Serum uric acid and cardiovascular disease according to metabolic risk factors: the Korean Heart Study

Eunjung Park

The Graduate School
Yonsei University
Department of Public Health

Serum uric acid and cardiovascular disease according to metabolic risk factors: the Korean Heart Study

A Dissertation
Submitted to the Department of Public Health
and the Graduate School of Yonsei University
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy in Public Health

Eunjung Park

June 2017

연세대학교
YONSEI UNIVERSITY

This certifies that the dissertation of Eunjung Park is approved.

Thesis Supervisor: Sun Ha Jee

Chungmo Nam: Thesis Committee Member #1

Heejin Kimm: Thesis Committee Member #2

Jae Woong Sull: Thesis Committee Member #3

Sung Kweon Cho: Thesis Committee Member #4

The Graduate School

Yonsei University

June 2017

CONTENTS

TABLE INDEX

FIGURE INDEX

APPENDIX INDEX

ABSTRACT

Serum uric acid and cardiovascular disease according to metabolic risk factors: the Korean Heart Study

Eunjung Park
Dept. of Public Health
The Graduate School
Yonsei University

Background and Aims: The aims of this epidemiological study was to characterize the association between serum uric acid (SUA) levels and the incidence of cardiovascular disease (CVD) in a large, sample of the Korean general population without or and without metabolic risk factors. Given the correlation with hypertension, inflammation, endothelial dysfunction, insulin resistance, and obesity, uric acid has recently been proposed to play a role as a risk factor for CVD, but the evidence is discordant. However, most studies have examined the relation of CVD with hyperuricemia, or have focused upon populations with existing morbidity.

Methods: The Korean Heart Study (KHS) enrolled 465,233 Korean adults who visited one of 18 health centers across the country between January1996 and December 31, 2004. In this study, a total of 322,467 Koreans, without CVD in the KHS who had baseline, SUA measurements were analyzed. Metabolic risk factors were defined using the modified National Cholesterol Education Program-Adult Treatment Panel III criteria, except for waist circumference. All statistical tests were 2-sided, and statistical significance was accepted for p-values < 0.05. Hazard ratios and 95% confidence intervals for CVD events were determined according to SUA quintiles using multivariable Cox proportional hazard models.

Results: The median follow-up was 9.5 years and we assessed the associations of SUA and CVD events (27,009 cases) after adjusting for potential confounders. Cox proportional hazards models were calculated to evaluate SUA by quintiles, as a predictive marker for CVD. SUA levels > 6.8mg/dL in men and > 4.8mg/dL in women were independently associated with an increased risk of CVD incidence; the adjusted hazard ratio (HR) for the highest versus lowest quintile of SUA was 1.22 (95% CI, 1.16-1.28) in men and 1.27 (95% CI, 1.19-1.35) in women. When stratified by conventional metabolic risk factors, SUA was significantly associated with ischemic heart disease (IHD) within CVD. However, in a subgroup analysis of participants without diabetes, the HR for IHD increased to 1.27 (95% CI, 1.14-1.41) in men and 1.51 (95% CI, 1.29-1.77) in women, and these findings showed a clear dose-response relationship.

Conclusions: Elevated serum uric acid levels were associated with IHD, independently of conventional CVD risk factors and metabolic syndrome. The increased risk of IHD associated with hyperuricemia was consistent across most subgroups. Hyperuricemia may increase the risk of IHD, particularly in females. Further research is needed to broadly evaluate the causal effects of multiple biomarkers on cardiovascular disease and metabolic risk traits using data from large-scale cohorts or GWAS including many different genetic variants.

Keywords: Serum Uric Acid, Metabolic risk factor, Cardiovascular disease, Cohort study

.

I. INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death worldwide and the second leading cause of death following malignant neoplasms and the utilization of medical institutions for CVD has increased sharply in Korea (Jo et al, 2016).

High levels of uric acid, produced during the breakdown of purine, a substance found in many foods, has been traditionally implicated in the development of gout, kidney stones and kidney failure. Given its correlations with hypertension, inflammation, endothelial dysfunction, insulin resistance, dyslipidemia, and obesity, uric acid has recently been proposed to play a role as a risk factor for CVD, but the evidence is discordant (Kavous et al., 2012; Storhaug et al., 2013; Chuang et al., 2012; Zalawadiya et al., 2015).

There is considerable documentation that serum uric acid (SUA) levels are correlated with many recognized cardiovascular risk factors, including age, male sex, hypertension, hypertriglyceridemia, obesity, insulin resistance, and consequently metabolic syndrome. Therefore, association observed between SUA elevations and CVD was long considered in terms of those correlations. However, recent evidence supports the possibility that hyperuricemia may be a significant and independent risk factor for hypertension and forms of CVDs, including ischemic heart disease (Bos et al., 2006; Krishnan et al., 2006; Holme et al., 2009; Li et al., 2011; Ito et al., 2011; Chuang et al., 2012; Juraschek et al., 2014; Lai et al., 2016).

Most studies have examined the relation of CVD with hyperuricemia, rather than uric acid levels in the normal range, or have focused upon populations with existing morbidity, including gout, hypertension, stroke, congestive heart failure, and/or diabetes. There is a notable paucity of general population-based studies. In the last few years, several meta-analyses of observational studies have found that hyperuricemia could significantly increase the risk of CVD events (Kim et al., 2010; Braga et al., 2016; Zuo et al., 2016; Li et al 2016). At present, the treatment of asymptomatic hyperuricemia is not considered beneficial or cost-effective, and generally is not recommended. Although recent studies on the relationship between hyperuricemia and the risk of CVD have been published, the results from cohort studies are still controversial. Furthermore, it remains unclear whether such risk factors modify the dose-response relationship between SUA level and CVD subtypes incidence.

Moreover, it is not clear whether there are any metabolic risk factors effects between serum uric acid and CVD in men and women. Clarifying this potential sex-specific association has important public health implications to choose effective treatments for prevention of CVD.

Therefore, we has to conduct this causal associate analysis of cohort study to determine whether sex modifies the association between SUA levels and risk of CVD and clarify the shape of the relationship between SUA and CVD. Additionally, we need to review published studies to clarify the associations between SUA levels and risk of CVD morbidity and mortality based on population studies.

II. OBJECTIVES

The objectives of this study was to characterize the association between SUA levels and the incidence of CVD in a large ample of the Korean general population with and without metabolic risk factors.

The main aims of this study were as follows:

1. To assess the association between SUA and metabolic risk factors
2. To explore the association between SUA and cardiovascular disease
3. To compare the association between SUA and IHD depending on the presence of metabolic risk factors
4. To compare the association between SUA and CVD in women depending on menopausal status

III. MATERIALS AND METHODS

A. Study population

The Korean Chronic Disease Epidemiologic Study is a retrospective cohort study based on private health examinations. We collected data from examinations conducted at 18 centers located in Korea. This study enrolled 465,233 Korean adults (284,232 men and 181,001 women) who visited one of 18 health centers across the country between January 1996 and December 31, 2004.

The record linkage resulted in 430,920 study members (266,782 men and 164,138 women) aged 30-74 years at the baseline health assessment. We have labeled this study as the Korean Heart Study (KHS) (Jee et al., 2014; Jee et al., 2014).

All Koreans are members of the National Health Insurance Service (NHIS) and the record linkage for mortality was based on an official personal identification number. To ensure anonymity, all linkages were carried out by NHIS staff.

For the current analyses, the exclusion criteria at baseline were as follows:

1) History of cardiac problems, cerebral infarction, or cancer according to self-report (19,762)

2) Missing values of age, SUA level, BMI, fasting blood glucose, blood pressure, lipid profile, creatinine, estimated cost of medical insurance, smoking history, or alcohol history (97,558)

3) Currently taking diuretics or anti-gout drugs (107)

4) Younger than 30 or older than 75 years old (25,339)

The analytical sample therefore comprised 322,467 individuals (Figure 1).

The Institutional Review Board of Human Research of Yonsei University approved the study (IRB approval number 4-2007-0065 and 4-2017-0186).

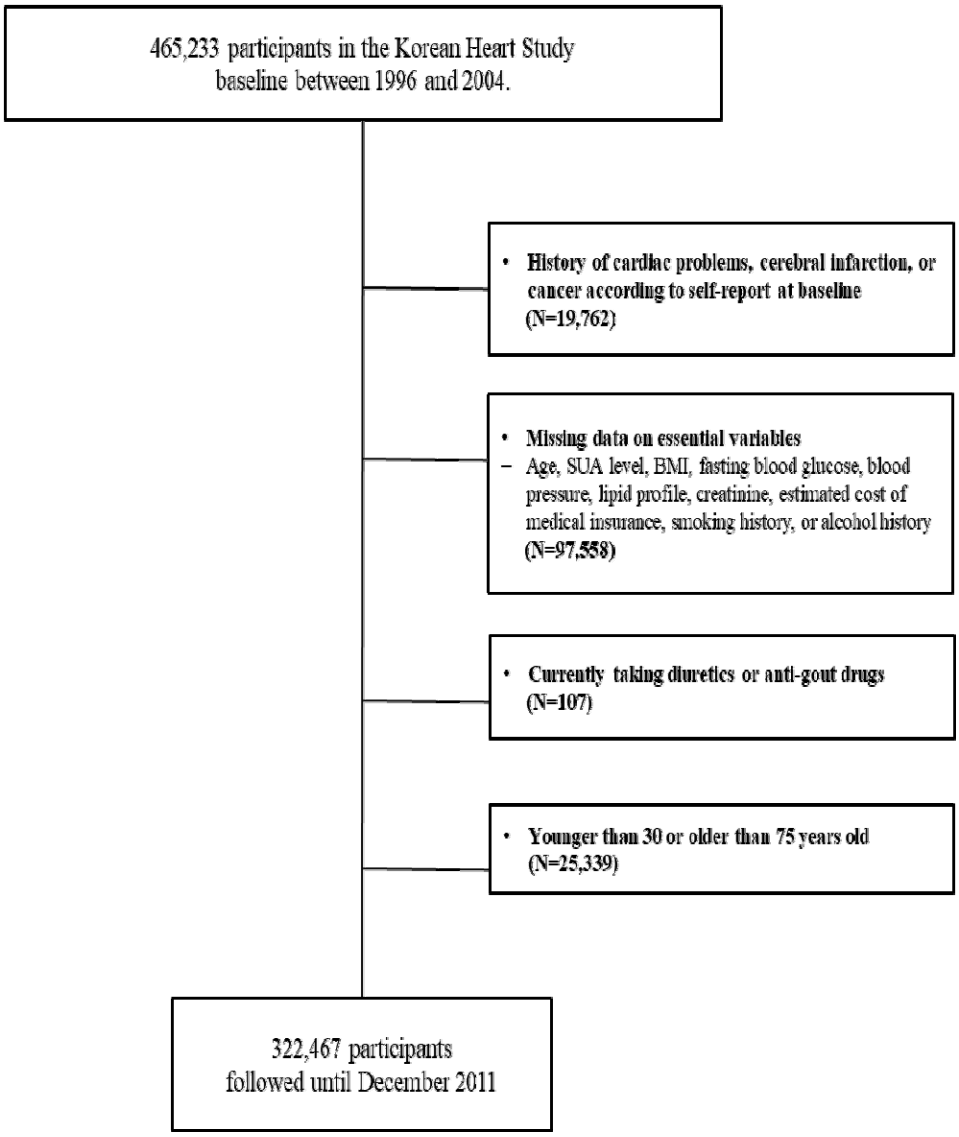


Figure 1. Flow chart describing the study population of the Korean Heart Study

B. Data collection

The content of the health examination included a structured questionnaire containing questions about demographic characteristics, medical history, medication, and lifestyle factors (personal habits, smoking, drinking and physical activity). A medical examination was also performed in which measurements of body weight, height, blood pressure, and fasting blood glucose were made.

Minor differences might have been present in the health questionnaires since they were used by different health centers nationwide. However, the questionnaires were sorted and reorganized according to the needs of this study design. Depending on smoking, participants were categorized as nonsmokers, current smokers, and ex-smokers. Participants were classified according to alcohol consumption as alcohol drinkers and non-drinkers, and exercise habits were classified as exercise and no exercise. Additionally, education level, family history, past medical history, medication history, and for women, history of menarche and menopause were added as variables.

The clinical tests included total cholesterol, triglycerides, high density lipoprotein (HDL) - cholesterol, low density lipoprotein (LDL) - cholesterol, and fasting blood glucose. LDL - cholesterol levels were measured using the Friedwald method or direct measurements depending on the health center. However, directly measured data were preferentially used when both types of measurement data had been collected. In addition, as a kidney function test, the glomerular filtration rate (GFR) was estimated by the

simplified Modification of Diet in Renal Disease equation, in which GFR ($mL/min/1.73m^2$) = 186 × [PCr (mg/dL)] $^{-1.154}$ × [age] $^{-0.203}$ × [1.21] in black subjects, where PCr refers to plasma creatinine (National KF, 2002).

Socioeconomic status was assessed using the amount of monthly deduction for health insurance that was estimated by the standards of the National Health Insurance Corporation (NHIC). These data were provided by the NHIC.

C. Outcome variables

We identified participants with CVD from NHIC health insurance claim data. Deaths among subjects were confirmed by matching the information to the death records. Death certificates from the National Statistical Office were identified using the identification numbers assigned to the subjects at birth.

The causes of death and the incidence of cardiovascular events were ascertained using the International Classification of Diseases-10th Revision codes (ICD-10). The accuracy rate of the ICD codes for cerebrovascular diseases in medical insurance claims for men in Korea was reported to be 83.0% in 2000 (Kimm et al., 2012).

CVD was defined as the incidence of ischemic heart disease, hard coronary heart disease (CHD), or stroke. We divided the category of CVD into stroke and heart disease, which was in turn divided into ischemic heart disease and hard CHD. Ischemic heart disease was defined using the ICD-10 codes I20-I25, and hard CHD was defined as I21-I24.

Ischemic stroke, hemorrhagic stroke, and all stroke types were defined according to the following ICD-10 codes: ischemic stroke, I63-I639; hemorrhagic stroke, I60-I629; and all stroke types, I60-I699.

D. Statistical analysis

Hazard ratios (HRs) and 95% confidence intervals (CIs) for CVD events were determined according to SUA quintiles using Cox proportional hazard models. Hyperuricemia was defined as a level ≥7.0 mg/dL in males and ≥6.5 mg/dL in females (Saggiani et al., 1996; Johnson et al., 1999).

The multivariable Cox models included 2 models. One adjusted for age and sex and the other model adjusted for age, sex, body mass index (BMI), cholesterol, HDL cholesterol, GFR, diabetes, hypertension, cigarette smoking, alcohol consumption, and exercise. Stratifications by sex and SUA level were applied to the HRs with adjustment for age, BMI, total cholesterol, HDL cholesterol, diabetes, hypertension, cigarette smoking, alcohol consumption, and exercise. Additionally, stratification by conventional metabolic risk factors was also applied to the HRs, with adjustment for age, BMI, cholesterol, triglycerides, diabetes, hypertension, cigarette smoking, alcohol consumption, and exercise.

All analyses were conducted using the SAS version 9.2 software package (SAS Institute Inc., Cary, NC, USA). All statistical tests were 2-sided, and statistical significance was accepted for p-values <0.05.

IV. RESULTS

A. General characteristics of the study population

Table 1 and 2 presents the baseline characteristics of the study participants, stratified by SUA quintile.

In this study, the mean age of the 322,467 participants was 44.61 (standard deviation [SD], 9.37) years in men, and 46.86 (SD, 1.06) years in women. The mean SUA level was 5.84 (SD, 1.23) mg/dL in men and 4.10 (SD, 0.91) mg/dL in women, and was significantly higher in men than in women. In additional, hyperuricemia was associated with sex, and the prevalence of hyperuricemia was 17.1% in men and 1.31% in women. The mean GFR was 82.57 (SD, 13.10) mL/min/1.73 m^2 in men and 82.85 (SD, 15.04) mL/min/1.73 m^2 in women. Levels of SUA significantly increased with age, weight, height, creatinine, and GFR (p for trend <0.05) in both men and women. However, SUA did not show a statistically significant association with the amount of the monthly deduction for health insurance (Table 1, Table 2).

B. Associations between serum uric acid and metabolic risk factors

The relationships of fasting SUA quintiles with metabolic and socioeconomic risk factors were assessed in the Korean population. In men, levels of SUA significantly increased with age, weight, height, BMI, systolic blood pressure, diastolic blood pressure, total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides (p for trend <0.05). However, SUA did not show a statistically significant relationship with fasting blood glucose (Table 1). Similar results were obtained in women (Table 2).

