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Baseline and change in uric acid concentration over time are associated with incident hypertension in large Korean cohort

Running title: uric acid and hypertension

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Abstract

Background It is uncertain whether high baseline uric acid (UA) or change in UA concentration over time is related to development of incident hypertension. To investigate relationships between: a) baseline serum uric acid concentration and b) change in UA concentration and incident hypertension.

Methods 96,606 Korean individuals (with follow up UA data available for 56,085 people) participating in a health check program was undertaken. Cox regression models were used to estimate adjusted hazard ratios (aHRs) and 95% confidence intervals (CI) for incident hypertension according to UA quartiles regarding the lowest UA quartile as the reference, and also according to change in UA concentration comparing individuals with an increase in UA to those with a decrease in UA concentration over time.

Results Total follow up time was 8 years (median follow-up 3.3 years; interquartile range, 1.9-5.1). 10,405 cases of incident hypertension occurred. In the fully adjusted regression models, the hazard ratios (95% CI) for incident hypertension comparing the highest vs. the lowest quartiles of UA were 1.29 (1.19–1.38) in men and 1.24 (1.09–1.42) in women, with statistically significant p for trend for both gender. Additionally, stable or increasing UA concentration over time was associated with increased risk of incident hypertension, particularly in participants with baseline UA concentration ≥median (aHRs 1.14; 95% CI [1.03-1.26] and 1.18 ; 95% CI [0.98-1.40] in men and women, respectively).

Conclusions High initial UA concentration and increases in UA concentration over time should be considered independent risk factors for hypertension.

Keywords: uric acid, hypertension, blood pressure, risk factors, risk

Introduction

High serum uric acid (UA) concentrations are associated with increased all-cause mortality[1], cardiovascular disease [2,3], metabolic syndrome [4-7], and kidney disease[8,9] and also with hypertension[10-12]. However, the causal nature of the relationship has been questioned, with a Mendelian randomization study suggesting that body mass index may confound the association between UA and ischemic heart disease and hypertension [13]. There has been a resurgence of interest in the relationship between UA metabolism and development of disease states, since experimental data demonstrates that oxidative stress is one of the earliest phenomena observed in vascular, renal, liver and adipocyte cells exposed to UA[14], potentially explaining a link between increased serum UA concentrations and incident disease.

A major unresolved question is the role of UA in the development of hypertension. A meta-analysis of 18 prospective cohorts including 55,607 participants found a 13% increase in incident hypertension associated with 1mg/dL increase in uric acid level[15], but there was substantial heterogeneity across studies and control for confounding was limited. Importantly, none of those studies was able to adjust simultaneously for kidney function and for insulin resistance, two major confounders of the association between UA and hypertension. Furthermore, no studies to date have investigated the relationship between change in UA concentrations over time and development of incident hypertension.

We hypothesized that both higher initial UA concentrations and further increases in UA concentration over time would be associated with increased risk of incident

hypertension. We have thus investigated the relationship between: a) baseline serum UA concentrations and b) change in UA concentrations over time, with the development of incident hypertension over 8 years of follow-up, adjusting for key potential confounders, including measures of renal function and insulin resistance.

Methods

The study population included South Korean men and women ≥ 18 years old who underwent a comprehensive health examination at the Kangbuk Samsung Hospital Health Screening Centers in Seoul and Suwon, South Korea, between 2002 and 2010. The purpose of the comprehensive health screening program is to promote health through early detection of chronic diseases and their risk factors. In Korea, the Industrial Safety and Health Law requires employees to participate in annual or biennial health examinations. About 80% of the participants were employees of various companies and local governmental organizations and their spouses with the remaining participants registering individually for the program.

The present analysis initially included all study participants with at least one follow-up visit for endpoint ascertainment between 2002 and 2010 (N = 136,158; 84,045 men and 52,113 women). Participants were excluded at baseline if they had hypertension (defined as self-reported history of hypertension, current use of antihypertensive medications, a systolic blood pressure ≥ 140 mm Hg or a diastolic blood pressure ≥ 90 mm Hg; N = 20,585), or if they reported a history of coronary artery disease, cardiovascular disease (CVD), cancer, diabetes, metabolic syndrome (N = 24,978). We further excluded participants with missing data at baseline for serum UA (N = 2) or any relevant adjustment covariates (N =

6,181). The final number of study participants was 96,606 (55,035 men and 41,571 women). To test the association between UA concentration change and incident hypertension, we restricted the analysis to participants with at least 3 visits (N = 61,777). The first two visits were used to determine UA concentration change (calculated as UA concentration in the second visit minus baseline UA concentration), and incident hypertension was determined from the second visit through the rest of follow-up. After excluding 5,692 individuals from the original cohort who had incident hypertension diagnosed at the second visit, this analysis included 56,085 participants (33,073 men and 23,012 women). The study was approved by the Institutional Review Board of Kangbuk Samsung Hospital. Individual informed consent was not required because all personal identifiable information was removed prior to accessing data collected for screening purposes.

