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Original Contribution

A Cohort Study of Hyperuricemia in Middle-aged South Korean Men

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Few prospective studies have assessed the incidence and determinants of asymptomatic hyperuricemia in free-living populations. The authors' goals in this study were to estimate the incidence of hyperuricemia and quantify the dose-response relations of specific risk factors with hyperuricemia in middle-aged South Korean male workers. The authors followed a cohort of 10,802 hyperuricemia-free men aged 30–59 years, examining them annually or biennially at a university hospital in Seoul, South Korea, from 2002 to 2009. A parametric Cox model and a pooled logistic regression model were used to estimate adjusted hazard ratios for incident hyperuricemia (defined as serum uric acid level $\geq$7.0 mg/dL) according to prespecified risk factors. During 51,210.6 person-years of follow-up, 2,496 men developed hyperuricemia (incidence rate = 48.7 per 1,000 person-years, 95% confidence interval: 46.8, 50.7). The incidence of hyperuricema increased across baseline categories of age, body mass index, alcohol intake, blood pressure, metabolic syndrome, high-sensitivity C-reactive protein, triglycerides, gamma-glutamyltransferase, and fatty liver, whereas fasting glucose, estimated glomerular filtration rate, and high density lipoprotein cholesterol levels were inversely associated with incident hyperuricemia. Development of hyperuricemia, a very common outcome among apparently healthy South Korean men, was predicted by a variety of cardiovascular and metabolic risk factors, suggesting that lifestyle modification may help reduce the incidence of hyperuricemia.

cohort studies; hyperuricemia; risk factors; uric acid

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyltransferase; HDL, high density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein; LDL, low density lipoprotein.

Uric acid, the final oxidation product of purine metabolism, is an established cause of gouty arthritis and kidney stones. Elevated serum uric acid levels may also contribute to the development of hypertension, kidney disease, and cardiovascular disease. The prevalence of hyperuricemia (serum uric acid concentration $\geq$7 mg/dL) in the United States is estimated to be 16% (1), while clinically manifest gout affects 1%–4% of the population in Western countries (2, 3). Uric acid concentrations in men have gradually increased from an average of $<$3.5 mg/dL in the 1920s to $>$6.0 mg/dL in the 1970s (4). Changes in dietary patterns and alcohol intake, increased prevalence of insulin resistance and chronic kidney disease, and use of certain medications such as diuretics and aspirin may partly account for the rising prevalence of hyperuricemia and gout (5), but the determinants of hyperuricemia in the general population are incompletely understood.

Despite abundant epidemiologic research on hyperuricemia, there have been almost no prospective studies on the incidence and determinants of asymptomatic hyperuricemia. In a 6-year longitudinal study of Japanese male office workers aged 30–54 years, obesity, high blood pressure, high triglyceride levels, and alcohol intake were associated with the development of hyperuricemia (6), but the sample size of the study did not allow for detailed analysis of dose-response relations. Consequently, our objective in this study was to evaluate the incidence and quantify the determinants of hyperuricemia in a large cohort of male South Korean workers followed for up to 7 years. The large number of incident cases allowed us

to obtain precise estimates of and dose-response relations for the association between potential risk factors and the development of incident hyperuricemia.

MATERIALS AND METHODS

Subjects

The study population comprised male workers from one of the largest semiconductor manufacturing companies in South Korea and its 13 affiliates (7, 8). In South Korea, the Industrial Safety and Health Law requires employees to participate in annual or biennial health examinations. The present cohort included all male workers aged 30–59 years from the above-mentioned semiconductor companies who participated in a comprehensive health examination at the Kangbuk Samsung Hospital in Seoul, South Korea, in 2002 ($n = 15,347$). We excluded 27 subjects who had a history of malignancy, 9 subjects with a history of liver cirrhosis, 3,239 subjects with hyperuricemia (serum uric acid concentration $\geq$7.0 mg/dL) at baseline, and 6 subjects who were taking medication for hyperuricemia or gout. Because some persons had more than one exclusion criterion, the total number of subjects eligible for the study was 12,080. We further excluded 1,278 subjects (10.6%) who did not engage in any follow-up visits between 2002 and 2009 and thus had no follow-up data. Participants excluded because of lack of follow-up data were on average 0.9 years older and more likely to be current smokers, to be alcohol drinkers, and to have diabetes compared with other participants in the cohort, but they showed no significant difference in terms of other study variables (not shown). The final sample size was 10,802 participants.

This study was approved by the institutional review board of Kangbuk Samsung Hospital. The study was exempted from the informed consent requirement by the institutional review board because we only retrospectively accessed a de-identified database for purposes of analysis.

Measurements

Baseline and follow-up examinations were conducted at the Kangbuk Samsung Hospital Health Screening Center. Study participants were examined annually or biennially until December 2009. The average follow-up period for participants who did not develop hyperuricemia was 5.4 years. During the health examinations, data were collected on medical history, medication use, health-related behaviors, physical measurements, and serum biochemical measurements (8). Questions pertaining to alcohol intake included weekly frequency of alcohol consumption and usual amount consumed daily. Questionnaire data were also used to identify current smokers and to assess the weekly frequency of moderate- or vigorous-intensity physical activity. Body weight was measured with light clothing and without shoes to the nearest 0.1 kg using a digital scale. Height was measured to the nearest 0.1 cm. Body mass index was calculated as weight in kilograms divided by height in meters squared. Trained nurses measured sitting blood pressure with a standard mercury sphygmomanometer.