Table 1. Baseline characteristics of study participants from the Korean Heart Study according to serum uric acid levels in men

(N=204,295)

	Mean (SD)	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P for trend
		≤ 4.9mg/dL	4.9-5.5mg/dL	5.5-6.1mg/dL	6.1-6.8 mg/dL	≥6.8mg/dL	
		40,558	36,505	42,585	41,247	43,400	
Age (years)	44.61 (9.37)	46.78 (9.78)	45.24 (9.36)	44.35 (9.17)	43.68 (9.02)	43.19 (9.11)	0.0054
Serum uric acid (mg/dL)	5.84 (1.23)	4.18 (0.57)	5.16 (0.17)	5.75 (0.17)	6.38 (0.20)	7.55 (0.74)	0.0008
Weight (kg)	69.24 (9.45)	66.18 (9.19)	67.57 (8.97)	68.96 (8.99)	70.45 (9.09)	72.61 (9.57)	0.0004
Height (cm)	169.95 (5.72)	169.31 (5.81)	169.78 (5.71)	170.04 (5.68)	170.22 (5.67)	170.35 (5.70)	0.0072
Body mass index (kg/m^2)	23.94 (2.81)	23.06 (2.76)	23.42 (2.71)	23.83 (2.69)	24.29 (2.67)	24.99 (2.78)	0.0012
Fasting blood glucose (mg/dL)	95.83 (22.84)	101.53 (34.79)	95.67 (22.54)	94.26 (18.73)	93.80 (16.96)	94.09 (15.47)	0.0904
Systolic blood pressure (mmHg)	122.24 (16.12)	121.29 (16.34)	121.07 (15.88)	121.69 (15.97)	122.49 (15.84)	124.43 (16.28)	0.0410
Diastolic blood pressure (mmHg)	77.71 (11.45)	76.55 (11.33)	76.70 (11.20)	77.36 (11.34)	78.12 (11.36)	79.58 (11.70)	0.0111
Serum total cholesterol (mg/dL)	193.30 (34.99)	187.66 (33.50)	189.62 (33.00)	192.15 (33.14)	195.14 (33.67)	201.05 (34.83)	0.0048
High-density lipoprotein cholesterol (mg/dL)	48.15 (9.94)	49.43 (10.73)	48.87 (10.26)	48.18 (9.77)	47.63 (9.48)	46.82 (9.27)	<0.0001
Low-density lipoprotein cholesterol (mg/dL)	116.82 (32.16)	113.61 (30.97)	115.20 (31.05)	116.57 (31.46)	117.97 (32.48)	120.35 (34.07)	0.0007
Triglyceride (mg/dL)	153.42 (92.40)	132.93 (79.60)	138.12 (80.67)	147.98 (85.90)	159.71 (92.12)	184.79(108.85)	0.0094
Creatinine (mg/dL)	1.06 (0.17)	1.02 (0.15)	1.04 (0.14)	1.06 (0.14)	1.07 (0.15)	1.11 (0.25)	0.0036
Glomerular filtration rate($mL/min/1.73\ m^2$)	82.57 (13.10)	85.66 (13.58)	84.99 (12.90)	82.80 (12.62)	81.63 (12.68)	79.16 (12.83)	0.0012
Amount of monthly deduction for health insurance (won)	153,819.42 (144,243.59)	148,8636.50 (13,9287.01)	154,405.27 (144,598.22)	155,153.84 (145,674.85)	155,493.71 (145,482.41)	155,269.58 (145,791.30)	0.1089

Table 2. Baseline characteristics of study participants from the Korean Heart Study according to serum uric acid levels in women

(N=118,172)

	Mean (SD)	Quintile 1 ≤3.4mg/dL 23,593	Quintile 2 3.4-3.8mg/dL 19,913	Quintile 3 3.8-4.3mg/dL 27,496	Quintile 4 4.3-4.8mg/dL 22,022	Quintile 5 ≥4.8mg/dL 25,148	P for trend
Age (years)	46.86 (10.06)	45.61 (9.56)	45.71 (9.65)	46.26 (9.88)	47.20 (10.17)	49.31 (10.50)	0.0230
Serum uric acid (mg/dL)	4.10 (0.91)	2.92 (0.37)	3.56 (0.11)	4.00 (0.14)	4.47 (0.14)	5.39 (0.62)	0.0011
Weight (kg)	56.97 (7.81)	55.03 (7.10)	55.68 (7.21)	56.51 (7.47)	57.61 (7.69)	59.77 (8.48)	0.0067
Height (cm)	156.97 (5.35)	157.19 (5.34)	157.28 (5.32)	157.11 (5.33)	156.92 (5.32)	156.46 (5.40)	0.0479
Body mass index (kg/m^2)	23.14 (3.09)	22.29 (2.79)	22.54 (2.83)	22.91 (2.94)	23.41 (3.05)	24.43 (3.32)	0.0089
Fasting blood glucose (mg/dL)	92.78 (19.63)	93.22 (25.22)	91.65 (19.79)	91.88 (17.80)	92.47 (17.12)	94.53 (17.19)	0.0429
Systolic blood pressure (mmHg)	118.78 (19.09)	116.29 (17.87)	116.63 (18.20)	117.88 (18.37)	119.43 (19.41)	123.26 (20.53)	0.0202
Diastolic blood pressure (mmHg)	73.63 (11.87)	72.15 (11.34)	72.38 (11.45)	73.19 (11.63)	74.14 (11.91)	76.03 (12.49)	0.0114
Serum total cholesterol (mg/dL)	192.90 (36.69)	184.70 (34.46)	187.55 (34.32)	191.15 (35.69)	195.98 (36.58)	204.06 (38.63)	0.0041
High-density lipoprotein cholesterol (mg/dL)	55.37 (12.56)	57.05 (12.65)	56.38 (12.55)	55.78 (12.57)	54.69 (12.38)	52.98 (12.25)	0.0058
Low-density lipoprotein cholesterol (mg/dL)	117.19 (33.48)	110.04 (31.17)	112.93 (31.17)	115.80 (32.73)	119.89 (33.48)	126.75 (35.72)	0.0028
Triglyceride (mg/dL)	111.45 (67.54)	96.65 (54.17)	99.99 (56.46)	106.94 (61.63)	116.83 (70.65)	134.63 (82.13)	0.0106
Creatinine (mg/dL)	0.81 (0.14)	0.78 (0.11)	0.80 (0.11)	0.81 (0.11)	0.82 (0.12)	0.85 (0.19)	0.0030
Glomerular filtration rate($mL/min/1.73\ m^2$)	82.85 (15.04)	87.94 (15.17)	85.00 (14.77)	83.39 (14.60)	81.31 (14.25)	78.07 (14.81)	0.0009
Amount of monthly deduction for health insurance (won)	140099.55 (136,015.43)	139,433.28 (133,157.98)	141,398.73 (137,5341.92)	141,330.43 (140,956.88)	139,613.25 (133,445.51)	138,775.95 (134,321.32)	0.5659

C. Associations between serum uric acid and cardiovascular disease

The KHS included 322,467 Korean adults with complete data on SUA and correlated variables who were retrospectively followed up for 9.5 years, with a total time at risk of 2,856,996 person-years.

The total CVD events comprised 27,009 cases in men (Table 3) and women (Table 4). In men, there were 3811 total cases of stroke, 2181 of ischemic stroke, 840 of hemorrhagic stroke, 6347 of ischemic heart disease, and 1197 of hard CHD. In women, there were 2533 total cases of stroke, 1343 of ischemic stroke, 561 of hemorrhagic stroke, 2865 of ischemic heart disease, and 308 of hard coronary heart disease.

In the Cox proportional hazards models adjusted for age, BMI, cholesterol, HDL cholesterol, GFR, diabetes, hypertension, cigarette smoking, alcohol consumption, and exercise, high SUA levels were positively related to the risk of total CVD in men (p for trend <0.0442) and in women (p for trend <0.0297).

The HR for total CVD was statistically significant, and the HR for ischemic heart disease in men with highest quintile of SUA was 1.17 (95% CI, 1.08-1.26) compared to those with the lowest quintile of SUA (p for trend=0.0542). However, there was no independent association between SUA and stroke. In men, the HRs of the highest versus the lowest quintile of SUA were 1.05 (95% CI, 0.95-1.16) for stroke and 1.05 (95% CI, 0.93-1.20) for ischemic stroke. No association was found between hyperuricemia and stroke in men (Table 3).

In women, the HRs (95% CI) of the highest versus the lowest quintile of SUA was 1.27 (1.19-1.35) for total CVD events, and a dose-response relationship also appeared among SUA quintiles (p for trend = 0.0297). Compared with the first SUA quartile, the HRs for incident ischemic heart disease in the second, third, fourth and fifth SUA quintiles in women were 1.12 (95% CI, 0.98-1.28), 1.07 (95% CI, 0.94-1.22), 1.14 (95% CI, 1.00-1.29) and 1.34 (95% CI, 1.19-1.51), respectively (p for trend <0.0310) in the fully adjusted model. The HRs of the highest versus lowest quintiles of SUA were 1.05 (95% CI, 0.93-1.18) for stroke and 1.09 (95% CI, 0.92-1.28) for ischemic stroke in women. Nonetheless, there was no independent association between hyperuricemia and hemorrhagic stroke in women (Table 4).

Men with hyperuricemia had a 1.21-fold increase in the risk of CVD and a 1.16-fold increase in risk of ischemic heart disease, and women with hyperuricemia had a 1.58-fold increase in the risk of CVD and 1.36-fold increase in the risk of ischemic heart disease (Figure 1).

Table 3. Hazard ratios (95% confidence intervals) for the relationship of serum uric acid with cardiovascular disease incidence in men

(N=204,295)

Types of CVD		Quintile 1 (40,558)	Quintile 2 (36,505)	Quintile 3 (42,585)	Quintile 4 (41,585)	Quintile 5 (41,247)	P for trend	HRs (95% CI) of hyperuricemia	HRs (95% CI) 1-SD increased
		≤4.9 mg/dL	4.9-5.5 mg/dL	5.5-6.1 mg/dL	6.1-6.8 mg/dL	≥6.8 mg/dL		≥7.0 mg/dL	per 1 mg/dL
Total CVD	Case	2,494	1,958	2,109	2,098	2,389	0.0442	1,969	11,048
	Rate	707	693	692	743	861		1.21 (1.16-1.26)	1.06 (1.05-1.08)
	HR	1.00	0.99 (0.95-1.05)	1.03 (0.98-1.08)	1.10 (1.05-1.16)	1.22 (1.16-1.28)			
IHD	Case	1,350	1,154	1,238	1,222	1,403	0.0542	1,181	6,367
	Rate	372	394	392	422	488		1.16 (1.09-1.24)	1.07 (1.04-1.09)
	HR	1.00	1.08 (0.99-1.17)	1.03 (0.95-1.11)	1.10 (1.01-1.19)	1.17 (1.08-1.26)			
Total stroke	Case	929	643	724	682	771	0.2626	612	3,749
	Rate	273	245	257	258	301		1.06 (0.97-1.15)	1.02 (0.98-1.05)
	HR	1.00	0.91 (0.83-1.01)	0.96 (0.87-1.05)	0.97 (0.87-1.07)	1.05 (0.95-1.16)			
Ischemic stroke	Case	584	399	432	394	477	0.6388	383	2,286
	Rate	174	160	163	151	194		1.05 (0.94-1.18)	1.02 (0.97-1.06)
	HR	1.00	0.95 (0.84-1.09)	0.98 (0.86-1.11)	0.98 (0.86-1.12)	1.05 (0.93-1.20)			
Hemorrhagic stroke	Case	203	136	165	167	169	0.1089	126	840
	Rate	61	49	53	63	65		1.00 (0.83-1.22)	1.02 (0.96-1.09)
	HR	1.00	0.78 (0.63-0.97)	0.95 (0.78-1.16)	0.95 (0.77-1.17)	0.96 (0.78-1.18)			

Hazard ratios (HRs) were adjusted for age, sex, body mass index, cholesterol, high-density lipoprotein cholesterol, diabetes, hypertension, cigarette smoking status (ex/never/current), and alcohol consumption, and were stratified by sex. Rates are age-standardized incidence rates per 100,000. Abbreviations: CI, confidence interval; CVD, cardiovascular disease; IHD, ischemic heart disease; SD, standard deviation.

Hyperuricemia was defined as a serum uric acid level of ≥7.0 mg/dL in men or ≥6.5 mg/dL in women.

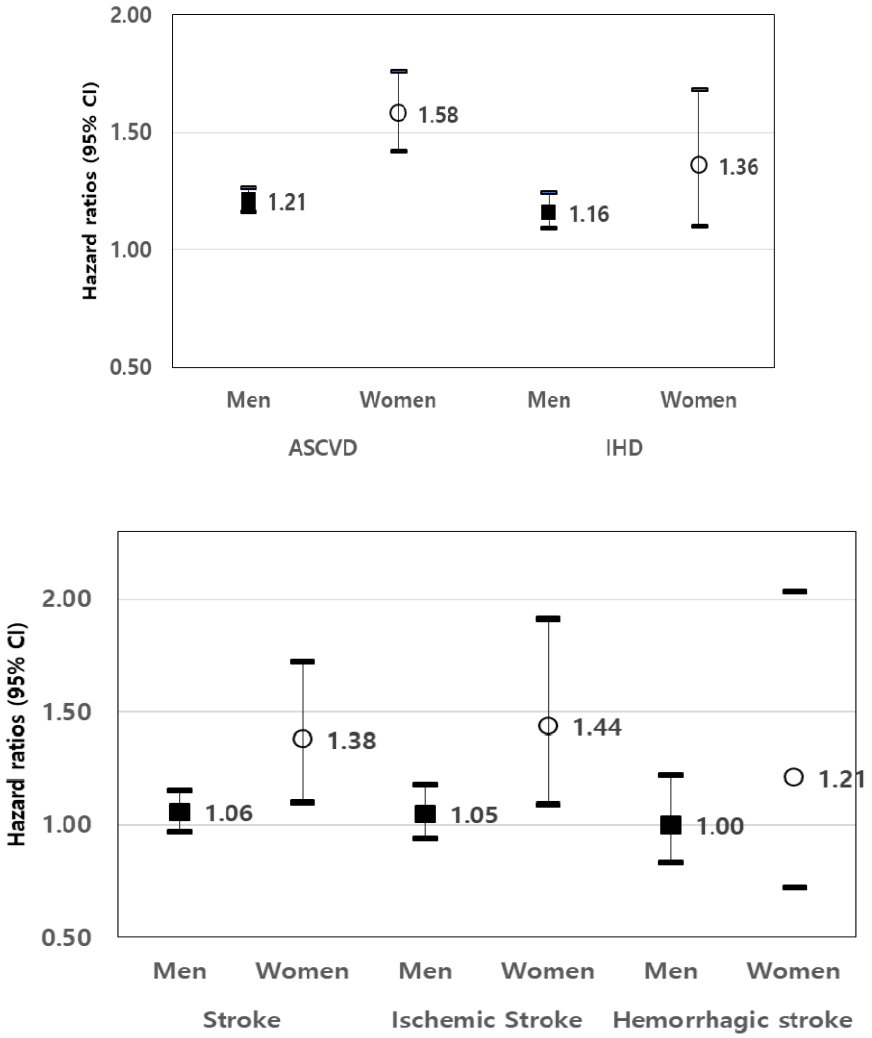
Table 4. Hazard ratios (95% confidence intervals) for the relationship of serum uric acid with cardiovascular disease incidence in women

(N=122,639)

Types of CVD		Quintile 1 (24,474)	Quintile 2 (20,587)	Quintile 3 (28,481)	Quintile 4 (22,807)	Quintile 5 (26,290)	P for trend	HRs (95% CI) of hyperuricemia	HRs (95% CI) 1-SD increased
		≤3.4mg/dL	3.4-3.8mg/dL	3.8-4.3mg/dL	4.3-4.8mg/dL	≥4.8mg/dL		≥6.5 mg/dL	per 1mg/dL
Total CVD	Case	885	822	1207	1132	1864	0.0297	302	5,910
	Rate	742	744	763	838	1017		1.58 (1.42-1.76)	1.11 (1.09-1.13)
	HR	1.00	1.04 (0.97-1.12)	1.03 (0.97-1.10)	1.10 (1.03-1.18)	1.27 (1.19-1.35)			
IHD	Case	358	357	530	520	843	0.0310	82	2,608
	Rate	282	308	328	401	445		1.36 (1.10-1.68)	1.11 (1.07-1.15)
	HR	1.00	1.12 (0.98-1.28)	1.07 (0.94-1.22)	1.14 (1.00-1.29)	1.34 (1.19-1.51)			
Total stroke	Case	385	332	499	445	734	0.1081	71	2,395
	Rate	336	319	330	326	432		1.38 (1.10-1.72)	1.04 (1.00-1.08)
	HR	1.00	0.95 (0.82-1.09)	0.95 (0.84-1.08)	0.97 (0.85-1.11)	1.05 (0.93-1.18)			
Ischemic stroke	Case	203	172	265	230	417	0.2354	40	1,287
	Rate	94	96	108	118	188		1.44 (1.09-1.91)	1.06 (1.01-1.11)
	HR	1.00	0.92 (0.75-1.12)	0.95 (0.76-1.13)	0.90 (0.75-1.08)	1.09 (0.92-1.28)			
Hemorrhagic stroke	Case	86	86	107	107	167	0.2921	20	553
	Rate	40	48	43	55	75		1.21 (0.72-2.03)	1.06 (0.98-1.14)
	HR	1.00	1.09 (0.81-1.46)	1.00 (0.76-1.32)	1.17 (0.89-1.55)	1.18 (0.91-1.54)			

Hazard ratios (HRs) were adjusted for age, sex, body mass index, cholesterol, high-density lipoprotein cholesterol, diabetes, hypertension, cigarette smoking status (ex/never/current), and alcohol consumption, and were stratified by sex. Rates are age-standardized incidence rates per 100,000. Abbreviations: CI, confidence interval; CVD, cardiovascular disease; IHD, ischemic heart disease; SD, standard deviation.