Data on medical history, medication use, and health-related behaviors were collected through a self-administered questionnaire. Questionnaire data included years of education, smoking status (never, current, or former), weekly frequency of physical activity, and average amount of alcohol intake each day.

Physical measurements and serum biochemical parameters were measured by trained staff. Body weight was measured in light clothing and no shoes to the nearest 0.1 kilogram using a digital scale. Height was measured to the nearest 0.1 centimeter. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Waist circumference was measured as the midpoint between iliac crest and rib cage at end-expiration. Blood pressure was measured in the seated position after a period of resting sitting upright with standard mercury

sphygmomanometers. If the systolic blood pressure was ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg, the measurement was repeated two more times after a rest at the same visit and then the values were averaged. At baseline and at each follow-up visit, hypertension was defined as a self-reported history of hypertension, current use of antihypertensive medications, a systolic blood pressure ≥ 140 mm Hg or a diastolic blood pressure ≥ 90 mm Hg.

Blood specimens were sampled from the antecubital vein after an overnight 12-hour fast. Biochemical analyses were performed centrally. The clinical laboratory has been accredited and participates annually in inspections and surveys by the Korean Association of Quality Assurance for Clinical Laboratories. Serum levels of glucose, total cholesterol, triglyceride, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol were measured using Bayer Reagent Packs (Bayer Diagnostics, Leverkusen, Germany) on an automated chemistry analyzer (Advia 1650™Autoanalyzer; Bayer Diagnostics, Leverkusen, Germany). Serum UA was measured using the Fossati enzymatic reaction using uricase with a Trinder-like endpoint (Advia 1650 auto analyzer; Bayer Diagnostics, Leverkusen, Germany). Insulin concentration was measured with an immunoradiometric assay (Biosource, Nivelle, Belgium) with an intra- and interassay coefficient of variation of 2.1–4.5% and 4.7–12.2%, respectively. Insulin resistance was estimated using fasting plasma insulin and the homeostasis model assessment of insulin resistance (HOMA-IR), calculated as insulin × glucose / 22.5. Fatty liver was diagnosed by the presence of liver fat identified by liver ultrasound examination. Serum creatinine was measured with the kinetic alkaline picrate (Jaffe) method. The within-batch and total coefficients of variation for

creatinine determinations were 1.4–3.9% for the duration of the study. We calculated eGFR using the Modification of Diet in Renal Disease Study equation.

Statistical analyses

Comparisons of the baseline characteristics of the study population were done with the χ2-test and student t-tests and transformations were conducted for nonparametric variables. The distributions of continuous variables were evaluated. The final number of study participants was categorized into 4 groups according to baseline serum uric acid level.

Cox proportional hazards models were used to estimate adjusted hazard ratios (HR) and 95% confidence intervals (CI) for incident hypertension, adjusted for pre-specified potential confounders measured at the baseline visit.

Since UA levels are higher in men compared to women, we conducted all analyses separately by sex. For the primary analyses, the study sample was divided in sex-specific quartiles of UA, and we estimated adjusted hazard ratios for incident hypertension comparing the three highest quartiles of UA to the lowest quartile in each sex. As secondary analysis, UA was modeled as a continuous variable in the regression models. The models were first adjusted for age, smoking status, alcohol intake, regular exercise and educational level (Model 1). Model 2 was further adjusted for systolic blood pressure and for BMI. Model 3 was further adjusted for insulin concentration and eGFR. For testing linear risk trends, we used the quartile rank as a continuous variable in the models. We checked the proportional hazards assumption by examining graphs of estimated log (-log) survival and there was no violation of the proportional hazards assumption.

To test the association between UA concentration change and incident hypertension, the study sample was classified in 4 groups depending on baseline (visit 1) UA concentrations (above vs. below median) and change in UA between visit 1 and 2 (decreased vs. stable or increased concentrations). The four groups generated were (a) baseline UA concentration < median and decline in UA concentration (reference group); (b) baseline UA concentration < median and stable or increased UA concentration; (c) baseline UA concentration ≥ median and decline in UA concentration; and (d) baseline UA concentration ≥ median and stable or increased UA concentration.

Sensitivity and subgroup analyses were undertaken by repeating the analyses after: a) exclusion of all subjects who were taking antihypertensive medications during follow up, b) stratification according to age and drinker.

The statistical analysis was performed using STATA version 11.2 (StataCorp LP, College Station, TX, USA). All reported *p* values are two-tailed, and $P < 0.05$ was considered statistically significant.