Blood specimens were sampled from the antecubital vein after more than 12 hours of fasting. Serum levels of glucose, uric acid, total cholesterol, triglycerides, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, gamma-glutamyltransferase (GGT), alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase were measured using Bayer Reagent Packs on an automated chemistry analyzer (Advia 1650 AutoAnalyzer; Bayer Diagnostics, Leverkusen, Germany). Measurement techniques included the hexokinase method for glucose, an enzymatic colorimetric assay for serum lipids, and an immunoradiometric assay for insulin (BioSource, Nivelles, Belgium). Serum uric acid was measured on the basis of the Fossati enzymatic reaction using uricase with a Trinder-like endpoint (Advia 1650 AutoAnalyzer). Insulin resistance was assessed with homeostasis model assessment of insulin resistance (HOMA-IR), according to the following equation: fasting blood insulin (μU/mL) $\times$ fasting blood glucose (mmol/L)/22.5. High-sensitivity C-reactive protein (hsCRP) was analyzed by means of particle-enhanced immunonephelometry with the BNII System (Dade Behring, Marburg, Germany) using a lower detection limit of 0.175 mg/L. The clinical laboratory used has been accredited and participates annually in inspections and surveys conducted by the Korean Association of Quality Assurance for Clinical Laboratories.

Hyperuricemia was defined as a serum uric acid concentration $\geq$7.0 mg/dL or current treatment for hyperuricemia (9). Metabolic syndrome was defined as the presence of 3 or more Adult Treatment Panel III criteria (10): 1) abdominal obesity; 2) fasting blood glucose level $\geq$110 mg/dL; 3) triglyceride level $\geq$150 mg/dL; 4) HDL cholesterol level $<$40 mg/dL; and 5) blood pressure $\geq$130/85 mm Hg. Since waist circumference measurements were not available for all subjects, we substituted overall adiposity (i.e., a body mass index $\geq$25, which has been proposed as a cutoff for the diagnosis of obesity in Asians (11)) for abdominal obesity. Diabetes was defined as a fasting serum glucose level $\geq$126 mg/dL or current use of blood glucose-lowering agents. Estimated glomerular filtration rate (eGFR) was calculated by using the simplified Modification of Diet in Renal Disease Study equation (12).

Abdominal ultrasonography was performed with a 3.5-MHz transducer (Logic Q700 MR; General Electric, Milwaukee, Wisconsin) by 12 experienced radiologists who were unaware of the aims of the study and were blinded to laboratory values. Images were captured in a standard fashion while the patient lay in the supine position with the right arm raised above the head (8). An ultrasonographic diagnosis of fatty liver was defined as the presence of a diffuse increase of fine echoes in the liver parenchyma compared with the kidney or spleen parenchyma (13). Fatty liver was determined by the radiologists using live images.

Statistical analysis

Follow-up extended from the baseline examination to the development of hyperuricemia or the last health examination conducted for each participant. Since we knew that hyperuricemia had arisen between 2 visits but did not know the precise time of hyperuricemia development, we used a parametric Cox model to take into account this type of interval censoring (14). In these models, the baseline hazard function

was parameterized with restricted cubic splines in log time with 4 degrees of freedom. We estimated adjusted hazard ratios for incident hyperuricemia for prespecified potential risk factors measured at the baseline visit (the first visit for each participant). For time-dependent analyses, we used a pooled logistic regression model that closely approximates a Cox model when the risk of outcome between intervals is low (15).

In addition to age, we considered cigarette smoking (none, ex-smoker, or current smoker), alcohol intake (<10, 10–19.9, or ≥20 g ethanol/day), regular exercise (none, <1 time per week, or ≥1 time per week), body mass index (<18.5, 18.5–22.9, 23.0–24.9, or ≥25.0), glucose category (fasting glucose <100 mg/dL, fasting glucose 100–125 mg/dL, or diabetes), blood pressure category (<120/80, ≥120/80 and <140/90, or ≥140/90 mm Hg or medication use), HOMA-IR (quartiles among participants without diabetes), hsCRP (mg/L; quartiles), triglycerides (mg/dL; quartiles), HDL cholesterol (mg/dL; quartiles), eGFR (mL/minute/1.73 m^2; quartiles), and GGT (units/L; quartiles). To further explore the shape of the dose-response relation between potential risk factors and hyperuricemia incidence, we used restricted quadratic splines with knots at the 5th, 50th, and 95th percentiles of each determinant distribution. We checked the proportional hazards assumption by examining graphs of estimated log(-log) survival. Statistical analyses were carried out using Stata, version 11.0 (StataCorp LP, College Station, Texas). Parametric Cox models with interval censoring were fitted using the *stpm* command in Stata. All reported *P* values are 2-tailed, and those less than 0.05 were considered statistically significant.

RESULTS

At baseline, the mean age of study participants was 37.3 years (standard deviation, 5.0). The prevalences of diabetes, hypertension, and metabolic syndrome were 1.9%, 16.1%, and 11.7%, respectively. In contrast to participants who did not develop hyperuricemia during follow-up, those with incident hyperuricemia were more likely to drink alcohol, to have metabolic syndrome, to have hypertension, to have a higher average body mass index, and to have higher levels of total cholesterol, LDL cholesterol, triglycerides, liver enzymes, hsCRP, and HOMA-IR at baseline (Table 1). The presence of diabetes and high levels of HDL cholesterol and eGFR at baseline were inversely associated with incident hyperuricemia.