Hyperuricemia was defined as a serum uric acid level of ≥7.0 mg/dL in men or ≥6.5 mg/dL in women.



Hazard ratios (HRs) were adjusted for age, sex, body mass index, cholesterol, high density lipoprotein cholesterol, diabetes, hypertension, cigarette smoking status (ex/never/current), and alcohol consumption, and were stratified by sex.
ASCVD = atherosclerotic cardiovascular disease; IHD = ischemic heart disease.
Hyperuricemia was defined as a serum uric acid level of ≥7.0 mg/dL in men or ≥6.5 mg/dL in women.

Figure 2. Hazard ratios of all forms of cardiovascular diseases according to hyperuricemia.

D. Serum uric acid and ischemic heart disease with or without metabolic risk factors

The association between serum uric acid and ischemic heart disease with or without metabolic risk factors was evaluated in Korean men and women. In both genders, those without diabetes, hypertension, hyperlipidemia or obesity-related risk factors had higher HRs for the incidence of CVD associated with SUA than those with such factors. Additionally, in the absence of metabolic risk factors, compared to those in the lowest quartile of SUA, participants in the fourth and fifth SUA quintiles had a significantly increased risk of ischemic heart disease.

However, with an increase of 1 mg/dL of SUA, the incidence of ischemic heart disease in men with normal HDL cholesterol and low HDL cholesterol increased, but not significantly [normal HDL cholesterol: HR = 1.10 (95% CI, 1.06-1.13); low HDL cholesterol: HR = 1.03 (95% CI, 0.98-1.08)] (Supplementary Figure 1, Supplementary Figure 2). In the relationship of SUA with the incidence of ischemic heart disease according to each metabolic risk factor, the HRs for the incidence of ischemic heart disease significantly increased with increases of 1 mg/dL of SUA in the presence of each metabolic risk factor in both men and women. In women, with an increase of 1 mg/dL of SUA, the HRs for incidence of ischemic heart disease among those with and without diabetes increased to the greatest extent [with diabetes: HR = 1.15 (95% CI, 1.09-1.20); without diabetes: HR= 1.08 (95% CI, 1.02-1.14)].

1. Diabetes

In men with diabetes, the HR of the highest versus the lowest quintile of SUA was 0.97 (95% CI, 0.87-1.09) for ischemic heart disease events, and was not statistically significant (Figure 4). However, in men without diabetes, the HR of the highest versus the lowest quintile of SUA was 1.24 (95% CI, 1.11-1.38). The highest quintile of SUA showed a significantly greater risk of ischemic heart disease incidence in the absence of diabetes. Additionally, a dose-response relationship also appeared among the SUA quintiles in men (Figure 3).

In women without diabetes, compared with the first SUA quartile, the HRs for ischemic heart disease incidence in the second, third, fourth and fifth SUA quintiles were 1.13 (95% CI, 0.94-1.36), 1.18 (95% CI, 1.00-1.40), 1.26 (95% CI, 1.07-1.50) and 1.52 (95% CI, 1.29-1.78), in the fully adjusted model, and a dose-response relationship also appeared among SUA quintiles (Figure 5). In women with diabetes, the HR of the highest versus the lowest quintile of SUA was 1.16 (95% CI, 0.94-1.43) for ischemic heart disease events, and was not statistically significant (Figure 6).

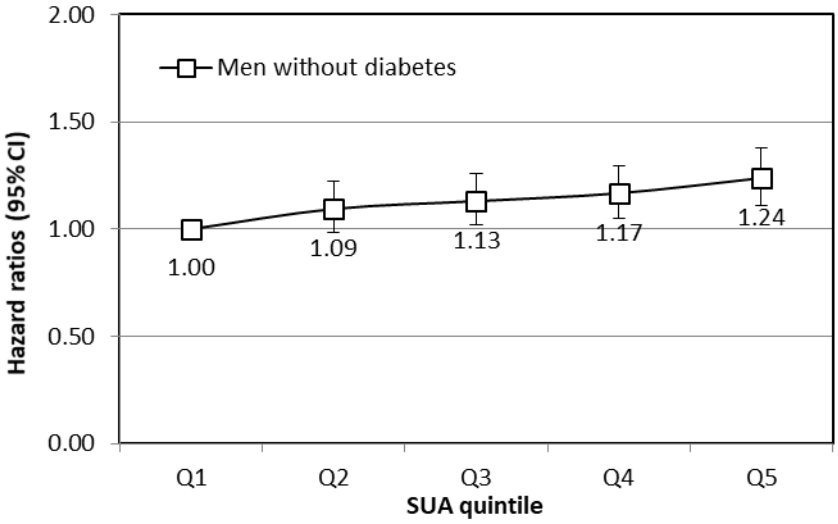


Figure 3. Hazard ratios of ischemic heart disease incidence in the study population without diabetes according to serum uric acid levels in men.

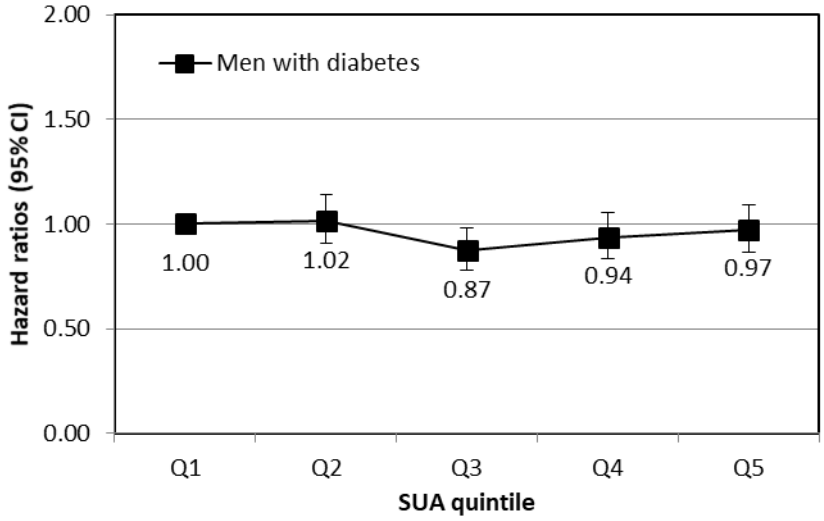


Figure 4. Hazard ratios of ischemic heart disease incidence in the study population with diabetes according to serum uric acid levels in men.

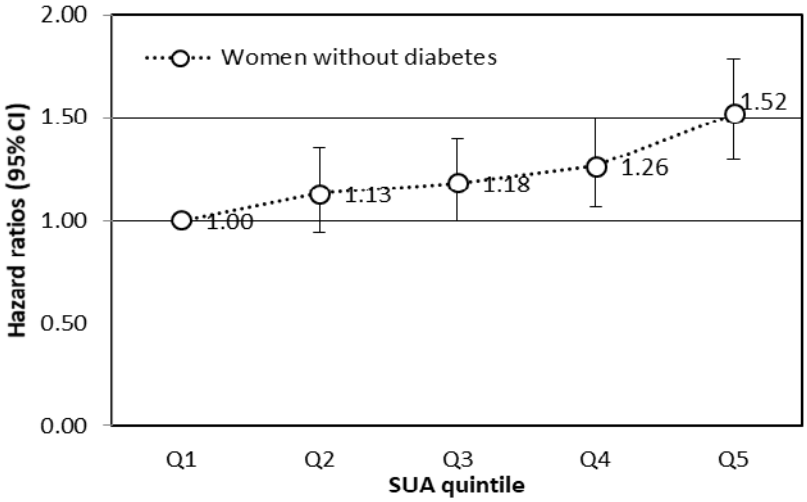


Figure 5. Hazard ratios of ischemic heart disease incidence in the study population without diabetes according to serum uric acid levels in women.

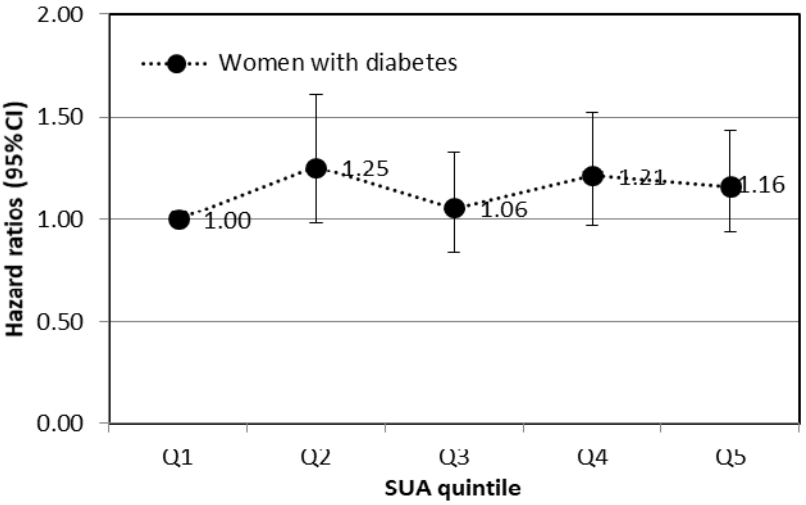


Figure 6. Hazard ratios of ischemic heart disease incidence in the study population with diabetes according to serum uric acid levels in women.

2. Hypertension

In men without hypertension, the HR of the highest versus the lowest quintile of SUA was 1.21 (95% CI, 1.08-1.37) for ischemic heart disease events (Figure 7). In men with hypertension, the HR of the highest versus the lowest quintile of SUA was 1.15 (95% CI, 1.03-1.28) for ischemic heart disease events (Figure 8).

In women without hypertension, compared with the first SUA quartile, the HRs for ischemic heart disease incidence in the second, third, fourth and fifth SUA quintiles were 1.10 (95% CI, 0.98-1.23), 1.08 (95% CI, 0.97-1.21), 1.04 (95% CI, 0.93-1.16) and 1.15 (95% CI, 1.03-1.28) in the fully adjusted model, and a dose-response relationship appeared among SUA quintiles (Figure 9). Women with hypertension also showed similar results (Figure 10).

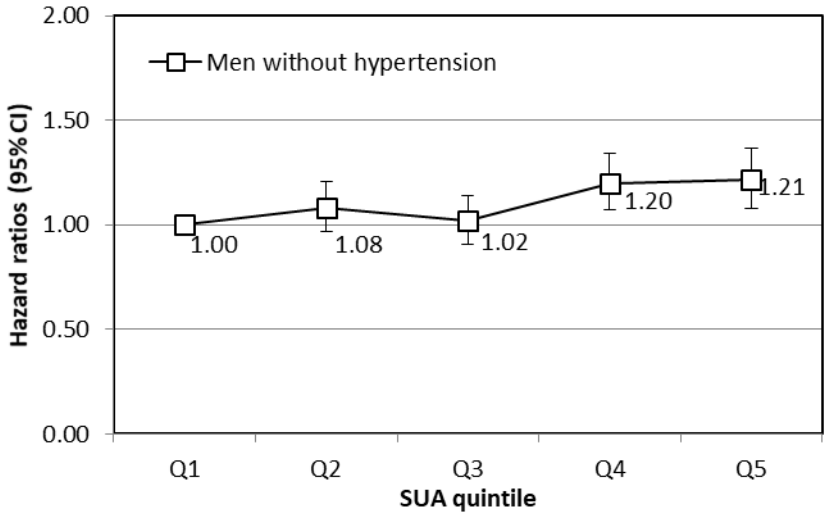


Figure 7. Hazard ratios of ischemic heart disease incidence in the study population without hypertension according to serum uric acid levels in men.

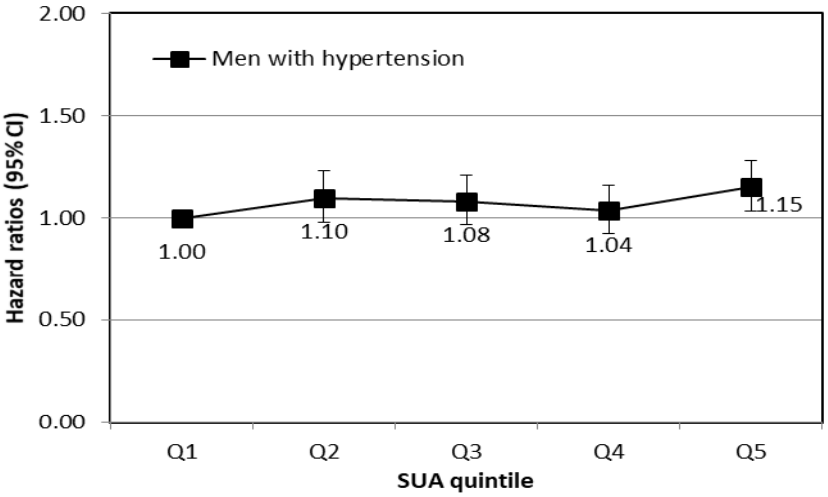


Figure 8. Hazard ratios of ischemic heart disease incidence in the study population with hypertension according to serum uric acid levels in men.

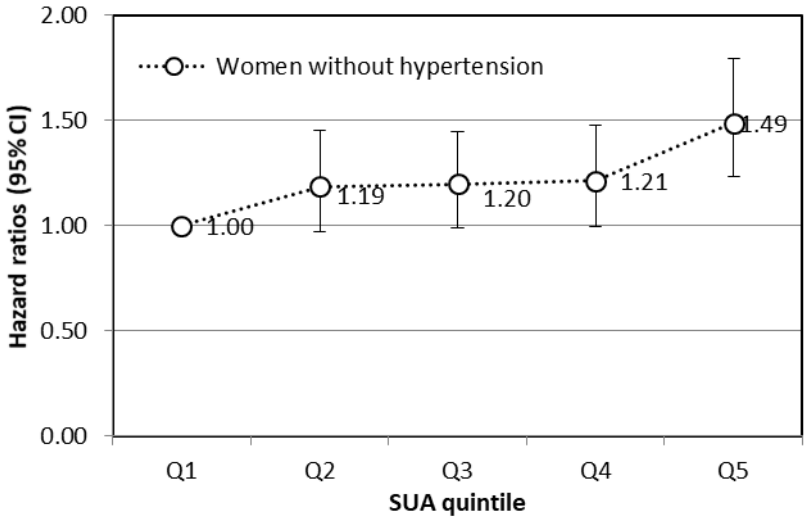


Figure 9. Hazard ratios of ischemic heart disease incidence in the study population without hypertension according to serum uric acid levels in women.

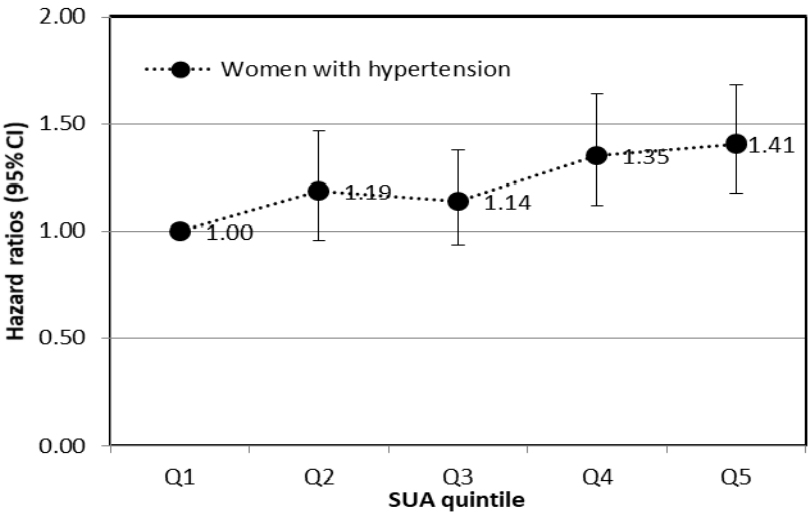


Figure 10. Hazard ratios of ischemic heart disease incidence in the study population with hypertension according to serum uric acid levels in women.

3. Dyslipidemia

In men with dyslipidemia, the HR of the highest versus the lowest quintile of SUA was 1.02 (95% CI, 0.88-1.19) for ischemic heart disease events (Figure 12). Additionally, in the absence of dyslipidemia, the HR of the highest versus the lowest quintile of SUA was 1.27 (95% CI, 1.16-1.39) for ischemic heart disease events, and a dose-response relationship appeared among SUA quintiles (Figure 11).

In women without dyslipidemia, compared with the first SUA quartile, the HRs for ischemic heart disease incidence in the second, third, fourth and fifth SUA quintiles were 1.21 (95% CI, 0.99-1.47), 1.19 (95% CI, 0.99-1.43), 1.30 (95% CI, 1.08-1.56), and 1.51 (95% CI, 1.26-1.80) in the fully adjusted model, and a dose-response relationship appeared among SUA quintiles (Figure 13). Women with dyslipidemia showed similar results (Figure 14).