Results

We followed 96,606 non-hypertensive subjects at baseline for up to 8 years (total median follow-up time 3.3 years; interquartile range (IQR), 1.9 to 5.1 years). The median follow up time from baseline to 1st visit was 1.88 years, and 3.59 years from 1st visit to 2nd visit. At the end of follow-up, 10,405 participants had developed hypertension (incidence rate 30.9 per 1,000 person-years). As expected, participants who developed hypertension were more likely to be male, older, to have a higher baseline BMI, blood pressure, HOMA-IR, and to have a lower eGFR

compared to those who did not develop hypertension **(Supplement Table 1)**. Baseline mean (SD) UA concentration was 309.30 (83.27) μmol/L [5.2 (1.4) mg/dL] in individuals without hypertension at follow up, compared with 344.98 (83.27) μmol/L [5.8 (1.4) mg/dL] in those with hypertension at follow up (P <0.001). In both men and women, UA concentrations were inversely associated with age and eGFR, and positively associated with BMI, blood pressure, and HOMA-IR **(Table 1 and 2)**.

The risk of incident hypertension increased progressively across the quartiles of UA in both men and women **(Table 3)**. In the fully adjusted regression model, including adjustments for insulin concentration and eGRF, the hazard ratios (95% CI) for incident hypertension comparing the highest vs. the lowest quartiles of UA were 1.29 (1.19–1.38) in men and 1.24 (1.09–1.42) in women, with statistically significant P value for trend for both gender. When UA was included as a continuous variable in the models, the fully adjusted hazard ratios for incident hypertension associated with a 1 SD increase in UA [1 SD = 82.68 μmol/L (1.39 mg/dL)] were 1.11 (1.08-1.15) and 1.17 (1.08-1.26) for men and women, respectively.

UA concentration increased in 3,266 participants (2,555men and 711 women) among those who had more than 3 visits and no hypertension at baseline. Among participants with baseline UA concentrations ≥median, the fully adjusted hazard ratios for incident hypertension comparing participants with stable or increased to those with decreased UA concentration were 1.14 (1.03–1.26) and 1.18 (0.98–1.40) in men and women, respectively **(Table 4)**. Among participants with baseline

UA concentration <median, the corresponding hazard ratios were 1.05 (0.94–1.17) and 1.00 (0.82–.22) for men and women, respectively.

Since those with a history of coronary artery disease, CVD, cancer, diabetes and metabolic syndrome at baseline were excluded, the cox proportional methods were repeated after inclusion of these populations to warrant the robustness of the results. Including those subjects did not alter the results with the fully adjusted hazard ratio (95% CI) for incident HTN 1.22(1.15-1.30) in men and 1.25(1.10-1.41) in women **(Supplement Table 2)**. Other additional analyses of risk for incident hypertension in individuals not on antihypertensive treatment during follow up, stratified according to age and drinking status, and stratified according to incident diabetes are described, respectively **(Supplement Table 3-5)**. Excluding those who were on antihypertensive medication during follow up did not change the results with aHR(95% CI) 1.26(1.17-1.36) for men and 1.24(1.07-1.44) for women. Stratification according to drinking status did not affect the results whereas age and incident diabetes showed significant P value for interaction, 0.015, 0.017 respectively. We also conducted an additional analyses to seek whether control of gender difference and family history of hypertension would affect the result, respectively, which found to be not **(Supplement Table 6 and 7)**.

Discussion

In this large cohort of apparently healthy men and women, high UA concentrations were associated with an increased risk of incident hypertension, independent of age, smoking status, alcohol intake, exercise, education level, insulin resistance and renal function. The increase in risk was particularly evident in participants with high initial UA concentrations and increasing UA concentrations between the first

and second visits. Our findings support the hypothesis that high and increasing UA concentration over time should be considered risk factors for the development of hypertension.

The association between UA concentrations and incident hypertension has been controversial, partly due to heterogeneity across multiple small studies reported in the literature. A meta-analysis of 18 prospective cohorts that included data from 55,607 people found a 13% increased risk in incident hypertension in subjects with hyperuricemia [15]. Heterogeneity across the studies was considerable (I^2=73.4%), and some of these studies adjusted for very few confounders, including one study reporting only unadjusted findings. In this meta-analysis, the association between UA and hypertension was stronger in younger study populations. Our study, with almost double the combined sample size of the studies included in the previous meta-analysis, found a graded association between UA concentrations and incident hypertension across the range of UA levels which persisted after adjusting for multiple risk factors. Moreover, a recent Mendelian randomization study suggested that body mass index may confound the association between UA and ischemic heart disease and hypertension [13]. That said, it is plausible that the genetic probe (SLC2A9) used in the Mendelian randomization study was not ideal, since SLC2A9 is involved in renal UA transport and may only affect UA concentration in subjects with renal impairment [16].