During 51,210.6 person-years of follow-up, 2,496 participants developed hyperuricemia. The incidence rate was 48.7 per 1,000 person-years (95% confidence interval (CI): 46.8, 50.7), resulting in a 7-year cumulative incidence of 23.1%. By age, the incidence of hyperuricema was highest among participants aged 40–44 years (Table 2). In multivariable Cox models, the hazard ratios for hyperuricemia comparing participants with body mass indices of 18.5–22.9, 23.0–24.9, and ≥25.0 with those with a body mass index less than 18.5 were 2.00 (95% CI: 1.25, 3.19), 2.84 (95% CI: 1.78, 4.53), and 3.46 (95% CI: 2.17, 5.52), respectively (*P*-trend < 0.001; Table 3). For alcohol intake, the multivariable hazard ratios for hyperuricemia comparing participants with alcohol intakes of 10–19.9 g ethanol/day and ≥20.0 g ethanol/day with those consuming <10 g ethanol/day were 1.13 (95% CI: 1.03, 1.25) and 1.20 (95% CI: 1.08, 1.34), respectively (*P*-trend < 0.001). Smoking and regular exercise were not significantly related to incident hyperuricemia.

Table 4 shows the risk of incident hyperuricemia according to baseline levels of other metabolic factors. In multivariable models, the hazard ratios for hyperuricemia when participants with prehypertension and hypertension were compared with those with normal blood pressure were 1.02 (95% CI: 0.93, 1.12) and 1.24 (95% CI: 1.10, 1.39), respectively (*P*-trend 0.001). In contrast, the hazard ratios for hyperuricemia when participants with elevated fasting glucose levels and diabetes were compared with those with normal fasting glucose levels were 0.87 (95% CI: 0.78, 0.98) and 0.47 (95% CI: 0.32, 0.67), respectively (*P*-trend < 0.001). For other metabolic factors, the multivariable-adjusted hazard ratios comparing the highest quartiles in the distribution with the lowest were 1.14 (95% CI: 1.02, 1.28; *P*-trend = 0.07) for hsCRP, 0.79 (95% CI: 0.70, 0.89; *P*-trend < 0.001) for eGFR, 1.47 (95% CI: 1.27, 1.71; *P*-trend < 0.001) for triglycerides, and 0.83 (95% CI: 0.72, 0.95; *P*-trend = 0.003) for HDL cholesterol. Total and LDL cholesterol were not significantly related to incident hyperuricemia. After adjustment for age, alcohol intake, and exercise, the hazard ratio for hyperuricemia when participants with the metabolic syndrome at baseline were compared with those without it was 1.41 (95% CI: 1.26, 1.58; *P* < 0.001).

Table 5 shows the risk of incident hyperuricemia by baseline level of liver function and the presence of fatty liver. In multivariable models, the risk of hyperuricemia increased with increasing quartiles of GGT (*P*-trend < 0.001). Fatty liver at baseline was associated with a significantly increased risk of hyperuricemia (hazard ratio = 1.13, 95% CI: 1.02, 1.25). However, alanine aminotransferase and aspartate aminotransferase levels were not significantly related to the incidence of hyperuricemia.

In multivariate-adjusted spline regression models (Figure 1), hyperuricemia was strongly and progressively associated with increasing baseline body mass index, triglyceride levels, and GGT levels and inversely associated with eGFR and glucose levels. For hsCRP, the risk of hyperuricemia increased only at high levels. The findings obtained using time-dependent models were similar to those based on models using baseline data only (Tables 3–5).

DISCUSSION

In this follow-up study of apparently healthy South Korean men aged 30–59 years, the incidence of hyperuricemia was very high (48.7 per 1,000 person-years, for a 7-year cumulative incidence of 23.1%), and it was strongly predicted by body mass index and a variety of cardiometabolic risk factors, particularly increasing triglyceride levels, and decreasing eGFR and glucose levels. Alcohol intake, increasing GGT concentrations, and the presence of fatty liver were also associated with increasing incidence of hyperuricemia. Our findings indicate that adiposity is a primary determinant of the onset of hyperuricemia in this population.

Other studies have also identified a positive association between body mass index and hyperuricemia (6, 16–19), and

Table 1. Baseline Characteristics of the Study Population According to Diagnosis of Incident Hyperuricemia During Follow-up, South Korea, 2002–2009