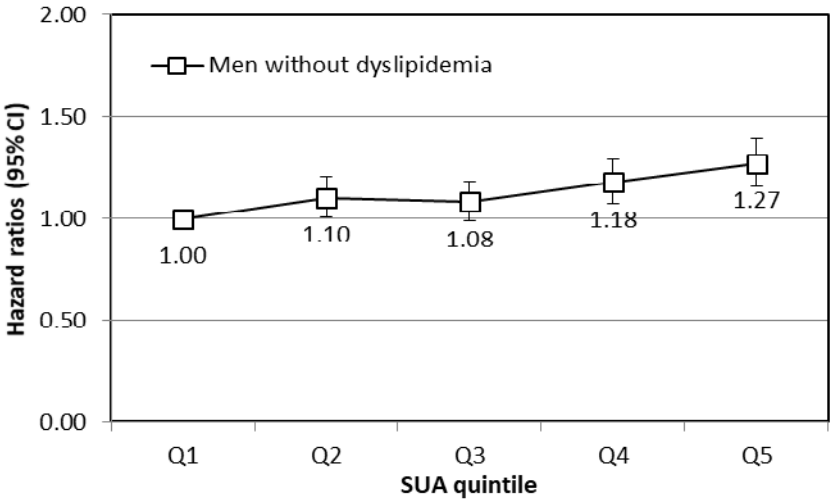


Figure 11. Hazard ratios of ischemic heart disease incidence in the study population without dyslipidemia according to serum uric acid levels in men.

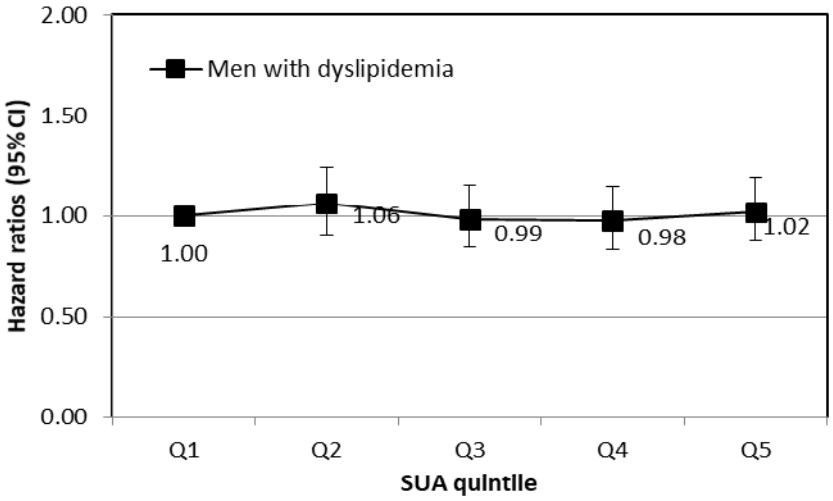


Figure 12. Hazard ratios of ischemic heart disease incidence in the study population with dyslipidemia according to serum uric acid levels in men.

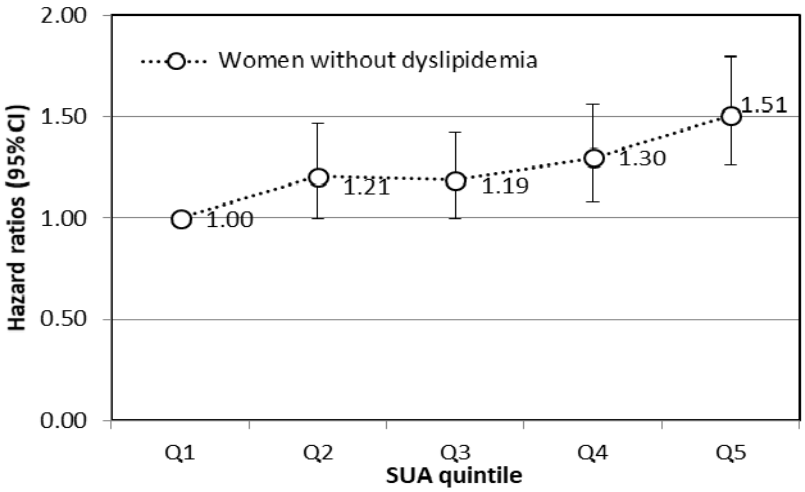


Figure 13. Hazard ratios of ischemic heart disease incidence in the study population without dyslipidemia according to serum uric acid levels in women.

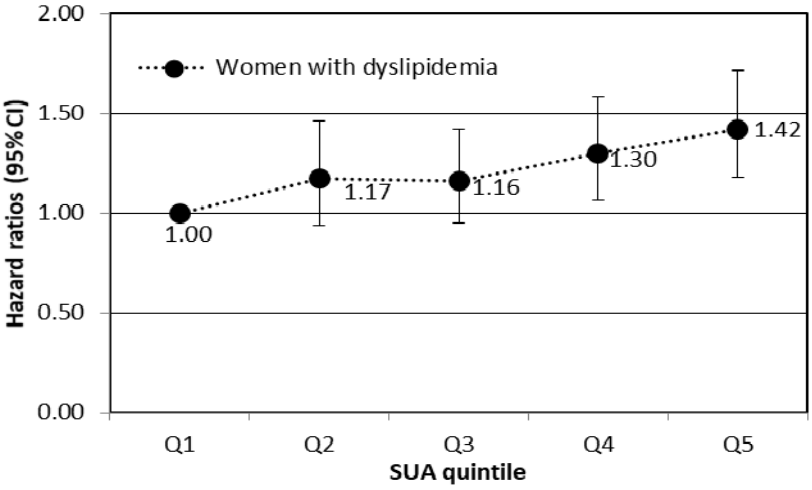


Figure 14. Hazard ratios of ischemic heart disease incidence in the study population with dyslipidemia according to serum uric acid levels in women.

4. Obesity

In men with obesity, the HR of the highest versus the lowest quintile of SUA was 1.05 (95% CI, 0.93-1.18) for ischemic heart disease events and was not statistically significant (Figure 16). Additionally, in the absence of obesity, the HR of the highest versus the lowest quintile of SUA was 1.19 (95% CI, 1.07-1.32). The group with the highest quintile of SUA had a significantly greater risk of ischemic heart disease incidence (Figure 15).

In women without obesity, compared with the first SUA quartile, the HRs for ischemic heart disease incidence in the second, third, fourth and fifth SUA quintiles were 1.28 (95% CI, 1.07-1.54), 1.21 (95% CI, 1.02-1.43), 1.32 (95% CI, 1.11-1.57), and 1.45 (95% CI, 1.22-1.71) in the fully adjusted model, and a dose-response relationship appeared among SUA quintiles (Figure 17). Women with dyslipidemia showed similar results (Figure 18).

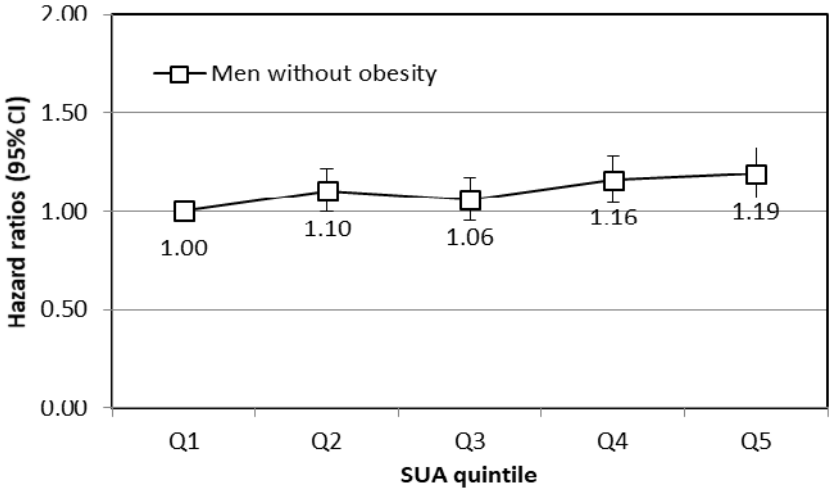


Figure 15. Hazard ratios of ischemic heart disease incidence in the study population without obesity according to serum uric acid levels in men.

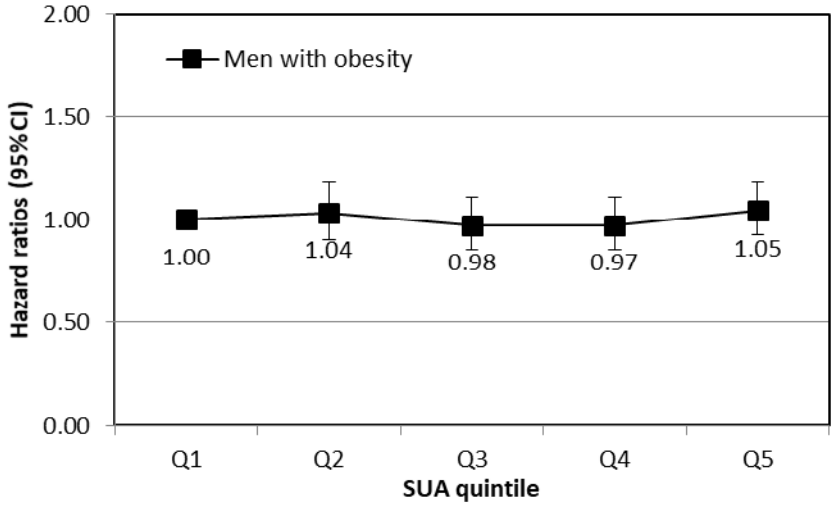


Figure 16. Hazard ratios of ischemic heart disease incidence in the study population with obesity according to serum uric acid levels in men.

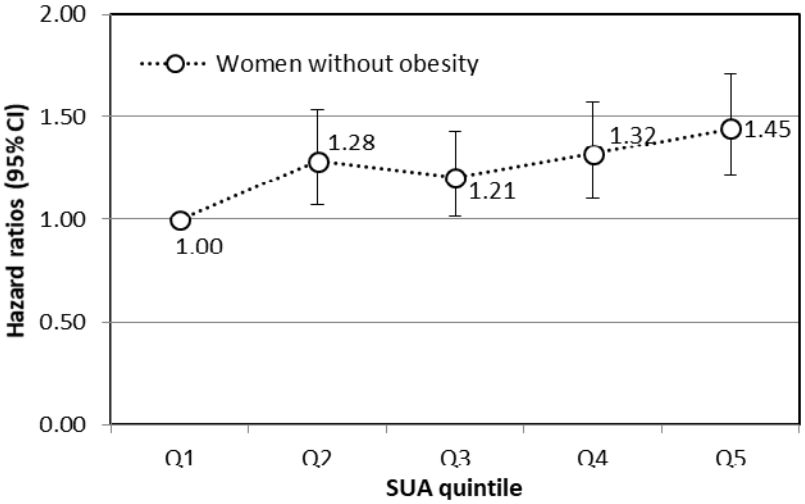


Figure 17. Hazard ratios of ischemic heart disease incidence in the study population without obesity according to serum uric acid levels in women.

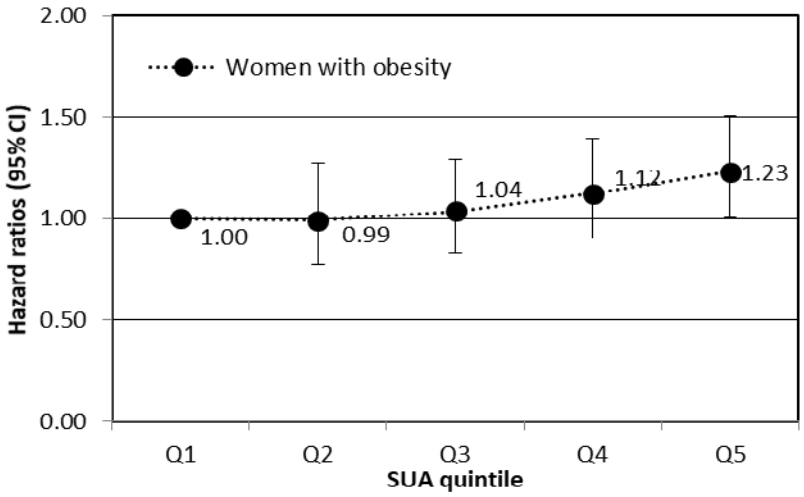


Figure 18. Hazard ratios of ischemic heart disease incidence in the study population with obesity according to serum uric acid levels in women.

5. Menopausal status in women

We determined the HRs for all forms of cardiovascular disease by menopausal status and SUA quintile. The adjusted HRs for incidence significantly increased as SUA levels increased in women. For the HRs for atherosclerotic cardiovascular disease and ischemic heart disease according to SUA quintiles, the menopause-specific patterns similarly showed slight dose-response curves in women regardless of menopausal status.

As shown in Figure 19, the non-menopausal group with highest quintile of SUA had a significantly greater risk of all forms of CVD than the menopause group with the highest quintile of SUA.

In particular, for total stroke and ischemic stroke, a difference in the curve was found among those with metabolic risk factors according to SUA quintile. The menopause group had flat curves, whereas the women who had not undergone menopause showed dose-response curves (Figure 23).

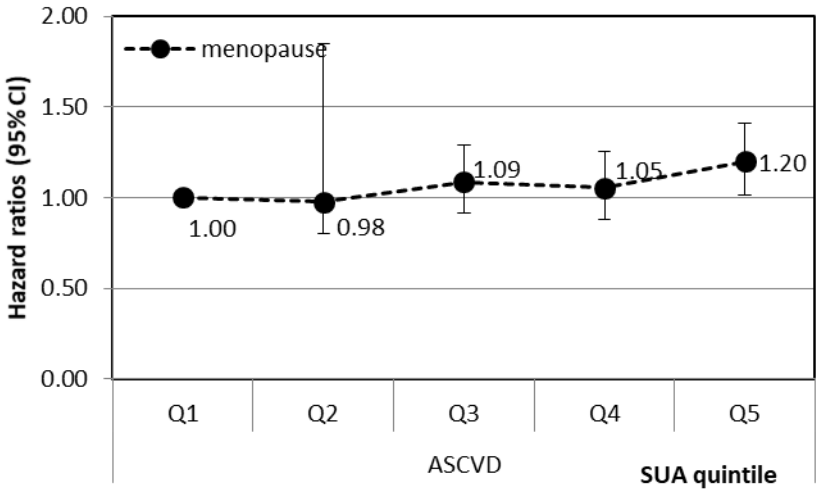


Figure 19. Hazard ratios of ASCVD incidence in subjects with menopause according to serum uric acid levels. ASCVD, atherosclerotic cardiovascular disease.

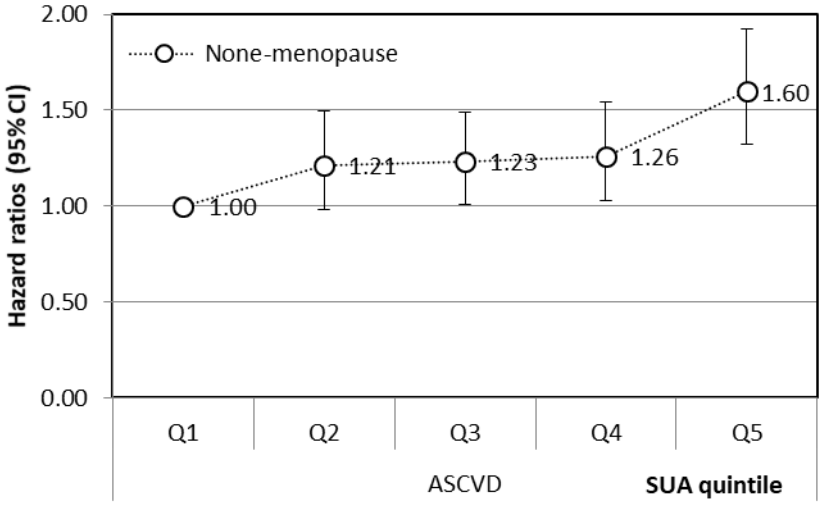


Figure 20. Hazard ratios of ASCVD incidence in the subjects without menopause according to serum uric acid levels. ASCVD, atherosclerotic cardiovascular disease.

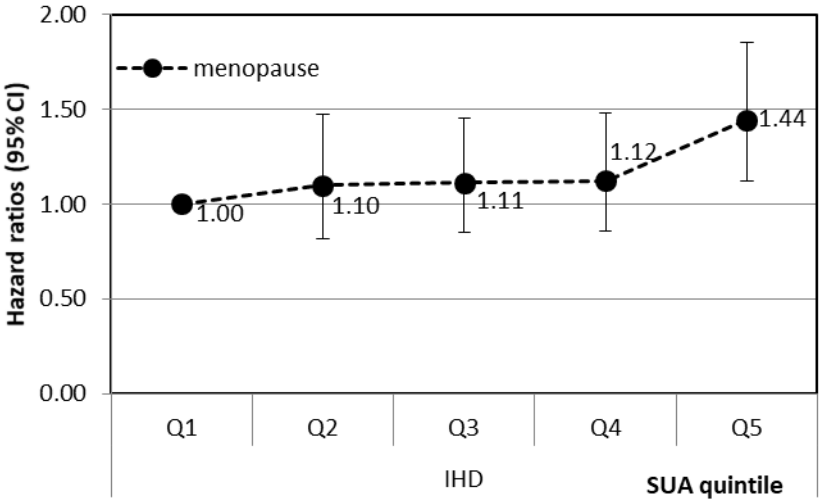


Figure 21. Hazard ratios of ischemic heart diseases incidence in subjects with menopause according to serum uric acid levels.