There is very limited data in the literature as to whether changes in UA concentrations over time influence the risk of developing hypertension. Our data support the notion that stable or increasing UA concentrations over time in

298 subjects with higher baseline UA concentrations are associated with increased risk
299 of developing incident hypertension and add to the relevance of UA in the
300 development of hypertension.
301
302 Several mechanisms may explain a hypertensive effect of UA. Inhibition of uricase
303 in rat models results in a rise in serum UA concentration and in the development
304 of systemic hypertension that is preventable by lowering UA with either xanthine
305 oxidase inhibitors or uricosuric agents[17-19]. A recent meta-analysis of xanthine
306 oxidase found that, following xanthine oxidase inhibition, brachial artery flow
307 mediated dilatation and forearm blood flow responses to acetylcholine infusion
308 increased compared with changes in the non-infused control arm [20]. Reduction of
309 UA concentration lowers blood pressure, suggesting a direct pathophysiological
310 role of UA in the development of hypertension, and consequently there has been
311 renewed interest in whether allopurinol treatment lowers blood pressure. The
312 change in blood pressure after allopurinol initiation has been studied [21] and
313 allopurinol usage was independently associated with a fall in both systolic and
314 diastolic blood pressure.
315
316 UA has both pro-oxidant and anti-oxidant capabilities and it has been suggested
317 that there may be a molecular switch to regulate the role of UA as anti- or pro-
318 oxidant in different tissues[14]. This may contribute to the difficulty in establishing a
319 relationship between serum UA and chronic diseases. UA upregulates RAS and
320 angiotensin II and causes an increase in reactive oxygen species production in
321 human endothelial cells [22] and in adipose tissue[23]. This mechanism may thus
322 provide a direct pathway by which UA may affect blood pressure.

There are some limitations to our study that need to be considered. First of all, the diagnoses of hypertension at each screening visit were based on measurement taken at a single visit, which may induce unreliable result and lead to misclassification of blood pressure status. Furthermore, random measurement error may also affect UA and other confounders, after the effect of random measurement error is likely to attenuate the observed associations. As with other observational studies, we cannot exclude the possibility of residual confoundings, although we adjusted for BMI, eGFR, insulin concentration and several other risk factors. Finally, our study comprised of apparently healthy young and middle-aged Korean men and women. Approximately 80% of the participants were employees of various companies and therefore these individuals are not entirely representative of the whole population of Korea. Thus our findings may not apply to other age groups or to other race/ethnicities.

Several advantages of this cohort, however, add to the strength of the findings. In addition to the large sample size, the data was collected under standardized conditions and followed uniform procedures by trained staffs. Laboratory methods also were carefully standardized with rigorous internal and external quality controls. Finally a major advantage of our study is that our sample was comprised of young and middle-aged apparently healthy men and women, while participants in many other cohorts tended to be older. Our findings are thus less likely to be affected by selection bias and other biases due to disease development, presence of co-morbidities, and use of multiple medications that affect older cohorts.

In conclusion, high initial UA concentration and increases in UA concentration over time increase the risk for incident hypertension therefore UA concentration should be considered as independent risk factors for hypertension.

Disclosure

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Conflict of Interest All authors have no conflicts of interest.

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Table 1. Baseline characteristics of men by uric acid quartile

Characteristics	Overall	Uric acid quartiles				*P* for trend
		Q1 (<5.5mg/dl)	Q 2 (5.5-6.1mg/dl)	Q 3 (6.2-6.8mg/dl)	Q 4 (≥6.9 mg/dl)	
N=55,035						
Age (years)	37.1 (6.8)	38.2 (7.4)	37.2 (6.7)	36.7 (6.5)	36.4 (6.2)	<0.001
BMI (kg/m^2)	23.7 (2.6)	22.9 (2.5)	23.4 (2.5)	23.9 (2.5)	24.6 (2.6)	<0.001
Systolic BP (mmHg)	112.5 (9.0)	112.0 (9.2)	112.3 (9.0)	112.7 (9.0)	113.1 (8.8)	<0.001
Diastolic BP (mmHg)	73.4 (6.9)	72.8 (7.0)	73.2 (6.9)	73.5 (6.8)	74.0 (6.6)	<0.001
Higher education (%)[a]	83.5	80.2	83.4	85.1	85.7	<0.001
Regular exercise (%)[b]	14.0	14.0	13.6	13.6	15.2	0.014
Smoking status (%)						
Never smoker	29.4	30.2	30.1	29.0	28.3	<0.001
Former smoker	26.3	25.1	25.8	26.7	27.8	<0.001
Current smoker	44.3	44.7	44.2	44.3	44.0	0.278
Alcohol intake (%)						
0g/day	18.1	20.5	18.3	17.7	15.7	<0.001
10g/day	64.1	62.7	64.7	64.4	64.7	0.002
20g/day	17.8	16.8	17.0	17.9	19.6	<0.001
Alcohol Intake	8(3-15)	6(3-15)	8(3-15)	8(3-15)	8(3-15)	<0.001