Characteristic or Risk Factor	Total (n = 10,802)			No Hyperuricemia (n = 8,306)			Hyperuricemia (n = 2,496)			*P* Value
	%	Mean (SD)	Mean (IQR)	%	Mean (SD)	Mean (IQR)	%	Mean (SD)	Mean (IQR)	
Age, years		37.3 (5.0)			37.3 (5.1)			37.2 (4.7)		0.17
Body mass index[a]		23.9 (2.7)			23.7 (2.7)			24.5 (2.7)		<0.001
Current smoker	46.4			46.4			46.6			0.82
Alcohol intake[b]	18.1			17.5			20.1			0.003
Regular exercise[c]	12.4			12.5			12.0			0.49
Metabolic syndrome	11.7			10.6			15.3			<0.001
Type 2 diabetes	1.9			2.1			1.2			0.005
Hypertension	16.1			15.0			19.7			<0.001
Systolic blood pressure, mm Hg		115.7 (12.9)			115.3 (12.6)			117.0 (13.8)		<0.001
Diastolic blood pressure, mm Hg		75.2 (10.3)			74.8 (10.1)			76.3 (11.1)		<0.001
Fasting glucose category, mg/dL										0.01
<100	81.8			81.8			81.7			
100–125	16.3			16.1			17.1			
≥126 or medication use	1.9			2.1			1.2			
Fasting glucose, mg/dL[d]		91.0 (9.4)			90.9 (9.4)			91.3 (9.3)		0.05
Total cholesterol, mg/dL		200.8 (34.4)			200.0 (34.5)			203.4 (33.9)		<0.001
Low density lipoprotein cholesterol, mg/dL		120.0 (29.3)			119.1 (29.3)			121.2 (29.1)		0.002
High density lipoprotein cholesterol, mg/dL		52.3 (11.6)			52.7 (11.6)			50.7 (11.6)		<0.001
Triglycerides, mg/dL			125.0 (91.0–178.0)			121.0 (87.0–171.0)			140.0 (102.0–197.0)	<0.001
Metabolic syndrome	11.7			10.6			15.3			<0.001
Gamma-glutamyltransferase, units/L			25.0 (18.0–39.0)			24.0 (17.0–38.0)			28.5 (20.0–44.0)	<0.001
Alanine aminotransferase, units/L			25.0 (19.0–37.0)			24.0 (18.0–36.0)			28.0 (20.0–40.0)	<0.001
Aspartate aminotransferase, units/L			23.0 (20.0–28.0)			23.0 (20.0–28.0)			24.0 (21.0–29.0)	<0.001
High-sensitivity C-reactive protein, mg/L			0.5 (0.3–1.0)			0.5 (0.2–0.9)			0.6 (0.3–1.1)	<0.001
Estimated glomerular filtration rate, mL/minute/1.73 m^2		79.5 (9.9)			79.8 (10.0)			78.5 (9.6)		<0.001
Insulin, μU/dL[d]		7.5 (2.8)			7.4 (2.7)			8.1 (2.9)		<0.001
HOMA-IR[d]		1.7 (0.7)			1.7 (0.7)			1.8 (0.7)		<0.001

Abbreviations: HOMA-IR, homeostasis model assessment of insulin resistance; IQR, interquartile range; SD, standard deviation.
[a] Weight (kg)/height $(m)^2$.
[b] ≥20 g ethanol/day.
[c] ≥1 time/week.
[d] In nondiabetics only (no hyperuricemia, $n = 8,135$; hyperuricemia, $n = 2,466$).

Table 2. Hazard Ratios for Incident Hyperuricemia by Age Group, South Korea, 2002–2009

Age Group, years	No. of Subjects	Person-Years of Follow-up	No. of Cases	Incidence Rate (per 1,000 Person-Years)	95% CI	Crude Hazard Ratio	95% CI
30–34	4,245	20,620.50	973	47.2	44.3, 50.2	Reference	
35–39	2,765	14,455.80	675	46.7	43.2, 50.3	1.01	0.91, 1.11
40–44	2,932	12,903.50	685	53.1	49.2, 57.2	1.11	1.01, 1.22
≥45	860	3,230.80	163	50.5	43.0, 58.8	1.02	0.86, 1.20
Total				48.7	46.8, 50.7		

Abbreviation: CI, confidence interval.

in one of them, weight gain in adulthood was associated with a higher prevalence of hyperuricemia in middle-aged Chinese men (16). Furthermore, weight loss has been associated with decreases in plasma uric acid levels (18), and obesity is a classical risk factor for the occurrence of gout. Increased adiposity is related to hyperuricemia via both increased production and decreased renal excretion of uric acid (20). Hyperinsulinema is a likely link between adiposity and hyperuricemia, since higher insulin levels reduce renal urate excretion (21, 22). Indeed, in our study, the incidence of hyperuricemia was associated with markers of insulin resistance (increased triglyceride concentrations and decreased HDL cholesterol concentrations) and with the presence of the metabolic syndrome.

While insulin resistance is associated with a markedly increased incidence of hyperuricemia, the presence of diabetes was a strong negative predictor of hyperuricemia (23–25). This effect is probably mediated through the uricosuric effects

Table 3. Hazard Ratios for Incident Hyperuricemia According to Behavioral and Anthropometric Risk Factors, South Korea, 2002–2009