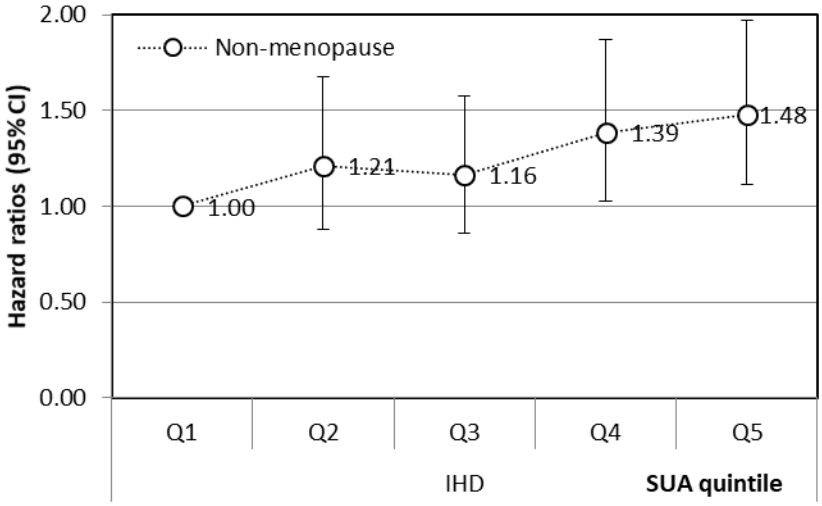


Figure 22. Hazard ratios of ischemic heart diseases incidence in subjects without menopause according to serum uric acid levels.

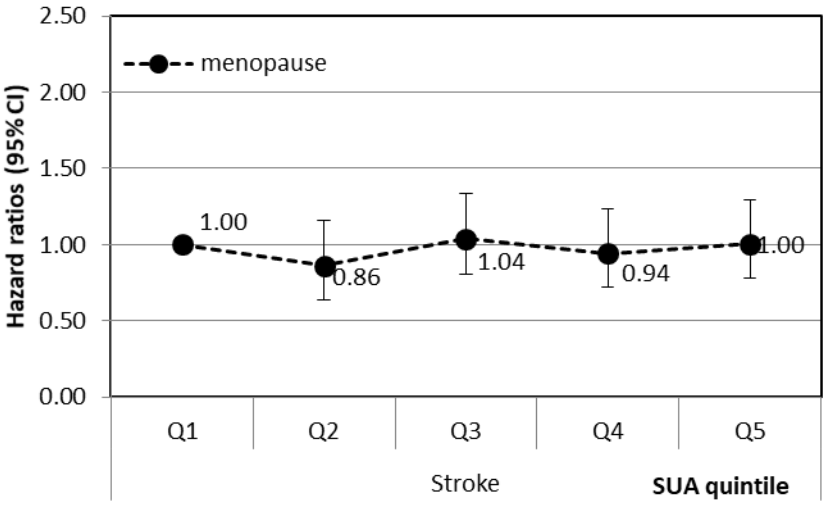


Figure 23. Hazard ratios of stroke incidence in subjects with menopause according to serum uric acid levels.

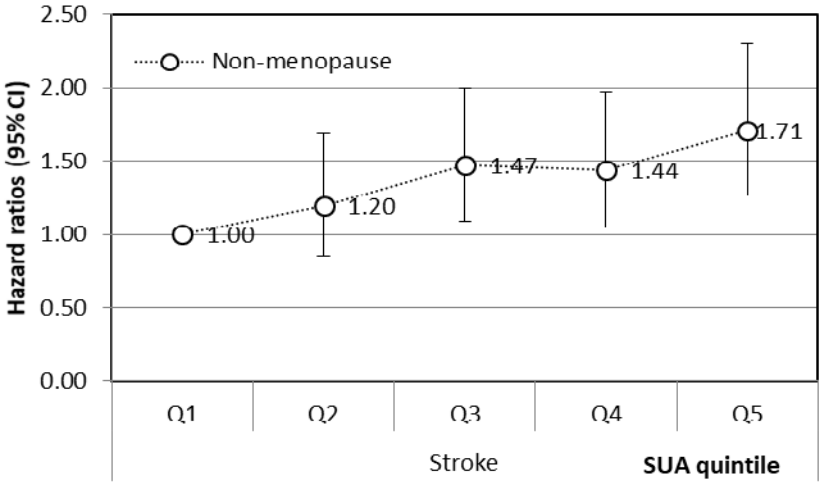


Figure 24. Hazard ratios of stroke incidence in subjects without menopause according to serum uric acid levels.

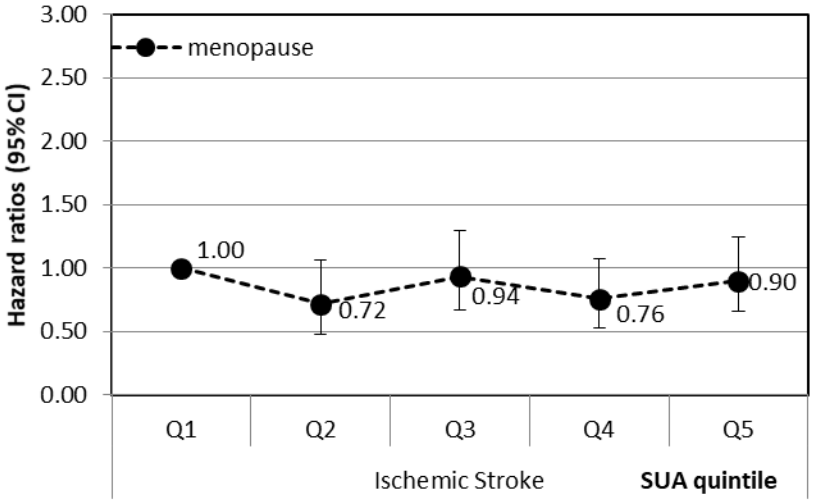


Figure 25. Hazard ratios of ischemic stroke incidence in subjects with menopause according to serum uric acid levels.

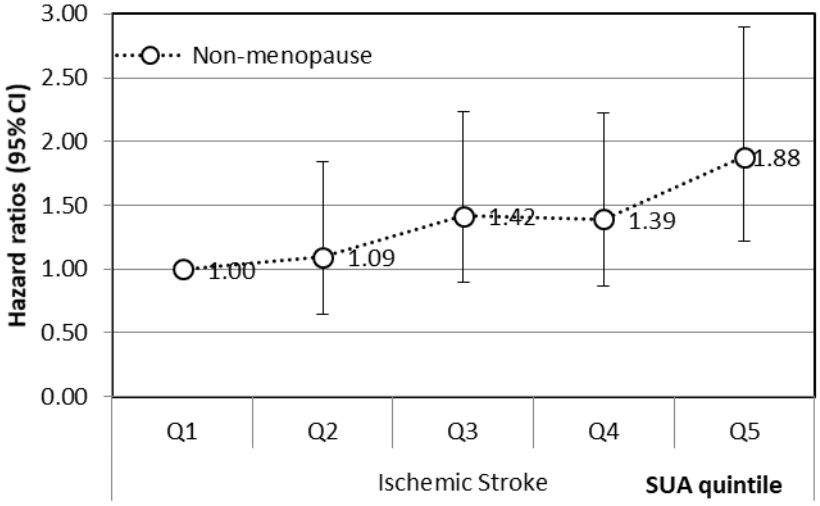


Figure 26. Hazard ratios of ischemic stroke incidence in subjects without menopause according to serum uric acid levels.

V. DISCUSSION

In the KHS, the highest quintile of SUA levels was associated with an increase in the risk of subsequently developing ischemic heart disease among 332,462 healthy adults without CVD at baseline. We also found that the risk for ischemic heart disease associated with SUA was significantly greater in adults without metabolic risk factors in the highest SUA quintile. In particular, there was a clear dose-response relationship between SUA and ischemic heart disease incidence in subjects without diabetes. Furthermore, in our subgroup analysis of menopausal and non-menopausal women, there was a positive association between SUA levels and CVD in the pre-menopausal group. However, in menopausal group, there was no relationship between SUA and CVD, especially stroke

In the KHS, we found SUA levels to be a predictor of total CVD events with or without hypertension and diabetes, as was recently reported in a cohort study from Taiwan (Chen et al., 2009).

Our data provided an angle to examine the connection between hyperuricemia and the components of metabolic syndrome. In addition to providing general findings for the healthy population, we demonstrated a significant risk associated with elevated SUA levels for ischemic heart disease in a subgroup with low metabolic risk factors. This result may further support the proposal that hyperuricemia poses a risk for the development of ischemic heart disease in the general population without metabolic risk factors.

1. Relationship between SUA and metabolic risk factors

Despite the association of hyperuricemia with cardiovascular risk factors, it remains controversial whether SUA is an independent predictor of cardiovascular disease.

Considerable evidence suggests that SUA levels are associated with many cardiovascular risk factors, including age, male sexual function, hypertension, hypertriglyceridemia, obesity, insulin resistance and, consequently, metabolic syndrome.

Several studies have suggested that hyperuricemia has a pathogenic role and predictive value in the development of hypertension. Therefore, a causal link to the development of hypertension is a plausible explanation for the possible increased cardiovascular risk in patients with hyperuricemia (Baker et al., 2005; Zuo et al., 2016). Hyperuricemia is frequently encountered in hypertensive patients. Having hyperuricemia and hypertension is associated with a 3- to 5-fold increase in CHD compared to patients with normal SUA levels (Alderman et al., 2004). The Losartan Intervention for Endpoint Reduction in Hypertension study was the first to demonstrate that reducing SUA levels was associated with a reduction of cardiovascular events in hypertensive patients (Dahlof et al., 2002).

Numerous studies have shown that hyperlipidemia is traditional cardiovascular risk factor and increases the risk of cardiovascular events (Verdecchia et al 2000, Puddu et al 2001). Increased SUA levels may encourage lipid peroxidation and promote the oxidation of LDL cholesterol, which may play a role in the development of atherosclerosis and

would also explain its association with CHD (Gomez et al., 2014; Zuo et al., 2016). Because human atherosclerosis plaques contain more uric acid than normal artery walls, researchers have proposed that SUA may play a direct role in the atherosclerosis process (Zuo et al., 2016). Increased SUA concentrations may be associated with the increasing prevalence of insulin resistance, abdominal obesity, hyperlipidemia, and hypertension.

2. Relationship between SUA and CVD events

Numerous studies have shown that hyperuricemia predicts an increased risk of cardiovascular events and death from cardiovascular causes and from all other causes (Verdecchia et al. 2000; Puddu et al 2001; Hoieggen et al., 2004; Niskanen et al., 2004; Hakoda et al. 2005; Ioachimescu et al., 2008; Strasak et al., 2008; Chen et al., 2009), while others have not found such an independent association (Sakata et al., 2001; Jee et al., 2004; Strasak et al., 2008).

Higher SUA concentrations have been proposed to be independently associated with an increased risk of developing ischemic heart disease, and a number of prospective studies have examined this association (Zoppini et al., 2009; Ioachimescu et al., 2008; Strasak et al., 2008; Chen et al., 2009, Mazza et al 2007, Meisinger 2008; Navaneethan 2009. Okura et al 2009; Ong et al., 2010). Of these, only 1 study has documented a direct association with incident CVD in the general population (Puddu et al., 2001), and 2 studies have investigated the association of SUA with cardiovascular events in patients (Navaneethan et al., 2009; Okura et al 2009).

Although positive associations have been previously reported between SUA levels and CVD risk, some of these associations failed to show statistical significance after adjusting for additional confounders. In addition, the Fremantle Diabetes study showed that baseline SUA levels were not independently associated with either CVD mortality or all- cause death after adjustment for other risk factors in a community-based cohort of

patients with type 2 diabetes who were followed for a mean of >10 years (Ong et al., 2010).

Most of these reports did not fully adjust for other biochemical variables such as renal function, glucose, use of medication and measures of lipid profiles. Controlling for these factors is important since higher uric acid levels may be a comorbidity of alterations in these other metabolic variables.

Famous studies such as the Atherosclerosis Risk in Communities study (Moriarity et al., 2000; Hozawa et al., 2006) and the Framingham Study (Ioachimescu et al., 2008; Culleton et al., 1999) were not consistent with SUA being an independent risk factor for CHD. Other studies have not shown elevated SUA levels to be an independent predictor of CHD mortality. The NHANES I Epidemiologic Follow-up Study (Fang et al., 2000), reported that the association of serum uric acid levels after controlling for potential risk factors with cardiovascular mortality persisted. Even among subjects with low cardiovascular risk (ie, those without an increased cholesterol level, hypertension, or diabetes), they found that increased serum uric acid levels were a predictor of cardiovascular mortality. This association is unlikely to be confounded by other factors in these low-risk subjects (Fang et al., 2000).

Hyperuricemia in this study did not significantly contribute to coronary disease-related mortality. However, hyperuricemia was found to affect ischemic stroke in the Rotterdam study (Bos et al., 2006). The discrepancy between the findings of the Rotterdam study and the present study may be due to the relatively low risk of CHD and

hemorrhagic stroke in Koreans (Song et al., 2001; Song et al., 2004). .Additionally, a lack of statistical significance can be attributable to small sample size and insufficient power. Adjusting for all variables and analyzing the incidence of all cardiovascular events in participants with hyperuricemia stratified by sex, our study showed a significant positive relationship with CVD and ischemic heart disease. In our study with a large sample size, the association between high SUA levels and CVD, particularly ischemic heart disease, was statistically significant after multivariate adjustment, and women with hyperuricemia had a 2.09-fold increase in the risk of hard CHD (95% CI, 1.27-3.42; data not shown).

3. Gender differences in SUA and CVD events

In the KHS, we found that there were gender differences in the association between SUA levels and stroke. In particular, a unique finding from the current study is that the relationships between SUA and the incidence of various types of CVD, particularly stroke, were different in women according to menopausal status. Furthermore, in our subgroup analysis results comparing menopausal and non-menopausal women, we found evidence of a dose-response association between SUA level and CVD events in pre-menopausal group. However, we found no significant association between the risk of CVD events and the SUA level among the menopausal group.

Previous studies showed that the SUA level associated with the development of hypertension or cardiovascular mortality was significantly higher in women than in men (Zhang et al., 2009; Freedman et al., 1995; Zhang et al., 2016). The relationship of uric acid with cardiovascular events is particularly strong, in patients at high risk for heart disease and in women (Baker et al., 2005).

Recent meta-analyses have demonstrated that hyperuricemia increased the risk of CHD events, particularly cardiovascular mortality in women, and that the risk of mortality was greater in women than in men (Kim et al., 2010; Braga et al., 2016; Zuo et al., 2016; Li et al., 2016). However, another meta-analysis showed that elevated SUA levels appeared to significantly increase the risk of all-cause mortality in men, not in women (Zhao et al., 2013).

In general, women usually have lower SUA levels than men. The association between SUA and CVD events in the general population is reported to be stronger in women than in men. This reason for this is that men are subject to other risk factors that more significantly influence mortality from CVD (Kawabe et al., 2016). However, the mechanisms that cause SUA to be less strongly related to CVD events in men than women remain uncertain.

Previous studies have showed a strong association between SUA level and cardiovascular mortality after adjustment for menopausal status in healthy women (Fang et al., 2000; Strasak et al., 2008). Interestingly, in our study, although increasing SUA level after menopause might have influenced the outcome, elevated SUA appeared to have significantly increased the risk of all CVD events in premenopausal women, but not in postmenopausal women. The changing level of serum uric acid concentration in women at menopause suggests an interaction with sex hormones (Fang et al., 2000; Levine et al., 1989). Hyperuricemia in women could possibly be a hallmark of escape from estrogen protection and this phenomenon may possibly be related to estrogen levels (Zhang et al., 2016).

According to a study using National Health and Nutrition Examination Survey-I data (Fang et al., 2000), elevated SUA levels in women were associated with higher cardiovascular risk than in men. This finding of a difference in the relationship between SUA level and CVD between men and women is similar to the findings of our study. The cardioprotective role of estrogen helps to explain why women, have an overall lower risk,

of ischemic heart disease. However, in menopausal women, men, and those with metabolic risk factors, a dose-response relationship was not found in stroke incidence according to SUA levels. The presence of low SUA levels in women may be explained because the secretion of uric acid is maintained in the kidney, while resorption in the renal tubule degrades due to female hormones and female sex hormones in postmenopausal women (Sumino et al., 1999).