(g/d) [c]						
Insulin (pmol/L) [c]	52.09(41.04-66.32)	49.03(38.68-62.57)	51.11(40.56-65.07)	52.99(42.02-67.02)	55.56(43.34-70.21)	<0.001
Glucose (mg/dl)	91.9(8.0)	91.6(8.2)	91.8(7.9)	92.1(7.9)	92.4(7.9)	<0.001
Total cholesterol (mg/dl) [c]	197.0(33.9)	190.7(32.6)	194.5(32.9)	198.5(33.5)	205.2(35.0)	<0.001
LDL-C (mg/dl)	117.1(28.5)	112.0(27.8)	115.4(27.7)	118.5(28.5)	122.9 (29.1)	<0.001
HDL-C (mg/dl)	53.0(10.5)	54.4(11.1)	53.2(10.5)	52.7(10.3)	51.7(9.7)	<0.001
Triglycerides (mg/dl)	115(85-156)	103(77-138)	110(82-147)	118(88-160)	132(97-184)	<0.001
HOMA IR [c]	1.70(1.31-2.19)	1.60(1.24-2.06)	1.66(1.30-2.13)	1.73(1.35+-2.22)	1.82(1.40-2.34)	<0.001
eGFR (ml/min)	79.1(9.2)	81.4(9.4)	79.9(9.1)	78.4(8.8)	76.3(9.0)	<0.001
HOMA IR 75%	16.1	12.3	14.4	16.8	21.2	<0.001
Glucose ≥ 100mg/dl (%)	14.7	14.8	14.1	15.1	15.0	0.228
SBP ≥ 130 or DBP ≥85 (%)	7.7	7.6	7.5	7.8	7.9	0.328

[a]≥ college graduate

[b]≥3 times per week

[c] =Median (IQR)

Data are % or means±SD unless otherwise specified

SI unit conversion (Multiply the conversion factor to obtain SI unit): glucose, 0.0555(mmol/L); total cholesterol, 0.0259(mmol/L); LDL-C, 0.0259(mmol/L); HDL-C, 0.0259(mmol/L); Triglyceride, 0.0113(mmol/L); uric acid, 59.48(μmol/L)

Table 2. Baseline characteristics of women by uric acid quartile

Characteristics	Overall	Uric acid quartiles				*P* for trend
		Q1 (<3.7mg/dl)	Q 2 (3.7-4.1mg/dl)	Q 3 (4.2-4.7mg/dl)	Q 4 (≥4.8 mg/dl)	
N=41,571						
Age (years)	36.8(6.8)	37.1(6.5)	37.0(6.7)	36.6(6.8)	36.5(7.3)	<0.001
BMI (kg/m^2)	21.7(2.6)	21.2(2.4)	21.5(2.4)	21.7(2.5)	22.3(2.8)	<0.001
Systolic BP (mmHg)	106.2(10.6)	106.0(10.6)	106.3(10.6)	106.2(10.6)	106.6(10.6)	<0.001
Diastolic BP (mmHg)	67.8(7.8)	67.5(7.8)	67.8(7.8)	67.9(7.8)	68.1(7.8)	<0.001
Higher education (%)[a]	65.6	64.7	65.6	66.1	66.0	0.058
Regular exercise (%)[b]	15.1	14.8	14.8	15.0	16.0	0.018
Smoking status (%)						
Never smoker	94.8	95.4	95.2	94.9	93.6	<0.001
Former smoker	3.1	2.8	2.8	3.1	3.8	<0.001
Current smoker	2.1	1.9	2.0	2.0	2.6	<0.001
Alcohol intake (%)						
0g/day	70.3	73.1	71.0	69.2	67.6	<0.001
10g/day	28.7	26.2	28.0	30.0	31.1	<0.001
20g/day	1.0	0.7	1.0	0.8	1.4	<0.001

Alcohol intake (g/d)[c]	0(0-3)	0(0-3)	0(0-3)	0(0-3)	0(0-3)	<0.001
Insulin (pmol/L) [c]	53.82(43.06)	53.06(42.78-65.91)	53.34(42.57-66.46)	54.24(43.34-67.30)	54.93(43.55-69.52)	<0.001
Glucose (mg/dl)	89.8(7.7)	89.5(7.7)(	89.7(7.5)	89.9(7.7)	90.2(7.9)	<0.001
Total cholesterol (mg/dl)	184.8(32.6)	180.6(31.7)	183.6(31.5)	185.2(32.3)	190.4(34.0)	<0.001
LDL-C (mg/dl)	103.5(27.0)	99.6(25.6)	102.4(26.2)	104.0(26.7)	108.6(28.9)	<0.001
HDL-C (mg/dl)	60.7(12.6)	61.1(12.7)	61.0(12.6)	60.4(12.5)	60.0(12.6)	<0.001
Triglycerides (mg/dl) [c]	77(59-103)	74(58-97)	75(58-99)	77(59-103)	82(62-112)	<0.001
HOMA IR [c]	1.71(1.34-2.18)	1.68(1.33-2.13)	1.69(1.33-2.15)	1.72(1.35-2.18)	1.76(1.36-2.27)	<0.001
eGFR (ml/min)	78.8(9.8)	81.2(10.1)	79.0(9.4)	78.1(9.5)	76.3(9.6)	<0.001
HOMA IR 75%	15.8	13.8	14.5	15.6	19.6	<0.001
Glucose ≥ 100mg/dl (%)	9.5	9.0	8.7	9.9	10.6	<0.001
SBP ≥ 130 or DBP ≥85 (%)	3.5	3.3	3.7	3.6	3.6	0.289