	No. of Subjects	Person-Years of Follow-up	No. of Cases	Incidence Rate (per 1,000 Person-Years)	Age-Adjusted HR	95% CI	Multivariable-Adjusted[a]			
							Model Using Baseline Data		Model Using Time-Varying Covariates	
							HR	95% CI	HR	95% CI
Body mass index[b]										
<18.5	201	1,070.30	18	16.8	Reference		Reference		Reference	
18.5–22.9	3,826	19,015.80	673	35.4	2.07	1.30, 3.31	2.00	1.25, 3.19	1.56	0.94, 2.60
23.0–24.9	3,152	14,786.00	762	51.5	3.00	1.88, 4.80	2.84	1.78, 4.53	2.26	1.36, 3.77
≥25.0	3,623	16,338.50	1,043	63.8	3.70	2.32, 5.90	3.46	2.17, 5.52	2.92	1.76, 4.86
P-trend					<0.001		<0.001		<0.001	
Smoking										
Never smoker	3,186	15,345.10	721	47.0	Reference		Reference		Reference	
Ex-smoker	2,408	11,420.00	566	49.6	1.05	0.94, 1.17	0.99	0.88, 1.10	0.97	0.85, 1.10
Current smoker	4,846	22,753.30	1,124	49.4	1.05	0.95, 1.15	1.00	0.91, 1.10	0.99	0.89, 1.11
P-trend					0.35		0.98		0.90	
Alcohol intake, g ethanol/day										
<10.0	6,508	31,396.60	1,419	45.1	Reference		Reference		Reference	
10.0–19.9	2,342	10,891.60	576	52.9	1.16	1.05, 1.28	1.13	1.03, 1.25	1.06	0.93, 1.22
≥20.0	1,952	8,922.30	501	56.2	1.22	1.11, 1.36	1.20	1.08, 1.34	1.13	0.98, 1.29
P-trend					<0.001		<0.001		0.07	
Exercise										
No exercise	5,219	24,994.70	1,194	47.8	Reference		Reference		Reference	
<1 time/week	3,948	18,465.90	936	50.7	1.05	0.97, 1.15	1.02	0.93, 1.11	0.97	0.88, 1.07
≥1 time/week	1,296	6,108.60	290	47.5	0.98	0.86, 1.12	0.93	0.81, 1.05	0.93	0.80, 1.08
P-trend					0.76		0.46		0.30	

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] Adjusted for age and for all other variables in the table.
[b] Weight (kg)/height $(m)^2$.

Table 4. Hazard Ratios for Incident Hyperuricemia According to Metabolic Risk Factors, South Korea, 2002–2009

	No. of Subjects	Person-Years of Follow-up	No. of Cases	Incidence Rate (per 1,000 Person-Years)	Age-Adjusted HR	95% CI	Multivariable-Adjusted[a]			
							Model Using Baseline Data		Model Using Time-varying Covariates	
							HR	95% CI	HR	95% CI
Blood pressure, mm Hg										
<120/80					Reference		Reference		Reference	
120/80–<140/90	4,371	20,986.00	1,023	48.7	1.13	1.03, 1.23	1.02	0.93, 1.12	1.09	0.97, 1.22
≥140/90 or medication use	1,741	7,533.80	491	65.2	1.47	1.32, 1.64	1.24	1.10, 1.39	1.19	1.03, 1.37
P-trend					<0.001		0.001		0.01	
Fasting glucose, mg/dL										
<100	8,836	42,086.60	2,040	48.4	Reference		Reference		Reference	
100–125	1,765	8,183.10	426	52.1	1.06	0.96, 1.18	0.87	0.78, 0.98	0.86	0.76, 0.97
≥126 or medication use	201	940.8	30	31.9	0.63	0.44, 0.91	0.47	0.32, 0.67	0.42	0.29, 0.62
P-trend					0.61		<0.001		<0.001	
HOMA-IR (in nondiabetics)										
Q1 (<1.20)	2,721	13,434.70	483	36.0	Reference		Reference		Reference	
Q2 (1.20–1.59)	2,717	12,826.90	589	45.9	1.28	1.13, 1.44	1.06	0.94, 1.21	1.03	0.86, 1.23
Q3 (1.60–2.13)	2,670	12,644.70	658	52.0	1.45	1.29, 1.64	1.09	0.96, 1.24	1.11	0.93, 1.32
Q4 (≥2.14)	2,694	12,304.30	766	62.2	1.78	1.59, 2.00	1.13	0.98, 1.29	1.22	1.01, 1.47
P-trend					<0.001		0.09		0.01	
High-sensitivity C-reactive protein, mg/L										
Q1 (<0.4)	3,749	18,165.80	735	40.5	Reference		Reference		Reference	
Q2 (0.4–0.5)	1,837	8,681.10	444	51.1	1.26	1.12, 1.41	1.05	0.93, 1.18	1.10	0.96, 1.28
Q3 (0.6–1.0)	2,263	10,720.10	539	50.3	1.24	1.11, 1.38	0.97	0.87, 1.09	1.08	0.94, 1.24
Q4 (≥1.1)	2,377	10,999.60	643	58.4	1.44	1.29, 1.60	1.14	1.02, 1.28	1.22	1.08, 1.39
P-trend					<0.001		0.07		0.004	
Estimated glomerular filtration rate, mL/minute/1.73 m^2										
Q1 (<73.0)	2,710	12,397.00	705	56.9	Reference		Reference		Reference	
Q2 (73.0–79.1)	2,708	12,465.00	624	50.1	0.88	0.79, 0.98	0.92	0.82, 1.03	0.89	0.78, 1.01
Q3 (79.2–85.3)	2,685	13,289.00	642	48.3	0.88	0.79, 0.99	0.95	0.84, 1.07	0.84	0.73, 0.98
Q4 (≥85.4)	2,699	13,059.60	525	40.2	0.72	0.64, 0.80	0.79	0.70, 0.89	0.73	0.63, 0.84
P-trend					<0.001		<0.001		<0.001	

Table continues

of glycosuria (24, 25), and low serum uric acid concentrations have been identified as a marker of poor diabetes control. In our study, participants with impaired fasting glucose levels (fasting serum glucose concentrations 100–126 mg/dL) had a modestly but statistically significantly reduced incidence of hyperuricemia. In contrast to our findings, in a cohort of male civil servants, Herman and Goldbourt (23) found that the prevalence of hyperuricemia was 74% higher in participants who later developed diabetes (prediabetes) compared with normal participants. Consistent with our study, the prevalence of hyperuricemia was substantially reduced in participants with type 2 diabetes. Further characterization of serum uric acid levels in the prediabetes and early diabetes stages is warranted.

