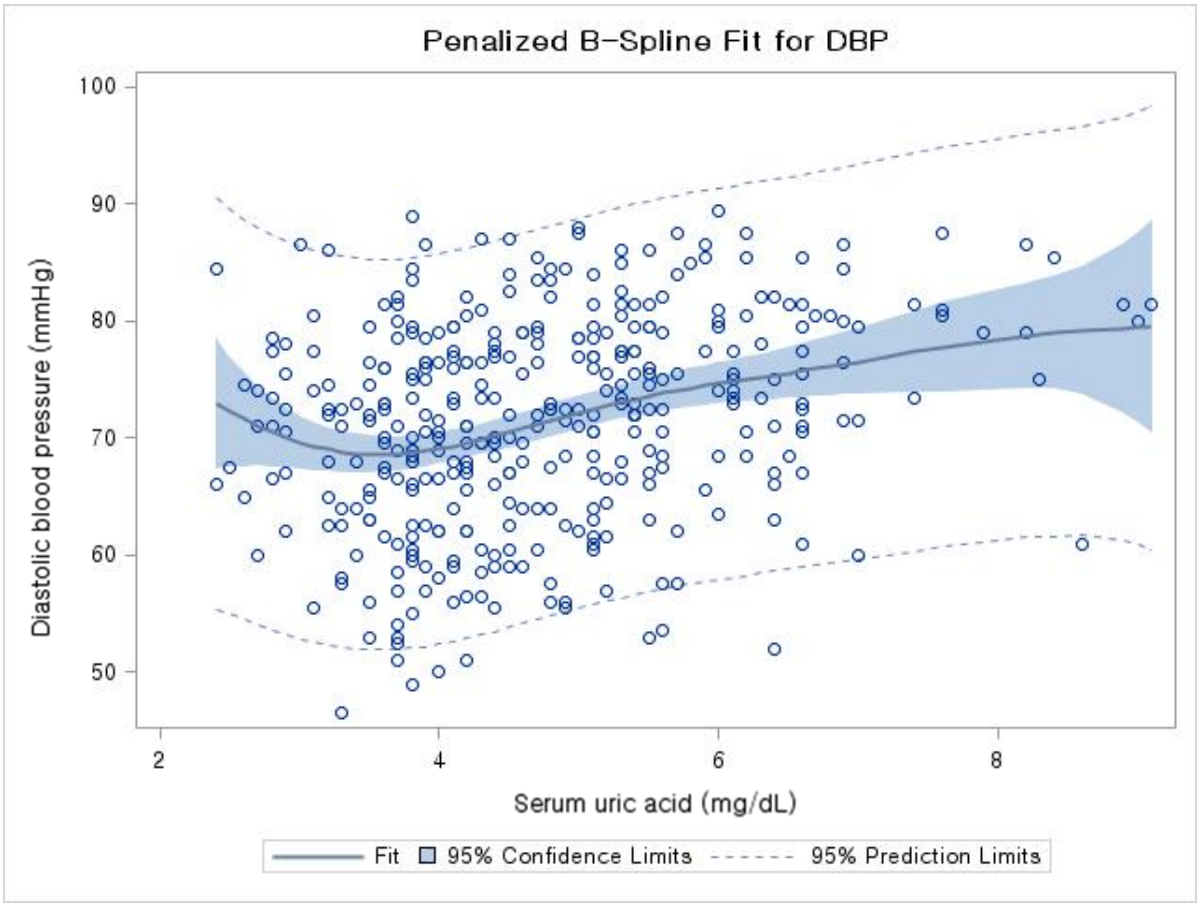

Figure A3. The association between uric acid and diastolic blood pressure at baseline among people < 55 years old fitted by B-spline methods