[a]≥ college graduate, [b]≥3 times per week, [c] =Median (IQR)

Data are % or means±SD unless otherwise specified

SI unit conversion (Multiply the conversion factor to obtain SI unit): glucose, 0.0555(mmol/L); total cholesterol, 0.0259(mmol/L); LDL-C, 0.0259(mmol/L); HDL-C, 0.0259(mmol/L); Triglyceride, 0.0113(mmol/L); uric acid, 59.48(μmol/L)

Table 3. Risk of incident hypertension according to baseline uric acid quartiles by cox proportional model

Uric acid quartiles (mg/dL)	Person-years	Number people	Incidence Rate (1000 person-years)	Age-adjusted HR (95% CI)	Multivariable HR*(95% CI)		
					Model 1	Model 2	Model 3
Men (N=55,035)							
Q1 (0.6-5.4)	50,021.8	1,803	36.0	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2 (5.5-6.1)	50,326.9	1,989	39.5	1.16 (1.09-1.24)	1.16(1.08-1.24)	1.11(1.03-1.19)	1.10(1.02-1.18)
Q3 (6.2-6.8)	51,779.9	2,248	43.4	1.30(1.22-1.39)	1.30(1.21-1.39)	1.14(1.07-1.22)	1.15(1.07-1.23)
Q4 (6.9-15.1)	41,883.2	2,189	52.3	1.59(1.49-1.69)	1.57(1.46-1.68)	1.28(1.19-1.37)	1.29(1.19-1.38)
***P* for trend**				<0.001	<0.001	<0.001	<0.001
Women(N=41,571)							
Q1 (0.3-3.6)	40,611.8	520	12.8	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2 (3.7-4.1)	36,166.9	520	14.3	1.13(1.00-1.28)	1.11(0.97-1.26)	1.04(0.92-1.19)	1.05(0.92-1.20)
Q3 (4.2-4.7)	32,511.4	512	15.7	1.27(1.12-1.43)	1.22(1.07-1.39)	1.12(0.98-1.28)	1.13(0.99-1.30)
Q4 (4.8-11.4)	33,154.8	624	18.8	1.50(1.33-1.68)	1.49(1.32-1.69)	1.25(1.10-1.42)	1.24(1.09-1.42)
***P* for trend**				<0.001	<0.001	<0.001	0.001

* Model 1: adjustment for age, smoking status, alcohol intake, regular exercise, education level; Model 2: Model 1 plus adjustment for systolic blood pressure and BMI; Model 3: Model 2 plus insulin and eGFR

Table 4. Risk of hypertension according to lower (<50th centile) versus higher (≥50th centile) uric acid concentration at baseline and change in uric acid concentration over time in men and women by cox proportional model

Uric acid group	Person-years	Number of events	Incidence Rate (1000 person-years)	Age- adjusted HR (95% CI)	Multivariable HR*(95%CI)		
					Model 1	Model 2	Model 3
Men (N=33,073)							
Baseline uric acid <50th centile							
uric acid decline over time	28,796.6	580	20.1	**REFERENCE**	**REFERENCE**	**REFERENCE**	**REFERENCE**
uric acid change stable/increased over time	52,126.9	1,138	21.8	1.11(1.00-1.22)	1.09(0.98-1.21)	1.06(0.95-1.18)	1.05(0.94-1.17)
Baseline uric acid ≥50th centile							
uric acid decline over time	42,610.6	1,031	24.2	**REFERENCE**	**REFERENCE**	**REFERENCE**	**REFERENCE**
uric acid change stable/increased over time	31,546.0	869	27.5	1.15(1.05-1.26)	1.15(1.05-1.27)	1.14(1.03-1.26)	1.14(1.03-1.26)
Women (N=23,012)							
Baseline uric acid <50th centile							
uric acid decline over time	19,403.0	174	9.0	**REFERENCE**	**REFERENCE**	**REFERENCE**	**REFERENCE**
uric acid change stable/increased over time	37,803.3	359	9.5	1.07(0.89-1.28)	1.07(0.89-1.29)	1.04(0.86-1.26)	1.00(0.82-1.22)