Alcohol intake, blood pressure, and eGFR—3 well-established determinants of serum uric acid levels—were also significant predictors of incident hyperuricemia in our study. The relation between alcohol intake and hyperuricemia has been noted since the early descriptions of gout in the literature (16, 26). Alcohol intake increases uric acid production (27, 28) by increasing the degradation of adenosine triphosphate to the uric acid precursor adenosine diphosphate (27), and it decreases urate excretion (29) via conversion of ethanol to lactic acid and competitive inhibition of uric acid secretion by the proximal tubule (20). In our study, we found a clear dose-response trend of increasing incidence of hyperuricemia with increasing alcohol intake. Given the high frequency of social drinking among male South Korean workers, moderation of alcohol intake may be an important strategy for controlling the risk of hyperuricemia in this population.

While hypertension and hyperuricemia are clearly associated (9, 30, 31), the direction of the causal effects has been long debated, and it is still unclear whether the increased

Table 4. Continued

	No. of Subjects	Person-Years of Follow-up	No. of Cases	Incidence Rate (per 1,000 Person-Years)	Age-Adjusted HR	95% CI	Multivariable-Adjusted[a]			
							Model Using Baseline Data		Model Using Time-varying Covariates	
							HR	95% CI	HR	95% CI
Total cholesterol, mg/dL										
Q1 (<177.0)	2,755	13,388.00	568	42.4	Reference		Reference		Reference	
Q2 (177.0–199.0)	2,709	12,887.30	602	46.7	1.09	0.97, 1.23	0.93	0.82, 1.05	0.87	0.76, 1.01
Q3 (200.0–223.0)	2,741	12,948.90	657	50.7	1.19	1.06, 1.33	0.93	0.82, 1.05	0.94	0.81, 1.08
Q4 (≥224.0)	2,597	11,986.40	669	55.8	1.29	1.16, 1.45	0.95	0.83, 1.08	0.90	0.77, 1.06
P-trend					<0.001		0.52		0.36	
Low density lipoprotein cholesterol, mg/dL										
Q1 (<99.6)	2,704	12,925.70	570	44.1	Reference		Reference		Reference	
Q2 (99.6–118.3)	2,703	12,926.30	621	48.0	1.09	0.97, 1.22	0.99	0.88, 1.11	0.98	0.86, 1.13
Q3 (118.4–138.0)	2,705	12,788.60	624	48.8	1.10	0.98, 1.24	0.97	0.86, 1.09	1.00	0.87, 1.15
Q4 (≥138.1)	2,690	12,569.90	681	54.2	1.22	1.09, 1.36	1.01	0.89, 1.14	0.99	0.86, 1.14
P-trend					0.001		0.94		0.96	
Triglycerides, mg/dL										
Q1 (<92.0)	2,792	14,021.50	440	31.4	Reference		Reference		Reference	
Q2 (92.0–125.0)	2,627	12,617.70	587	46.5	1.47	1.30, 1.67	1.31	1.15, 1.49	1.34	1.14, 1.57
Q3 (126.0–178.0)	2,713	12,764.40	667	52.2	1.65	1.46, 1.87	1.30	1.13, 1.48	1.52	1.29, 1.79
Q4 (≥179.0)	2,670	11,806.90	802	67.9	2.13	1.90, 2.40	1.47	1.27, 1.71	1.70	1.43, 2.02
P-trend					<0.001		<0.001		<0.001	
High density lipoprotein cholesterol, mg/dL										
Q1 (<44.1)	2,732	12,467.70	753	60.4	Reference		Reference		Reference	
Q2 (44.1–51.0)	2,844	13,324.20	695	52.1	0.87	0.78, 0.96	0.94	0.85, 1.05	1.01	0.89, 1.14
Q3 (51.1–59.0)	2,663	12,920.30	574	44.4	0.74	0.66, 0.83	0.87	0.77, 0.98	0.95	0.82, 1.09
Q4 (≥59.1)	2,563	12,498.40	474	37.9	0.63	0.56, 0.71	0.83	0.72, 0.95	0.94	0.80, 1.11
P-trend					<0.001		0.003		0.35	
Metabolic syndrome										
No	9,537	47,573.35	2,115	44.5	Reference		Reference		Reference	
Yes	1,264	5,792.49	381	65.8	1.47	1.32, 1.64	1.41	1.26, 1.58	1.57	1.38, 1.79
P value					<0.001		<0.001		<0.001	

Abbreviations: CI, confidence interval; HOMA-IR, homeostasis model assessment of insulin resistance; HR, hazard ratio; Q, quartile.