Differences in age, sex, and other baseline characteristics of the study, as well as differences in the design of the analyses may explain these disparate conclusions. Another factor may be that in previous analyses of CVD, there was no systematic comparison of the effects of SUA levels across a mild range of CVD events between the sexes. Changes in the SUA level according to menopausal status suggest that there is an interaction with sex hormones, but, this remains a matter for further research.

4. Mechanism of uric acid-induced CVD events

High levels of uric acid, produced during the breakdown of purine, a substance found in many foods, have traditionally been implicated in the development of gout, kidney stones, and kidney failure. Given its correlations with hypertension, inflammation, endothelial dysfunction, insulin resistance, dyslipidemia, and obesity, a role for uric acid as a risk factor for CVD has recently been suggested, but the evidence is discordant (Zoppini, 2009).

In recent decades, hyperuricemia has been strongly associated with peripheral, carotid, and coronary vascular disease, with the development of stroke, with preeclampsia, and with vascular dementia (Feig et al., 2008). Therefore, epidemiological studies have reported that multiple lines of evidence link SUA levels to metabolic risk factors. Although the role that elevated SUA plays in vascular disease and renal disease development and mortality remains unclear, the evidence suggests the following possible mechanisms.

Hyperuricemia may induce endothelial dysfunction, which is predicted to promote the early development of atherosclerosis and precede plaque formation (Higgins et al., 2012). The deposition of urate crystals on the vessel walls could cause an inflammatory reaction, then directly injure the vascular intima and ultimately activate the platelet and blood coagulation system. Additionally, high SUA levels also promote thrombosis and

activate monocyte chemotactic protein-1, an important chemokine involved in atherosclerosis (Baker et al., 2005, Zuo et al., 2016).

Previous studies have shown that uric acid is an antioxidant that may prevent stress-induced cell transformations and oxidant-induced cardiac and renal toxicity (Johnson et al., 2003). Increased serum concentrations of uric acid in the blood vessels may decrease the activity of nitric oxide and antioxidant substances in the blood vessels by degrading the function of vascular smooth muscle and endothelial cells. Thus, platelet aggregation and adhesion have been found to contribute to the development of cardiovascular disease (Johnson et al., 2003; Alderman et al., 2004).

Several potential pathophysiological mechanisms have been summarized, including the enhancement of lipid peroxidation and platelet adhesiveness, stimulation of vascular smooth cell proliferation, vascular inflammation, damage to endothelial cells, the aggregation of erythrocytes, and the acceleration of atherosclerosis (Carmelinda et al., 2006; Kanellis et al. 2005; Li et al., 2016; Waring et al., 2003; Montalcini et al., 2007; Sloop et al., 2016, Zhong et al., 2017).

5. Causal inference in Mendelian randomization study

Mendelian randomization (MR) is a study design in which genetic variants are employed as instrumental variables for estimating the unconfounded effect of an exposure on CVD (Timpson et al., 2012).

Although common genetic variants typically have only small effects on complex diseases, the combined use of multiple variants as instruments increases the statistical power to detect associations between exposures and outcomes (Palmer et al., 2013; Burgess et al., 2014; Burgress et al., 2015). Because MR studies make use of the random assortment of alleles at meiosis, their estimates are much less vulnerable to confounding than observational epidemiologic studies.

Furthermore, because allele assignment at meiosis precedes the onset of CHD, MR studies are not prone to reverse causation. Finally, MR studies describe the effect of lifetime exposure to an allele, whereas randomized controlled trials assess the effect of an intervention, generally for less than a decade. For these reasons, when suitable genetic variants are available, MR studies can provide evidence in support of a causal association between exposures and outcomes (Ahmad et al., 2015).

The current study raised doubts about the etiological relevance of SUA in cardiovascular and metabolic diseases as suggested by prior epidemiological and model systems studies, which may have observed associations between increased uric acid

levels and higher risks of metabolic diseases due to residual confounding or reverse causality.

Although elevated SUA levels have been associated with an increased risk of metabolic diseases, a causal link has not been established. The results of a large MR study suggest that lowering SUA levels may not translate into reductions in the risk of coronary heart disease or ischemic stroke (Keenan et al., 2016).

In the last few years, several MR studies have provided no evidence for a causal role for SUA affecting metabolic risk factors or the incidence of ischemic heart disease (Table 5). However, a recent study documented results from multivariate and Egger MR analyses, which account for pleiotropy, and both analyses provided weak evidence for a causal association between urate and coronary heart disease. Therefore, these data suggest that the observed association between plasma urate and coronary heart disease is probably affected by confounding by risk factors such as blood pressure, LDL cholesterol, HDL cholesterol, and triglycerides (White et al., 2016).

Table 5. Overview of previously performed Mendelian randomization studies of uric acid, metabolic risk factor and cardiovascular disease.

№	Author, Year	Study	Participants	Uric acid-associated loci	Main outcome(s)	Causal estimate	Conclusions
Metabolic risk factors							
1	Yang, 2010	CHARGE Cohorts Yang, 2010	N=28,283, European	Genetic score: SLC22A11, GCKR, INHBC, RREB1, PDZK1, SLC2A9, ABCG2, SLC17A1	Fasting glucose	β -0.06 (95%CI: -0.13,0.02)mmol/L Per 100 µmol/L urate	Uric acid has no causal effect on fasting glucose.
2	Pfister, 2011	Cambridg-eshire, ADDITIO N-Ely and Norfolk Diabetes	N=16,064, with 7,504 type 2 diabetes (T2DM) cases	Genetic score: PDZK1, LRRC16A, SLC22A12, SLC16A9, SLC22A11, SLC17A1, ABCG2, SLC2A9	T2DM	Odds ratio 0.99 (95% CI: 0.94-1.04) Per genetic score tertile.	Uric acid has no causal effect on type 2 diabetes.
3	Parsa, 2012	Hereditary and Phenotype Interven-tion Heart Study	N=516, European	SLC2A9	Systolic blood pressure Diastolic blood pressure	Systolic blood pressure: β 2.2 (SE: 0.79) mmHg Diastolic blood pressure: β 0.42 (0.5) mmHg per 1 mg/dL change in uric acid.	Uric acid causally decreases systolic blood pressure, but not diastolic blood pressure

No	Author, Year	Study	Participants	Uric acid-associated loci	Main outcome(s)	Causal estimate	Conclusions
4	Oikonen, 2012	Cardiovascular Risk in Young Finns study	N=1,985, European	SLC2A9	Body mass index (BMI) Carotid intima media thickness	Carotid intima media thickness: β <0.0001 mm, P-value 0.99 among men. BMI: β 0.04 kg/m^2, P-value 0.82 among men and β 0.07 kg/m^2, P-value 0.57 among women per standard deviation (SD) increase in uric acid.	Uric acid has no causal effect on BMI or atherosclerosis
5	Lyngdoh, 2012	CoLaus study	N= 6,184, European	SLC2A9	Weight Fat mass BMI Waist circumference	Weight: β 0.01 (95% CI, -0.12 to 0.14) kg Fat mass: β 0.05 (95%CI, -0.10 to 0.19) kg Body mass index: β 0.01 (95% CI, -0.16 to 0.14)kg/m^2 Waist circumference β 0.08 (95%CI, -0.05 to 0.21)cm per SD increase in uric acid.	Uric acid is not causally related to measures of adiposity

No	Author, Year	Study	Participants	Uric acid-associated loci	Main outcome(s)	Causal estimate	Conclusions
6	Mallam-aci, 2014	Mallamaci,	N= 459, European	SLC2A9	Systolic blood pressure Diastolic blood pressure	Higher mean clinic systolic blood pressure among TT individuals. No difference in mean diastolic blood pressure.	Uric acid causally increases clinic systolic blood pressure, but not diastolic blood pressure.
7	Rasheed, 2014	Atheroscleros is Risk in Communities and Framingham Heart	N= 8,208, European	Genetic score of SLC2A9, ABCG2, SLC17A1, SLC22A11, SLC22A12	Triglycerides	β -1.01 (standard error: 0.80) mmol/L per unit change in uric acid.	Uric acid has no causal effect on triglycerides.
8	Sedaghat 2014	Rotterdam study	N= 5,791, European	Genetic score of 30 variants in loci listed in Köttgen et al	Systolic blood pressure Diastolic blood pressure	Systolic blood pressure: β -0.75 (95% CI, -1.31 to -0.19)mmHg Diastolic blood pressure: β -0.92 (95% CI, -1.62 to -0.23)mmHg per SD increase in genetic score.	Uric acid causally decreases systolic blood pressure and diastolic blood pressure.

No	Author, Year	Study	Participants	Uric acid-associated loci	Main outcome(s)	Causal estimate	Conclusions
Metabolic syndrome and Cardiovascular disease							
9	McKeigue 2010	ORCADES study	N=706, European	SLC2A9	Metabolic syndrome	Causal effect parameter βx : -1.25 (95% CI, -2.91 to 0.05)	Uric acid has no causal effect on metabolic syndrome.
10	Dai, 2013	Dongfeng-Tongji Cohort study	N= 23,345, Asian	Genetic score of SLC2A9, ABCG2	Metabolic syndrome	Odds Ratio 1.03 (95% CI, 0.98 to 1.09) Per uric acid increasing allele in the risk score	Uric acid is not causally related to metabolic syndrome.
11	Palmer, 2013	Copenhagen General Population Study and Copenhagen City Heart Study	N=68,674, with 7,172 ischemic heart disease events, European	SLC2A9 (rs7442295) FTO(rs9939609), MC4R (rs17782313), TMEM18 (rs6548238) for body mass index	Ischemic heart disease Systolic blood pressure Diastolic blood pressure	Ischemic heart disease: hazard ratio: 0.93 (95% CI: 0.79-1.09) Systolic blood pressure: β 0.65 mm Hg (95% CI: −0.54 to 1.85) Diastolic blood pressure: β 0.63 mmHg (95% CI: −0.04 to 1.29) per SD increase in uric acid.	Uric acid has no causal effect on ischemic heart disease, systolic blood pressure and diastolic blood pressure. However, evidence supports a causal effect between body mass index and uric acid level and hyperuricemia.

No	Author, Year	Study	Participants	Uric acid-associated loci	Main outcome(s)	Causal estimate	Conclusions
12	Testa et al. 2015	MAURO Study GHS (Gargano Heart Study) TVAS (Tor Vergata Atherosclerosis Study)	N= 1,227 high risk patients MAURO: 755 Chronic kidney disease; GHS: 353 type 2 diabetes and coronary heart disease; TVAS: 119 myocardial infarctions Italian	GLUT9 (rs734553) urate transporter gene	Cardiovascular death, and non-fatal myocardial infarction and stroke	The meta-analytical estimate (total number of patients, n=1,227; total cardiovascular events, n=222) of the hazard ratio (HR) for the combined end-point in TT/GT patient was twice higher (pooled HR: 2.04; 95% CI, 1.11-3.75; P= 0.02) than in GG homozygotes.	The T allele of the rs734553 polymorphism in the GLUT9 gene predicts a doubling in the risk for incident cardiovascular events in patients at high cardiovascular risk. The findings in this study are compatible with the hypothesis of a causal role of hyperuricemia in cardiovascular disease in high risk conditions.

No	Author, Year	Study	Participants	Uric acid-associated loci	Main outcome(s)	Causal estimate	Conclusions
13	Kleber et al., 2015,	Ludwigsha-fen Risk and Cardiovascu-lar Health Study	N= 3,316 South-western Germany	**GRS Non-pleiotropic SNPs** SLC2A9, NRXN2, UBE2Q2, A1CF, MAF, SFMBT1, HLF, BAZ1B, STC1, NF4G, ATXN2, 3GNT4, GF1R, NFAT5 **Pleiotropic SNPs** ABCG2, GCKR, TMEM171, SLC16A9, INHBB, RREB1, SLC17A1, PDZK1, INHBC, SLC22A11, ACVR1BL1, VEGFA, TRIM46, PRKAG2	Cardiovascul-ar death sudden cardiac death	In a multivariate model adjusted for factors including medication, causal HRs corresponding to each 1mg/dL increase in genetically predicted uric acid concentration were significant for cardiovascular death (HR, 1.77; 95% CI, 1.12 to 2.81) and sudden cardiac death (HR, 2.41; 95% CI, 1.16 to 5.00)	High uric acid is causally related to adverse cardiovascular outcomes, especially sudden cardiac death.

No	Author, Year	Study	Participants	Uric acid-associated loci	Main outcome(s)	Causal estimate	Conclusions
14	Keenan et al. 2016	PROMIS (Pakistan Risk of Myocardial Infarction Study)	N= 71,501, T2DM (26,488/ 83,964), Coronary heart disease (CHD) (54,501/ 68,275), Ischemic stroke (14,779/ 67,312) Heart Failure (HF) (4,526/ 18,400)	STC1, ACVR1B-L1, PRKAG2, TMEM171, HLF, HNF4G, SFMBT1 NRXN2, TRIM46, A1CF, PDZK1, RREB1, SLC22A11, SLC2A9	T2DM, CHD, ischemic stroke, or HF	A 1 SD increase in serum urate levels due to the genetic score was associated with increased risk of gout (odds ratio: 5.84; 95% CI: 4.56 to 7.49)	Evidence from this study does not support a causal role of circulating serum urate levels in T2DM, CHD, ischemic stroke, or HF. Decreasing serum urate levels may not translate into risk reductions for metabolic conditions.

No	Author, Year	Study	Participants	Uric acid-associated loci	Main outcome(s)	Causal estimate	Conclusions
15	White et al, 2016	MAGIC (Meta-Analyses of Glucose and Insulin-related traits Consortium), GIANT (Genetic Investigation of ANthropometric Traits), DIAGRAM (DIAbetes Genetics Replication And Metaanalysis) GLGC (Global Lipids Genetic Consortium), ICBP (International Consortium for Blood Pressure)	Meta-analysis of 17 prospective observational studies (166,486 individuals; 9,784 coronary heart disease events) Egger mendelian randomisati-on analysis (58 studies; 198,598 individuals; 65,877 events)	**31 urate-associated SNPs** PDZK1, GCKR, SLC2A9, ABCG2, RREB1, SLC17A1/SLC17A3 SLC16A9, SLC22A11, NRXN2/SLC22A12, INHBC/INHBE, TRIM46/PKLR, INHBB, SFMBT1/MUSTN1, TMEM171, VEGFA, BAZ1B/MLXIPL, PRKAG2, HNF4G, A1CF/ASAH2, OVOL1/LTBP3, ATXN2/PTPN11, UBE2Q2/NRG4, IGF1R, NFAT5, MAF, HLF, LRRC16A/LRRC16A, ORC4L/ACVR2A, STC1, BCAS3/C17orf82, QRICH2/PRPSAP1	Coronary heart disease	The corresponding odds ratio estimates from the conventional, multivariable adjusted, and Egger Mendelian randomisation analysis were 1·18 (95% CI, 1·08–1·29), 1·10 (1·00–1·22), and 1·05 (0·92–1·20), respectively, per 1 SD increment in plasma urate.	Genetic evidence based on conventional and novel Mendelian randomization approaches suggest a modest, if any, causal effect of plasma urate concentration in the development of coronary heart disease

6. Study limitations and strengths

This study has some limitations. As in most studies, we did not consider changes in SUA levels, which were determined from a single measurement. In addition, this study was carried out in health promotion centers, which may not be representative of the general population. At the time of data collection, some degree of recall bias may have been present regarding subjects' history of hypertension, diabetes, and frequency of cigarette and alcohol consumption. The effect of these factors as confounders on the independent predictive power of SUA levels on CVD events was considered minimal, in accordance with previous population-based studies.

The strength of this study is that it included a large sample size, a relatively long duration of follow-up and mostly accurate outcomes of cardiovascular events from death certificate data and hospitalization records. In addition, it has also been shown that hyperuricemia is associated with the development of all CVD forms, including ischemic and hemorrhagic stroke, although its effects on the severity of heart disease have not been previously reported to the best of our knowledge. Few studies have reported on the association between SUA and stroke in the general population and none of these studies divided stroke into ischemic and hemorrhagic.

VI. CONCLUSIONS

In conclusion, SUA was found to be an independent risk marker for atherosclerotic CVD in the general population without metabolic risk factors. SUA may be an important and clinically useful marker that can be used to predict ischemic heart disease, particularly in healthy men and women without major risk factors. Asymptomatic hyperuricemia was associated with the incidence of atherosclerotic CVD in the KHS.

Our study also demonstrated a dose-response effect of increased SUA levels on ischemic heart disease, particularly in women without metabolic risk factors. Most importantly, SUA levels were an independent predictor of ischemic heart disease in both men and women without diabetes. Further research is needed to broadly evaluate the causal effects of multiple biomarkers on cardiovascular disease and metabolic risk traits using data from large-scale cohorts or genome-wide association studies including many different genetic variants.

REFERENCES

Ahmad OS, Morris JA, Mujammami M, Forgetta V, Leong A, Li R, Turgeon M, Greenwood CM, Thanassoulis G, Meigs JB, Sladek R. A Mendelian randomization study of the effect of type-2 diabetes on coronary heart disease. Nature communications. 2015 May 28;6.

Alderman M, Aiyer KJ. Uric acid: role in cardiovascular disease and effects of losartan. Curr Med Res Opin. 2004;20(3):369-79.