Baseline uric acid ≥50th centile							
uric acid decline over time	28,566.8	311	10.9	**REFERENCE**	**REFERENCE**	**REFERENCE**	**REFERENCE**
uric acid change stable/increased over time	18,598.9	251	13.5	1.23(1.04-1.45)	1.17(0.99-1.39)	1.16(0.98-1.38)	1.18(0.98-1.40)

Model 1: adjustment for age, smoking status, alcohol intake, regular exercise, education level; Model 2: Model 1 plus adjustment for systolic blood pressure and BMI; Model 3: Model 2 plus insulin and eGFR

Supplement Table 1. Baseline characteristics of the cohort according to incident hypertension during follow up

Baseline characteristics		No HTN N=86,201	New HTN N=10,405	*P*
Number=96,606				
N (%) Men		54.3	79.1	
Age (years)		36.7(6.6)	39.8(7.6)	<0.001
BMI (kg/m^2)		22.6(2.7)	24.2(2.7)	<0.001
Systolic BP (mmHg)		109.0 (10.1)	116.2 (8.9)	<0.001
Diastolic BP (mmHg)		70.4 (7.7)	75.8 (6.5)	<0.001
Higher education (%)[a]		76.2	72.6	<0.001
Regular exercise (%)[b]		14.1	18.1	<0.001
Smoking status (%)				
	Never smoker	59.5	41.5	<0.001
	Former smoker	15.4	23.9	<0.001
	Current smoker	25.1	34.6	<0.001

Alcohol intake (%)				
	0g/day	42.2	26.9	<0.001
	10g/day	48.3	53.7	<0.001
	20g/day	9.5	19.4	<0.001
Median (IQR) Alcohol intake (g/d)		3 (0-10)	6 (0-15)	<0.001
Median (IQR) Insulin (pmol/L)		52.71(41.95-66.46)	53.96(41.88-68.34)	<0.001
Glucose (mg/dl)		90.9(7.9)	92.3(8.3)	<0.001
Total cholesterol (mg/dl)		190.2(33.5)	204.1(34.6)	<0.001
LDL-C (mg/dl)		110.1(28.4)	120.9(29.3)	<0.001
HDL-C (mg/dl)		56.5(12.1)	54.6(11.4)	<0.001
Triglycerides (mg/dl)		94(68-131)	119(87-164)	<0.001
HOMA IR		1.70(1.32-2.17)	1.78(1.35-2.28)	<0.001
HOMA IR ≥75th centile		15.7	18.3	<0.001
eGFR (ml/min)		79.1(9.5)	77.3(9.5)	<0.001
eGFR <60ml/min (%)		1.3	2.5	<0.001
Glucose ≥ 100mg/dl (%)		13.5	13.1	<0.001

Uric acid (mg/dL)	5.2(1.4)	5.8(1.4)	<0.001

[a]≥ college graduate

[b]≥3 times per week

Data are % or means±SD unless otherwise specified

SI unit conversion (Multiply the conversion factor to obtain SI unit): glucose, 0.0555(mmol/L); total cholesterol, 0.0259(mmol/L); LDL-C, 0.0259(mmol/L); HDL-C, 0.0259(mmol/L); Triglyceride, 0.0113(mmol/L); uric acid, 59.48(μmol/L)

Supplement Table 2. Risk of incident hypertension according to baseline uric acid quartiles (including people with CAD, CVD, cancer, DM, MetS)

Uric acid quartiles (mg/dL)	Person-years	Number people	Incidence Rate (1000 person-years)	Age-adjusted HR (95% CI)	Multivariable HR* (95% CI)		
					Model 1	Model 2	Model 3
Men (N=65,235)							
Q1 (0.6-5.4)	63,015.0	2,683	42.6	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2 (5.5-6.1)	57,305.0	2,556	44.6	1.12(1.06-1.18)	1.09(1.03-1.16)	1.02(0.97-1.09)	1.03(0.97-1.09)

Q3 (6.2-6.8)	51,226.2	2,536	49.5	1.26(1.20-1.33)	1.26(1.19-1.34)	1.08(1.02-1.15)	1.09(1.03-1.16)
Q4 (6.9-15.1)	51,651.7	3,157	61.1	1.57(1.50-1.66)	1.54(1.46-1.63)	1.21(1.14-1.28)	1.22(1.15-1.30)
***P* for trend**				<0.001	<0.001	<0.001	<0.001
Women(N=45,106)							
Q1 (0.3-3.6)	42,559.3	597	14.0	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2 (3.7-4.1)	37,949.3	605	15.9	1.15(1.03-1.29)	1.13(1.00-1.27)	1.06(0.94-1.19)	1.06(0.93-1.20)
Q3 (4.2-4.7)	39,928.2	724	18.1	1.33(1.19-1.48)	1.31(1.16-1.47)	1.15(1.03-1.30)	1.16(1.03-1.32)
Q4 (4.8-11.4)	31,509.7	766	24.3	1.70(1.53-1.89)	1.68(1.50-1.89)	1.27(1.13-1.43)	1.25(1.10-1.41)
***P* for trend**				<0.001	<0.001	<0.001	<0.001