[a] Adjusted for age, alcohol intake, body mass index, gamma-glutamyltransferase, fatty liver, and all other variables in the table except low density lipoprotein cholesterol, HOMA-IR, and metabolic syndrome. The results for low density lipoprotein cholesterol were adjusted for the same set of variables, except total cholesterol. The results for HOMA-IR were obtained within nondiabetics and were adjusted for the same set of variables, except fasting glucose. The results for metabolic syndrome were adjusted for age, alcohol intake, and exercise only.

risk of hyperuricemia in hypertensive persons with normal renal function is just a reflection of obesity and alcohol intake. Furthermore, some antihypertensive medications may increase serum uric acid concentrations. However, increased renal and systemic vascular resistance leading to reduced renal flow in patients with hypertension may contribute to increasing serum uric acid levels. In addition, renal urate excretion seems inappropriately low relative to glomerular filtration rate in patients with essential hypertension (32). In our study, participants with hypertension had a higher incidence of hyperuricemia even after adjustment for body mass index, eGFR, and other potential confounders, but participants with prehypertension were not at increased risk of hyperuricemia. These findings are in agreement with those from the longitudinal study of Japanese male office workers (6). Further research is needed to better characterize the role of hypertension in the development of hyperuricemia and the impact of hypertension control on serum uric acid levels.

Since uric acid is predominantly cleared by the kidneys, a decline in glomerular filtration rate from any cause is associated with increased serum uric acid concentrations (33). As expected, reduced eGFR was associated with a higher incidence of hyperuricemia in our study, and this association was observed throughout the whole range of glomerular filtration rates. Our study population was predominantly young and had a low prevalence of kidney dysfunction. Since

Table 5. Hazard Ratios for Incident Hyperuricemia According to Liver Function and the Presence of Fatty Liver, South Korea, 2002–2009

	No. of Subjects	Person-Years of Follow-up	No. of Cases	Incidence Rate (per 1,000 Person-Years)	Age-Adjusted HR	95% CI	Multivariable-Adjusted[a]			
							Model Using Baseline Data		Model Using Time-varying Covariates	
							HR	95% CI	HR	95% CI
Alanine aminotransferase, units/L										
Q1 (<20.0)	3,126	15,528.90	551	35.5	Reference		Reference		Reference	
Q2 (20.0–25.0)	2,382	11,284.50	533	47.2	1.32	1.17, 1.49	1.09	0.96, 1.25	1.04	0.88, 1.23
Q3 (26.0–37.0)	2,710	12,604.90	702	55.7	1.55	1.39, 1.74	1.06	0.92, 1.23	1.02	0.84, 1.23
Q4 (≥38.0)	2,584	11,792.30	710	60.2	1.68	1.50, 1.88	0.92	0.76, 1.11	1.04	0.82, 1.32
P-trend					<0.001		0.51		0.80	
Aspartate aminotransferase, units/L										
Q1 (<21.0)	3,049	14,938.60	618	41.3	Reference		Reference		Reference	
Q2 (21.0–23.0)	2,419	11,689.70	522	44.7	1.08	0.96, 1.21	0.93	0.82, 1.05	0.98	0.83, 1.15
Q3 (24.0–28.0)	2,884	13,439.90	694	51.6	1.23	1.11, 1.37	0.98	0.86, 1.12	1.00	0.85, 1.19
Q4 (≥29.0)	2,450	11,142.40	662	59.4	1.42	1.27, 1.58	1.04	0.88, 1.22	0.92	0.75, 1.12
P-trend					<0.001		0.62		0.51	
Gamma-glutamyltransferase, units/L										
Q1 (<19.0)	3,083	15,469.70	498	32.2	Reference		Reference		Reference	
Q2 (19.0–25.0)	2,496	11,980.00	550	46.2	1.43	1.27, 1.62	1.24	1.09, 1.41	1.34	1.13, 1.59
Q3 (26.0–39.0)	2,565	11,784.80	690	58.6	1.81	1.61, 2.03	1.41	1.23, 1.61	1.44	1.20, 1.72
Q4 (≥40.0)	2,658	11,976.10	754	62.9	1.93	1.72, 2.17	1.40	1.20, 1.63	1.48	1.21, 1.79
P-trend					<0.001		<0.001		<0.001	
Fatty liver										
No	7,794	37,703.50	1,616	42.9	Reference		Reference		Reference	
Yes	3,008	13,507.00	880	65.1	1.50	1.38, 1.63	1.13	1.02, 1.25	1.19	1.05, 1.35
P value					<0.001		0.02		0.01	

Abbreviations: CI, confidence interval; HR, hazard ratio; Q, quartile.

[a] Adjusted for age, alcohol intake, body mass index, blood pressure, fasting glucose, high-sensitivity C-reactive protein, estimated glomerular filtration rate, triglycerides, total cholesterol, high density lipoprotein cholesterol, and all other variables in the table.

creatinine-based formulae for estimating glomerular filtration rate are less accurate in people with normal renal function, our analyses may underestimate the role of kidney function in predicting hyperuricemia.

Our study also provides novel prospective data on the association of hsCRP, GGT, and fatty liver with hyperuricemia. While these associations have been observed in cross-sectional studies (34–36), no prospective studies have examined these associations before, to our knowledge. An increased serum GGT concentration is conventionally interpreted as a marker of alcohol abuse or clinical liver disease (37). Recently, serum GGT has also been proposed as a marker of oxidative stress (38), and higher uric acid levels in subjects with increased GGT levels may be a compensatory response to increased oxidative stress (39). Similarly, whether serum uric acid is a marker of a proinflammatory state or causes inflammation per se remains uncertain, although in our data, increased hsCRP levels were associated with the future incidence of hyperuricemia. Indeed, inflammatory cytokines may increase uric acid production by increasing xanthine oxidase activity (40). Finally, fatty liver was also associated with increased incidence of hyperuricemia, although the mechanisms underlying this association are unclear. Further study on the role of fatty liver in the development of hyperuricemia is needed.