Baker JF, Krishnan E, Chen L, Schumacher HR. Serum uric acid and cardiovascular disease: recent developments, and where do they leave us? Am J Med. 2005;118(8):816-26.

Braga F, Pasqualetti S, Ferraro S, Panteghini M. Hyperuricemia as risk factor for coronary heart disease incidence and mortality in the general population: a systematic review and meta-analysis. Clinical Chemistry and Laboratory Medicine (CCLM). 2016 Jan 1;54(1):7-15.

Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. Genetic epidemiology. 2013 Nov 1;37(7):658-65.

Burgess S, Daniel RM, Butterworth AS, Thompson SG. Network Mendelian randomization: using genetic variants as instrumental variables to investigate mediation in causal pathways. International journal of

epidemiology. 2014 Aug 22;44(2):484-95.

Burgess S, Thompson SG. Use of allele scores as instrumental variables for Mendelian randomization. International journal of epidemiology. 2013 Aug 1;42(4):1134-44.

Burgess S, Scott RA, Timpson NJ, Smith GD, Thompson SG, EPIC-InterAct Consortium. Using published data in Mendelian randomization: a blueprint for efficient identification of causal risk factors. European journal of epidemiology. 2015 Jul 1;30(7):543-52.

Bos MJ, Koudstaal PJ, Hofman A, Witteman JC, Breteler MM. Uric acid is a risk factor for myocardial infarction and stroke: the Rotterdam study. Stroke. 2006;37(6):1503-7.

Braga, F., Pasqualetti, S., Ferraro, S., & Panteghini, M. Hyperuricemia as risk factor for coronary heart disease incidence and mortality in the general population: a systematic review and meta-analysis. Clinical Chemistry and Laboratory Medicine (CCLM), 2016;54(1), 7-15.

Chen JH, Chuang SY, Chen HJ, Yeh WT, Pan WH. Serum uric acid level as an independent risk factor for all-cause, cardiovascular, and ischemic stroke mortality: a Chinese cohort study. Arthritis Rheum. 2009;61(2):225-32.

Chuang SY, Chen JH, Yeh WT, Wu CC, Pan WH. Hyperuricemia and increased risk of ischemic heart disease in a large Chinese cohort. International journal of cardiology. 2012 Feb 9;154(3):316-21.

Culleton BF, Larson MG, Kannel WB, Levy D. Serum uric acid and risk for

cardiovascular disease and death: the Framingham Heart Study. Ann Intern Med. 1999;131(1):7-13.

Dahlof B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, Fyhrquist F, Ibsen H, Kristiansson K, Lederballe-Pedersen O, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet. 2002;359(9311):995–1003.

Dai,X, Yuan,J, Yao,P, Yang,B, Gui,L, Zhang,X, Guo,H, Wang,Y, Chen,W, Wei,S, Miao,X, Li,X, Min,X, Yang,H, Fang,W, Liang,Y, Hu,FB, Wu,T, He,M: Association between serum uric acid and the metabolic syndrome among a middle- and old-age Chinese population. Eur J Epidemiol 28:669-676, 2013

Fang J, Alderman MH. Serum uric acid and cardiovascular mortality the NHANES I epidemiologic follow-up study, 1971-1992. National Health and Nutrition Examination Survey. JAMA. 2000;283(18):2404-10.

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

Freedman DS, Williamson DF, Gunter EW, Byers T. Relation of serum uric acid to mortality and ischemic heart disease: the NHANES I Epidemiologic Follow-up Study. American journal of epidemiology. 1995 Apr 1;141(7):637-44.

Gomez M, Vila J, Elosua R, Molina L, Bruguera J, Sala J, Masia R, Covas MI,

Marrugat J, Fito M. Relationship of lipid oxidation with subclinical atherosclerosis and 10-year coronary events in general population. Atherosclerosis. 2014;232(1):134–40.

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

Hakoda M, Masunari N, Yamada M, Fujiwara S, Suzuki G, Kodama K, et al. Serum uric acid concentration as a risk factor for cardiovascular mortality: a longterm cohort study of atomic bomb survivors. J Rheumatol. 2005;32(5):906-12.

Higgins P, Dawson J, Lees KR, McArthur K, Quinn TJ, Walters MR. Xanthine oxidase inhibition for the treatment of cardiovascular disease: a systematic review and meta-analysis. Cardiovasc Ther. 2012;30(4):217–26.

Hoieggen A, Alderman MH, Kjeldsen SE, Julius S, Devereux RB, De Faire U, et al. The impact of serum uric acid on cardiovascular outcomes in the LIFE study. Kidney Int. 2004;65(3):1041-9.

Holme I, Aastveit AH, Hammar N, Jungner I, Walldius G. Uric acid and risk of myocardial infarction, stroke and congestive heart failure in 417 734 men and women in the Apolipoprotein MOrtality RISk study (AMORIS). Journal of internal medicine. 2009 Dec 1;266(6):558-70.

Hozawa A, Folsom AR, Ibrahim H, Javier Nieto F, Rosamond WD, Shahar E. Serum uric acid and risk of ischemic stroke: the ARIC Study.

Atherosclerosis. 2006;187(2):401-7.

Ioachimescu AG, Brennan DM, Hoar BM, Hazen SL, Hoogwerf BJ. Serum uric acid is an independent predictor of all-cause mortality in patients at high risk of cardiovascular disease: a preventive cardiology information system (PreCIS) database cohort study. Arthritis Rheum. 2008;58(2):623-30.

Ito H, Abe M, Mifune M, Oshikiri K, Antoku S, Takeuchi Y, Togane M: Hyperuricemia is independently associated with coronary heart disease and renal dysfunction in patients with type 2 diabetes mellitus. PLoS One. 2011, 6: e27817-10.

Jee SH, Batty GD, Jang Y, Oh DJ, Oh BH, Lee SH, Park SW, Seung KB, Kimm H, Kim SY, Mok Y. The Korean Heart Study: rationale, objectives, protocol, and preliminary results for a new prospective cohort study of 430,920 men and women. European journal of preventive cardiology. 2014 Dec;21(12):1484-92.

Jee SH, Jang Y, Oh DJ, Oh BH, Lee SH, Park SW, Seung KB, Mok Y, Jung KJ, Kimm H, Yun YD. A coronary heart disease prediction model: the Korean Heart Study. BMJ open. 2014 May 1;4(5):e005025.

Jee SH, Lee SY, Kim MT. Serum uric acid and risk of death from cancer, cardiovascular disease or all causes in men. Eur J Cardiovasc Prev Rehabil. 2004;11(3):185-91.

Jo HJ, Lee YJ, Choi JH, Lee EJ, Kang JY. Prevalence of Depression and Depressive Symptoms in Cardiovascular Diseases in Korean Adults: The

Korean National Health and Nutrition Examination Survey in 2013~2014. Korean Journal of Family Practice. 2016 Oct 20;6(5):497-502.

Johnson RJ, Kivlighn SD, Kim YG, Suga S, Fogo AB. Reappraisal of the pathogenesis and consequences of hyperuricemia in hypertension, cardiovascular disease, and renal disease. American journal of kidney diseases. 1999 Feb 28;33(2):225-34.

Johnson RJ, Kang DH, Feig D, Kivlighn S, Kanellis J, Watanabe S, et al. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? Hypertension. 2003;41(6):1183-90.

Juraschek SP, Tunstall-Pedoe H, Woodward M: Serum uric acid and the risk of mortality during 23 years follow-up in the Scottish Heart Health Extended Cohort Study. Atherosclerosis. 2014, 233: 623-629.

Kanellis J, Kang DH. Uric acid as a mediator of endothelial dysfunction, inflammation, and vascular disease. InSeminars in nephrology 2005 Jan 31 (Vol. 25, No. 1, pp. 39-42). WB Saunders.

Kavousi M, Elias-Smale S, Rutten JH, Leening MJ, Vliegenthart R, Verwoert GC, Krestin GP, Oudkerk M, de Maat MP, Leebeek FW, Mattace-Raso FU. Evaluation of newer risk markers for coronary heart disease risk classification: a cohort study. Annals of Internal Medicine. 2012 Mar 20;156(6):438-44.

Kawabe M, Sato A, Hoshi T, Sakai S, Hiraya D, Watabe H, Kakefuda Y, Ishibashi M, Abe D, Takeyasu N, Aonuma K. Gender differences in the

association between serum uric acid and prognosis in patients with acute coronary syndrome. Journal of cardiology. 2016 Feb 29;67(2):170-6.

Keenan T, Zhao W, Rasheed A, Ho WK, Malik R, Felix JF, Young R, Shah N, Samuel M, Sheikh N, Mucksavage ML. Causal assessment of serum urate levels in cardiometabolic diseases through a Mendelian randomization study. Journal of the American College of Cardiology. 2016 Feb 2;67(4):407-16.

Kimm H, Yun JE, Lee SH, Jang Y, Jee SH. Validity of the diagnosis of acute myocardial infarction in korean national medical health insurance claims data: the korean heart study (1). Korean circulation journal. 2012 Jan 1;42(1):10-5.

Kim SY, Guevara JP, Kim KM, Choi HK, Heitjan DF, Albert DA. Hyperuricemia and coronary heart disease: a systematic review and meta□analysis. Arthritis care & research. 2010 Feb 1;62(2):170-80.

Kleber ME, Delgado G, Grammer TB, Silbernagel G, Huang J, Krämer BK, Ritz E, März W. Uric acid and cardiovascular events: a Mendelian randomization study. Journal of the American Society of Nephrology. 2015 Nov 1;26(11):2831-8.

Krishnan E, Baker JF, Furst DE, Schumacher HR: Gout and the risk of acute myocardial infarction. Arthritis Rheum. 2006, 54: 2688-2696.

Lai, X., Yang, L., Légaré, S., Angileri, F., Chen, X., Fang, Q. & Xu, C. Dose-response relationship between serum uric acid levels and risk of incident

coronary heart disease in the Dongfeng-Tongji Cohort. International Journal of Cardiology, 2016:224:299-304.

Levine W, Dyer AR, Shekelle RB, Schoenberger JA, Stamler J. Serum uric acid and 11.5-year mortality of middle-aged women: findings of the Chicago Heart Association Detection Project in Industry. Journal of clinical epidemiology. 1989 Jan 1;42(3):257-67.

Li, M., Hu, X., Fan, Y., Li, K., Zhang, X., Hou, W., & Tang, Z. Hyperuricemia and the risk for coronary heart disease morbidity and mortality a systematic review and dose-response meta-analysis. Scientific reports 2016; 6: 19520.

Li P, Zhang L, Zhang M, Zhou C, Lin N. Uric acid enhances PKC-dependent eNOS phosphorylation and mediates cellular ER stress: A mechanism for uric acid-induced endothelial dysfunction. International journal of molecular medicine. 2016 Apr 1;37(4):989-97

Li Q, Yang Z, Lu B, Wen J, Ye Z, Chen L, He M, Tao X, Zhang W, Huang Y, Zhang Z, Qu S, Hu R. Serum uric acid level and its association with metabolic syndrome and carotid atherosclerosis in patients with type 2 diabetes. Cardiovasc Diabetol. 2011; 10: 72-10.

Lyngdoh T, Vuistiner P, Marques-Vidal P, Rousson V, Waeber G, Vollenweider P, Bochud M. Serum uric acid and adiposity: deciphering causality using a bidirectional Mendelian randomization approach. PloS one. 2012 Jun 19;7(6):e39321.

Mallamaci F, Testa A, Leonardis D, Tripepi R, Pisano A, Spoto B, Sanguedolce MC, Parlongo RM, Tripepi G, Zoccali C. A polymorphism in the major gene regulating serum uric acid associates with clinic SBP and the white-coat effect in a family-based study. Journal of hypertension. 2014 Aug 1;32(8):1621-8.

Martínez-Quintana E, Tugores A, Rodríguez-González F. Serum uric acid levels and cardiovascular disease: the Gordian knot. Journal of Thoracic Disease. 2016 Nov;8(11):E1462.

Mazza A, Zamboni S, Rizzato E, Pessina AC, Tikhonoff V, Schiavon L, et al. Serum uric acid shows a J-shaped trend with coronary mortality in non-insulin-dependent diabetic elderly people. The CArdiovascular STudy in the ELderly (CASTEL). Acta Diabetol. 2007;44(3):99-105.

McKeigue PM, Campbell H, Wild S, Vitart V, Hayward C, Rudan I, Wright AF, Wilson JF. Bayesian methods for instrumental variable analysis with genetic instruments ('Mendelian randomization'): example with urate transporter SLC2A9 as an instrumental variable for effect of urate levels on metabolic syndrome. International journal of epidemiology. 2010 Jun 1;39(3):907-18.

Meisinger C, Koenig W, Baumert J, Doring A. Uric acid levels are associated with all-cause and cardiovascular disease mortality independent of systemic inflammation in men from the general population: the MONICA/KORA cohort study. Arterioscler Thromb Vasc Biol. 2008;28(6):1186-92.

Montalcini T, Gorgone G, Gazzaruso C, Sesti G, Perticone F, Pujia A. Relation between serum uric acid and carotid intima-media thickness in healthy postmenopausal women. Internal and emergency medicine. 2007 Mar 1;2(1):19-23.

Moriarity JT, Folsom AR, Iribarren C, Nieto FJ, Rosamond WD. Serum uric acid and risk of coronary heart disease: Atherosclerosis Risk in Communities (ARIC) Study. Ann Epidemiol. 2000;10(3):136-43.

National KF. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. American journal of kidney diseases: the official journal of the National Kidney Foundation. 2002 Feb;39(2 Suppl 1):S1.

Navaneethan SD, Beddhu S. Associations of serum uric acid with cardiovascular events and mortality in moderate chronic kidney disease. Nephrol Dial Transplant. 2009;24(4):1260-6.

Neogi T, Ellison RC, Hunt S, Terkeltaub R, Felson DT, Zhang Y: Serum uric acid is associated with carotid plaques: the National Heart, Lung, and Blood Institute Family Heart Study. J Rheumatol. 2009, 36: 378-384

Niskanen LK, Laaksonen DE, Nyyssonen K, Alfthan G, Lakka HM, Lakka TA, et al. Uric acid level as a risk factor for cardiovascular and all-cause mortality in middle-aged men: a prospective cohort study. Arch Intern Med. 2004;164(14):1546-51.

Okura T, Higaki J, Kurata M, Irita J, Miyoshi K, Yamazaki T, et al. Elevated

serum uric acid is an independent predictor for cardiovascular events in patients with severe coronary artery stenosis: subanalysis of the Japanese Coronary Artery Disease (JCAD) Study. Circ J. 2009;73(5):885-91.

Oikonen,M, Wendelin-Saarenhovi,M, Lyytikainen,LP, Siitonen,N, Loo,BM, Jula,A, Seppala,I, Saarikoski,L, Lehtimaki,T, Hutri-Kahonen,N, Juonala,M, Kahonen,M, Huupponen,R, Viikari,JS, Raitakari,OT: Associations between serum uric acid and markers of subclinical atherosclerosis in young adults. The cardiovascular risk in Young Finns study. Atherosclerosis 2012;223:497-503.

Ong G, Davis WA, Davis TM. Serum uric acid does not predict cardiovascular or all-cause mortality in type 2 diabetes: the Fremantle Diabetes Study. Diabetologia. 2010.

Palmer TM, Lawlor DA, Harbord RM, Sheehan NA, Tobias JH, Timpson NJ, Smith GD, Sterne JA. Using multiple genetic variants as instrumental variables for modifiable risk factors. Statistical methods in medical research. 2012 Jun;21(3):223-42.

Palmer TM, Nordestgaard BG, Benn M, Tybjærg-Hansen A, Smith GD, Lawlor DA, Timpson NJ. Association of plasma uric acid with ischaemic heart disease and blood pressure: mendelian randomisation analysis of two large cohorts. Bmj. 2013 Jul 18;347:f4262.

Parsa A, Brown E, Weir MR, Fink JC, Shuldiner AR, Mitchell BD, McArdle PF. Genotype-based changes in serum uric acid affect blood pressure. Kidney

international. 2012 Mar 1;81(5):502-7.

Pfister,R, Barnes,D, Luben,R, Forouhi,NG, Bochud,M, Khaw,KT, Wareham,NJ, Langenberg,C: No evidence for a causal link between uric acid and type 2 diabetes: a Mendelian randomisation approach. Diabetologia 2011;54:2561-2569.

Puddu PE, Lanti M, Menotti A, Mancini M, Zanchetti A, Cirillo M, et al. Serum uric acid for short-term prediction of cardiovascular disease incidence in the Gubbio population Study. Acta Cardiol. 2001;56(4):243-51.

Rasheed H, Hughes K, Flynn TJ, Merriman TR. Mendelian randomization provides no evidence for a causal role of serum urate in increasing serum triglyceride levels. Circulation: Cardiovascular Genetics. 2014 Sep 23:CIRCGENETICS-114.

Ruggiero C, Cherubini A, Ble A, Bos AJ, Maggio M, Dixit VD, Lauretani F, Bandinelli S, Senin U, Ferrucci L. Uric acid and inflammatory markers. European heart journal. 2006 Apr 12;27(10):1174-81.