* Model 1: adjustment for age, smoking status, alcohol intake, regular exercise, education level,; model 2: model 1 plus adjustment for systolic blood pressure and BMI. Model 3 model2 plus insulin, eGFR,

CAD, coronary artery disease; CVD, cardiovascular disease; DM, diabetes melliatus; MetS. Metabolic syndrome

Supplement Table 3. Risk of incident hypertension according to baseline uric acid quartiles (after excluding those who were taking antihypertensive medications (n= 1,960) during follow up)

	Uric acid quartiles (mg/dL)				P for trend	P for interaction
	Q1	Q2	Q3	Q4		
Men						
Multivariable HR*(95% CI)	1.00 (reference)	1.09(1.01-1.18)	1.13(1.05-1.22)	1.26(1.17-1.36)	<0.001	0.107

Women					
Multivariable HR*(95% CI)	1.00 (reference)	1.09(0.94-1.27)	1.11(0.95-1.29)	1.24(1.07-1.44)	0.001

*adjusted for age, smoking status, alcohol intake, regular exercise, education level, systolic blood pressure , BMI, insulin and eGFR

Supplement Table 4. Risk of incident hypertension according to baseline uric acid quartiles (stratification according to age and drinker)

	Uric acid quartiles (mg/dL)				P for trend	P for interaction
	Q1	**Q2**	**Q3**	**Q4**		
Drinking						
No drinker (N=39,211)						0.344
Multivariable HR*(95% CI)	**1.00 (reference)**	1.01(0.90-1.12)	1.13(0.98-1.31)	1.32(1.12-1.56)	0.002	
Drinker (N=57,395)						
Multivariable HR*(95% CI)	**1.00 (reference)**	1.11(0.99-1.25)	1.16(1.03-1.31)	1.33(1.18-1.50)	<0.001	
Age						

Age<50 (N=91,851)					0.015
Multivariable HR*(95% CI)	**1.00 (reference)**	1.04(0.95-1.13)	1.04(0.95-1.14)	1.12(1.01-1.23)	0.008
Age>=50(N=4,755)					
Multivariable HR*(95% CI)	**1.00 (reference)**	0.94(0.76-1.17)	1.08(0.85-1.37)	1.16(0.89-1.51)	0.125

*adjusted for age, smoking status, alcohol intake, regular exercise, education level, systolic blood pressure, BMI, insulin and eGFR

Supplement Table 5. Risk of incident hypertension according to baseline uric acid quartiles (stratification according to incident diabetes)

	Uric acid quartiles (mg/dL)				P for trend	P for interaction
	Q1	**Q2**	**Q3**	**Q4**		
No incident DM						
Multivariable HR*(95% CI)	1.00 (reference)	1.10(1.02-1.18)	1.14(1.06-1.23)	1.29(1.20-1.39)	<0.001	0.017
Incident DM						
Multivariable HR*(95% CI)	1.00 (reference)	1.31(0.64-2.70)	1.32(0.65-2.70)	1.69(0.84-3.39)	0.158	

*adjusted for age, sex, smoking status, alcohol intake, regular exercise, education level, systolic blood pressure , BMI, insulin and eGFR

Supplement Table 6. Risk of incident hypertension according to baseline uric acid quartiles (including sex as an adjustment variable)

	Uric acid quartiles (mg/dL)				P for trend
	Q1	**Q2**	**Q3**	**Q4**	
Multivariable HR*(95% CI)	1.00 (reference)	1.10(1.02-1.18)	1.15(1.07-1.23)	1.29(1.19-1.38)	<0.001

*adjusted for age, sex, smoking status, alcohol intake, regular exercise, education level, systolic blood pressure , BMI, insulin and eGFR

Supplement Table7. Risk of incident hypertension according to baseline uric acid quartiles (including family history of hypertension as an adjustment variable)

	Uric acid quartiles (mg/dL)				P for trend	P for interaction
	Q1	**Q2**	**Q3**	**Q4**		
Men						
Multivariable HR*(95% CI)	1.00 (reference)	1.09(1.02-1.17)	1.14(1.06-1.22)	1.28(1.19-1.38)	<0.001	0.057
Women						
Multivariable	1.00 (reference)	1.06(0.92-1.21)	1.15(1.00-1.31)	1.24(1.09-1.42)	<0.001	

HR* (95% CI)

*adjusted for age, smoking status, alcohol intake, regular exercise, education level, systolic blood pressure , insulin, eGFR, BMI, family history of hypertension