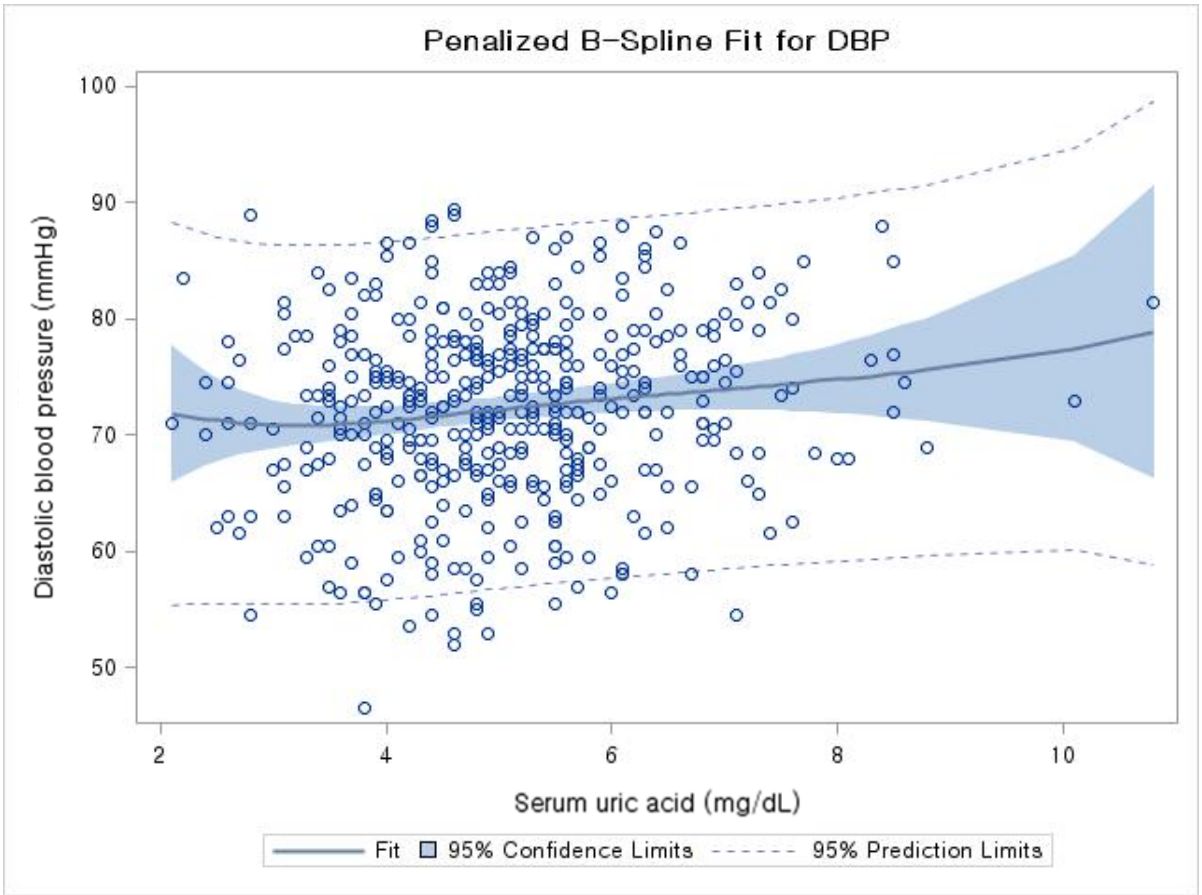

Figure A4. The association between uric acid and diastolic blood pressure at baseline among people ≥ 55 years old fitted by B-spline methods

ABSTRACT (In Korean)

연령에 따른 혈중 요산과 고혈압 발생의 관련성

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서론: 여러 선행연구들에서 높은 혈중 요산 수치가 고혈압 발생 위험 증가와 관련이 있었다. 그러나 혈중 요산 농도와 고혈압 발생의 관련성은 연령이나 성별, 혈중 지질, 비만도 등에 따라 달라지기도 하였다. 본 연구에서는 건강한 한국인을 대상으로 고혈압 발생에 대한 혈중 요산 농도의 관련성을 조사하고, 잘 알려진 고혈압 관련 위험요인에 의해 그 관련성이 달라지는지 알아보고자 하였다.

방법: 이 연구는 지역사회에 기반한 전향적 코호트 연구인 Korean Genome Epidemiology Study (KoGES-Kangwha)에 참여한 사람들 중 베이스라인에서 고혈압과 주요 심혈관 질환 과거력이 없었던 808명(40-79세)을 대상으로 하였다. 고혈압은 수축기 혈압이 140mmHg 이상, 이완기 혈압이 90mmHg 이상이거나, 항고혈압 약제 복용으로 정의하였다. 기반조사에서 혈중 요산 농도와 혈압의 단면적인 관련성을 알아보기 위하여 다중 선형회귀분석을 사용하였다. 공변량은 성별, 연령, 체질량지수, 고밀도지단백 콜레스테롤, 크레아티닌이었다. 혈중 요산 수준에 따른 고혈압 발생의 비교위험도를 구하기 위해 일반화 선형 모형을 사용하였고, 요산 농도와 고혈압 발생의 관련성이 관련 위험요인에 의해 달라지는지 알아보기 위해, 성별과 연령(<55, ≥55세), 체질량지수(<25, ≥25kg/m^2), 중성지방(<150, ≥150mg/dL), 고밀도지단백 콜레스테롤(40≤, >40mg/dL), 저밀도지단백 콜레스테롤(130≤, >130mg/dL), 공복혈당(110≤, >110mg/dL)에 따라 그룹을 나누어 z-test를 실시하였다.

결과: 본 연구에는 중년의 남자 314명과 여자 494명을 포함하였다. 평균 3.3년의 추적조사 기간 동안 고혈압이 발생한 사람은 남자 36명(11.5%)과 여자 53명(10.7%)이었다. 기반조사에서의 단면적 관련성을 분석했을 때, 혈중 요산 농도는 성별, 연령, 체질량지수, 고밀도지단백 콜레스테롤, 크레아티닌을 보정했을 때 남자에서만 이완기혈압과 양의 관련성이 있었다. 종적인 관련성을 보

았을 때는 대상자의 연령에 따라 혈중 요산 농도와 고혈압 발생의 관련성이 달라졌다(*p* for interaction=0.009). 연령이 55세 이상인 그룹에서는 혈중 요산 농도와 고혈압 발생이 유의한 관련성을 보이지 않았지만, 55세 미만에서는 유의한 관련성을 보였다(혈중 요산 농도 1.0 mg/dL 증가 당 비교위험도 1.74, *p*=0.002). 그러나 체질량지수, 중성지방, 공복혈당, 고밀도지단백 콜레스테롤, 저밀도지단백 콜레스테롤은 혈중 요산과 고혈압 발생의 관련성에 영향을 주지 못하였다.

고찰: 본 연구에서는 연령에 따라 혈중 요산 농도와 향후 고혈압 발생의 관련성이 다름을 확인하였다. 55세 이상인 사람들에서는 혈중 요산 농도와 고혈압 발생이 유의한 관련성이 없었지만, 55세 미만인 사람들에서는 높은 혈중 요산 농도가 고혈압 발생의 위험을 증가시키는 것으로 나타났다. 중년의 성인에서 고혈압 예방과 고위험군 선별을 위해서는 혈중 요산 농도의 측정과 관리가 도움이 될 것이다.

핵심 되는 말: 고혈압, 혈압, 혈중 요산, 교호작용, 위험요인, 연령