Saggiani F, Pilati S, Targher G, Branzi P, Muggeo M, Bonora E. Serum uric acid and related factors in 500 hospitalized subjects. Metabolism. 1996;45(12):1557-61.

Sakata K, Hashimoto T, Ueshima H, Okayama A. Absence of an association between serum uric acid and mortality from cardiovascular disease: NIPPON DATA 80, 1980-1994. National Integrated Projects for Prospective Observation of Non-communicable Diseases and its Trend in

the Aged. Eur J Epidemiol. 2001;17(5):461-8.

Savarese G, Ferri C, Trimarco B, Rosano G, Dellegrottaglie S, Losco T, Casaretti L, D'Amore C, Gambardella F, Prastaro M, Rengo G. Changes in serum uric acid levels and cardiovascular events: a meta-analysis. Nutrition, Metabolism and Cardiovascular Diseases. 2013;23(8):707-14

Sedaghat S, Pazoki R, Uitterlinden AG, Hofman A, Stricker BH, Ikram MA, Franco OH, Dehghan A. Association of Uric Acid Genetic Risk Score With Blood PressureNovelty and Significance. Hypertension. 2014 Nov 1;64(5):1061-6.

Sloop GD, Bialczak JK, Weidman JJ, St Cyr JA. Uric acid increases erythrocyte aggregation: Implications for cardiovascular disease. Clinical hemorheology and microcirculation. 2016 Jan 1;63(4):349-59.

Song YM, Sung J, Davey Smith G, Ebrahim S. Body mass index and ischemic and hemorrhagic stroke: a prospective study in Korean men. Stroke. 2004;35(4):831-6.

Song YM, Sung J. Body mass index and mortality: a twelve-year prospective study in Korea. Epidemiology. 2001;12(2):173-9.

Storhaug HM, Norvik JV, Toft I, Eriksen BO, Løchen ML, Zykova S, Solbu M, White S, Chadban S, Jenssen T. Uric acid is a risk factor for ischemic stroke and all-cause mortality in the general population: a gender specific analysis from The Tromsø Study. BMC cardiovascular disorders. 2013 Dec 11;13(1):115.

Strasak A, Ruttmann E, Brant L, Kelleher C, Klenk J, Concin H, et al. Serum uric acid and risk of cardiovascular mortality: a prospective long-term study of 83,683 Austrian men. Clin Chem. 2008;54(2):273-84.

Strasak AM, Kelleher CC, Brant LJ, Rapp K, Ruttmann E, Concin H, et al. Serum uric acid is an independent predictor for all major forms of cardiovascular death in 28,613 elderly women: a prospective 21-year follow-up study. Int J Cardiol. 2008;125(2):232-9.

Sumino H, Ichikawa S, Kanda T, Nakamura T, Sakamaki T. Reduction of serum uric acid by hormone replacement therapy in postmenopausal women with hyperuricaemia. Lancet. 1999;354(9179):650.

Testa A, Prudente S, Leonardis D, Spoto B, Sanguedolce MC, Parlongo RM, Tripepi G, Rizza S, Mallamaci F, Federici M, Trischitta V. A genetic marker of hyperuricemia predicts cardiovascular events in a meta-analysis of three cohort studies in high risk patients. Nutrition, Metabolism and Cardiovascular Diseases. 2015 Dec 31;25(12):1087-94.

Timpson NJ, Wade KH, Smith GD. Mendelian randomization: application to cardiovascular disease. Current hypertension reports. 2012 Feb 1;14(1):29-37.

Verdecchia P, Schillaci G, Reboldi G, Santeusanio F, Porcellati C, Brunetti P. Relation between serum uric acid and risk of cardiovascular disease in essential hypertension. The PIUMA study. Hypertension. 2000;36(6):1072-8.

Wang R, Song Y, Yan Y, Ding Z. Elevated serum uric acid and risk of cardiovascular or all-cause mortality in people with suspected or definite coronary artery disease: A meta-analysis. Atherosclerosis. 2016 Nov 30;254:193-9.

Waring WS, Maxwell SR, Webb DJ. Uric acid concentrations and the mechanisms of cardiovascular disease. European heart journal. 2002 Dec 1;23(23):1888-9.

Wheeler JG, Juzwishin KD, Eiriksdottir G, Gudnason V, Danesh J. Serum uric acid and coronary heart disease in 9,458 incident cases and 155,084 controls: prospective study and meta-analysis. PLoS medicine. 2005 Mar 29;2(3):e76.

White J, Sofat R, Hemani G, Shah T, Engmann J, Dale C, Shah S, Kruger FA, Giambartolomei C, Swerdlow DI, Palmer T. Plasma urate concentration and risk of coronary heart disease: a Mendelian randomisation analysis. The lancet Diabetes & endocrinology. 2016 Apr 30;4(4):327-36.

Yang Q, Köttgen A, Dehghan A, Smith AV, Glazer NL, Chen MH, Chasman DI, Aspelund T, Eiriksdottir G, Harris TB, Launer L. Multiple genetic loci influence serum urate levels and their relationship with gout and cardiovascular disease risk factors. Circulation: Cardiovascular Genetics. 2010 Dec 1;3(6):523-30. Yuan H, Yu C, Li X, Sun L, Zhu X, Zhao C, Zhang Z, Yang Z. Serum uric acid levels and risk of metabolic syndrome: a dose-response meta-analysis of prospective studies. The Journal of Clinical Endocrinology & Metabolism. 2015 Aug 26;100(11):4198-207.

Zalawadiya SK, Veeranna V, Mallikethi-Reddy S, Bavishi C, Lunagaria A, Kottam A, Afonso L. Uric acid and cardiovascular disease risk reclassification: findings from NHANES III. European journal of preventive cardiology. 2015 Apr;22(4):513-8.

Zhao G, Huang L, Song M, Song Y. Baseline serum uric acid level as a predictor of cardiovascular disease related mortality and all-cause mortality: a meta-analysis of prospective studies. Atherosclerosis. 2013 Nov 30;231(1):61-8.

Zhang XF, Attia J, D'este C, Ma XY. The relationship between higher blood pressure and ischaemic, haemorrhagic stroke among Chinese and Caucasians: meta-analysis. European Journal of Cardiovascular Prevention & Rehabilitation. 2006 Jun 1;13(3):429-37

Zhang W, Sun K, Yang Y, Zhang H, Hu FB, Hui R. Plasma uric acid and hypertension in a Chinese community: prospective study and meta-analysis. Clin Chem 2009;55:2026–34.

Zhang W, Iso H, Murakami Y, Miura K, Nagai M, Sugiyama D, Ueshima H, Okamura T. Serum uric acid and mortality form cardiovascular disease: EPOCH-JAPAN study. Journal of atherosclerosis and thrombosis. 2016 Jun 1;23(6):692-703.

Zhong C, Zhong X, Xu T, Xu T, Zhang Y. Sex□Specific Relationship Between Serum Uric Acid and Risk of Stroke: A Dose□Response Meta□Analysis of Prospective Studies. Journal of the American Heart Association. 2017 Apr 1;6(4):e005042.

Zoppini G, Targher G, Negri C, Stoico V, Perrone F, Muggeo M, et al. Elevated serum uric acid concentrations independently predict cardiovascular mortality in type 2 diabetic patients. Diabetes Care. 2009;32(9):1716-20.

Zuo, T., Liu, X., Jiang, L., Mao, S., Yin, X., & Guo, L. Hyperuricemia and coronary heart disease mortality: a meta-analysis of prospective cohort studies. BMC Cardiovascular Disorders, 2016:16(1):207.

APPENDIX

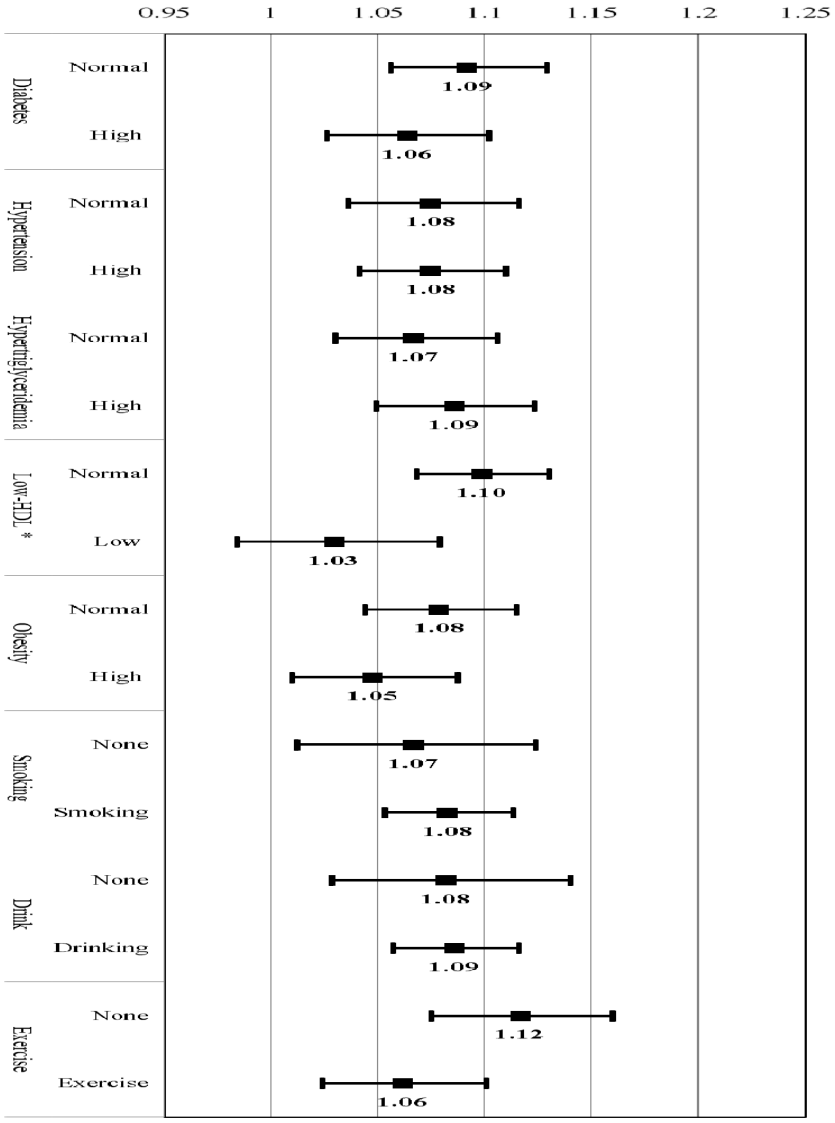


Figure A1. Hazard ratios for ischemic heart disease incidence to subgroup on the basis of uric acid in men.

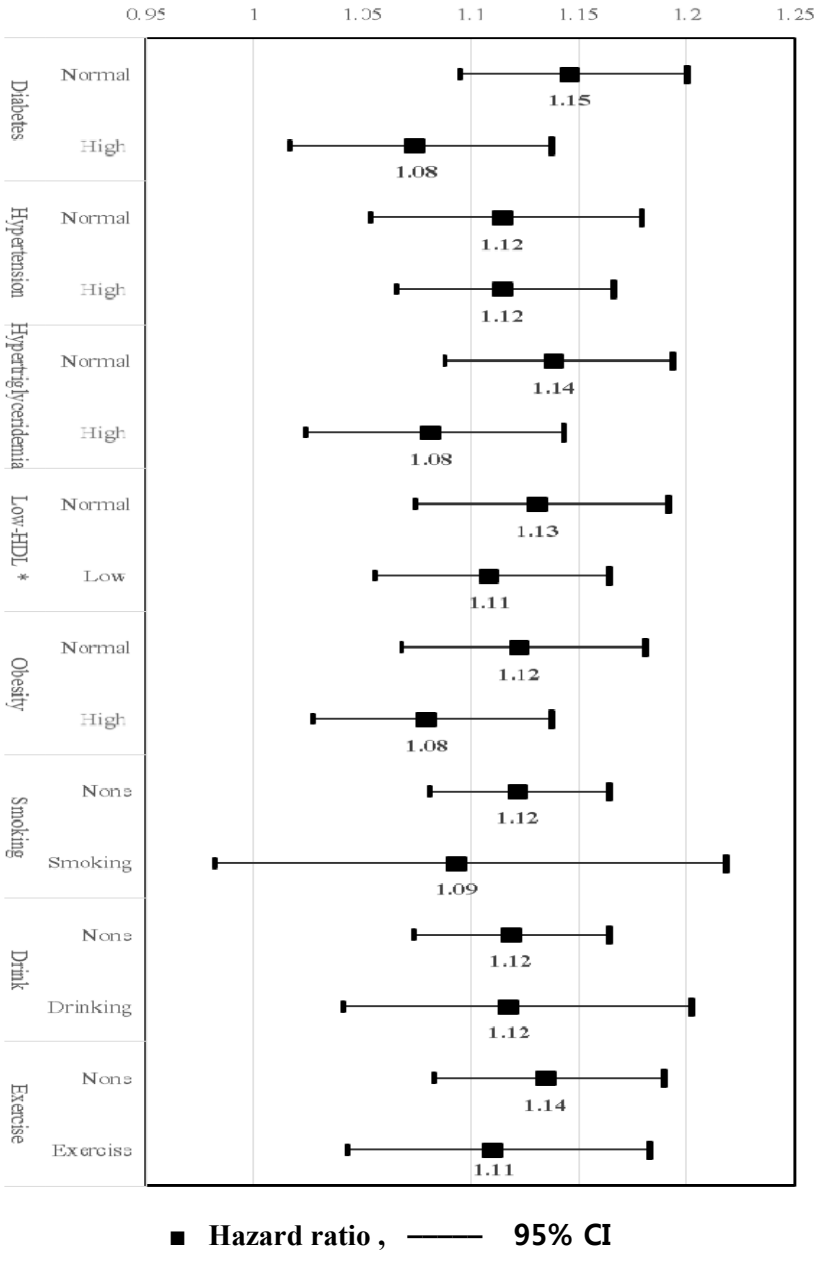


Figure A2. Hazard ratios for ischemic heart disease incidence to subgroup on the basis of uric acid in women.

ABSTRACT IN KOREAN

대사성 위험요인에 따른 혈청요산과 심혈관 질환: 한국인 심장병 연구

연세대학교 대학원 보건학과

박 은 정

배경 및 목적

고혈압, 염증, 내피기능의 부전, 인슐린 저항성, 비만 등과 관련성이 있으며, 최근 대규모 연구에서 고요산혈증이 심혈관 질환 발생의 독립적 위험인자로 보고하였으나, 연구결과 간에 차이를 보였다. 따라서, 이 연구의 목적은 대사성 위험요인의 유무에 따라, 대규모 한국인 일반인구집단에서 혈청요산수치와 심혈관 질환의 발생위험과의 관련성을 확인하는 것이다.

연구 방법

1996 부터 2004 년까지 전국 18 지점의 건강검진센터를 방문한 465,233 명의 한국인 심장병연구에 등록된 성인을 대상으로 과거 심혈관 질환이 없고 혈중 요산수치를 측정한 322,467 명을 대상으로 분석하였다. 대사성 위험요인의 정의는 허리둘레를 제외하고 수정된 NCEP-ATP III 기준을 정의하였으며, 혈중 요산수치의 5 분위수에 따라, Cox 비례위험모형을 사용하여 심혈관질환 발생 위험을 산출하였다.

연구 결과

총 추적관찰기간은 9.5 년 동안 잠재적 교란요인을 보정한 후, 혈중요산수치와 심혈관질환 발생(27,009 건)과의 관련성을 평가하였다. Cox 비례위험모형을 이용한 분석결과로는 혈청요산수치가 가장 높은 남자그룹(>6.8mg/dl 이상)과 여자그룹(4.8mg/dl 이상)이 심혈관 질환과 허혈성 심장질환의 발생위험이 증가하였다. 잠재적 위험요인들을 보정한 고요산혈증의 심혈관질환 위험은 정상수치에 비해 남성이 1.20 배(95 % CI, 1.12−1.30), 여성이 1.44 배(95 % CI, 1.27−1.63) 높았다. 기존의 대사성 위험인자별로 층화하여 허혈성 심장질환과의 관련성을 분석한 결과, 당뇨병이 없는 대상자의 하위 그룹분석에서 허혈성 심장질환의 발생위험은 남자가 1.24 배(95 % CI; 1.11−1.38), 여자는 1.52 배(95 % CI; 1.29−1.78) 높았다.

결론

높은 혈청요산수치는 심혈관질환 중에서 허혈성 심장병 발생과의 관련성은 기존 연구와 일치하였으며, 대사성 위험요인이 없는 성인에서 고요산혈증은 허혈성 심장병 위험이 높았고, 특히 남성보다 여성에서 더 유의하였다. 혈청요산수치와 심혈관계 질환의 원인인과관계를 확인하기 위하여 심혈관질환 및 대사위험인자에 대한 바이오마커와 다양한 유전변이들을 광범위하게 평가하는 추가 연구들이 필요하다.

핵심어: 요산, 심뇌혈관질환, 대사성 위험요인, 코호트 연구