Several limitations need to be considered when interpreting our findings. First, we did not have information on some important determinants of serum uric acid levels, including dietary habits. Dietary factors that contribute to hyperuricemia include the consumption of purine-rich foods, such as red meat or seafood (41), and fructose, which accelerates the catabolism of adenine nucleotides (42). In addition, information on medication use in study participants was limited. Data on dietary habits and medication use should be included in future studies that characterize hyperuricemia onset. Second, we excluded 10.6% of study participants who did not have any follow-up data. Participants without follow-up data were more likely to be alcohol drinkers and to have diabetes at baseline than participants included in the analytic cohort. Since diabetes and alcohol intake have opposite associations with incident hyperuricemia, the overall impact of these exclusions on the estimated incidence of hyperuricemia is likely to have been small. Finally, our study population was comprised of healthy,

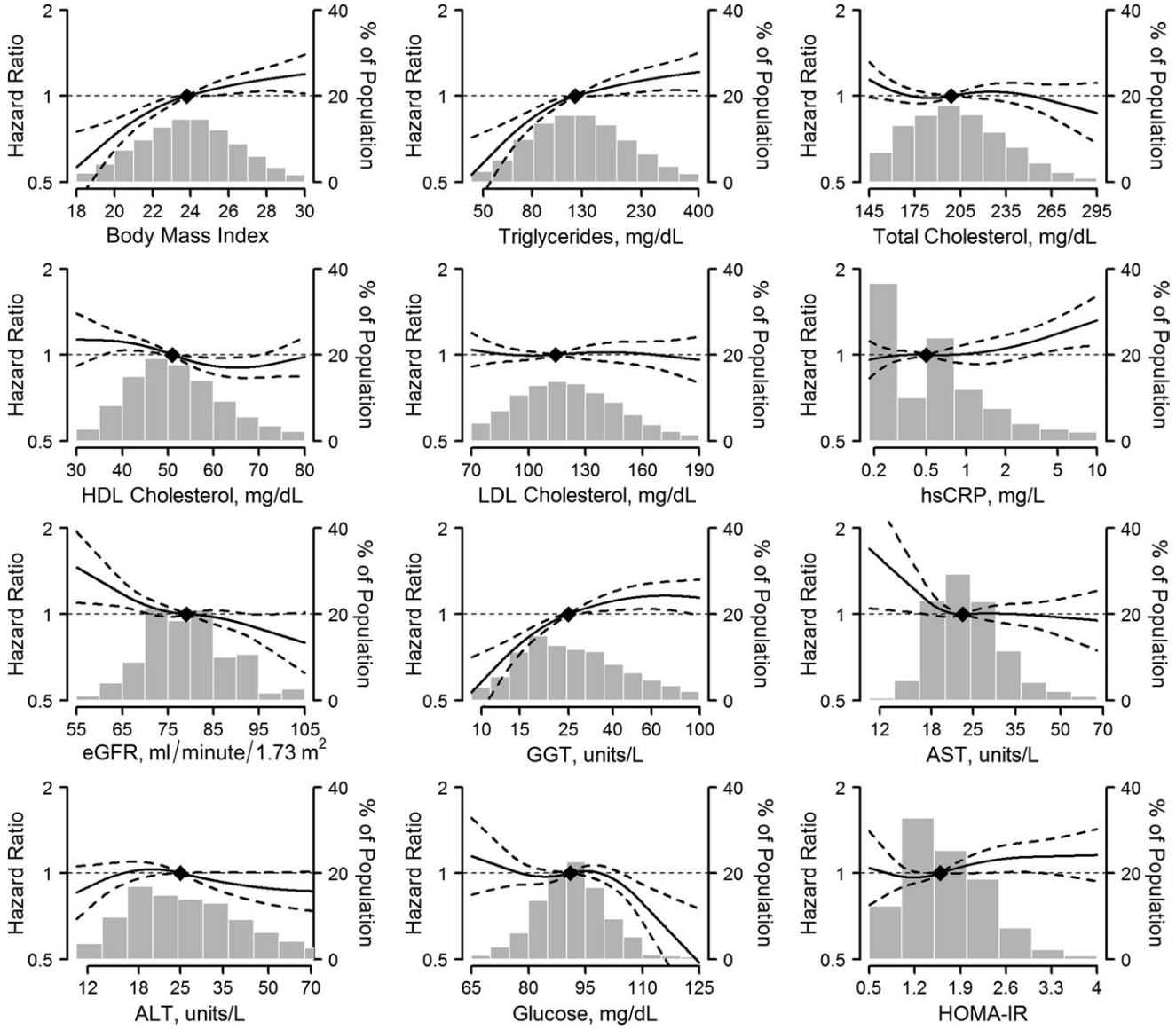

Figure 1. Hazard ratios for the relation between metabolic risk factors and incident hyperuricemia, South Korea, 2002–2009. Dose-response models were fitted using quadratic splines with knots at the 5th, 50th, and 95th percentiles of the distribution of each determinant in Cox proportional hazards models. The plots for glucose and homeostasis model assessment of insulin resistance (HOMA-IR) show data for nondiabetics only. All models in the figure, except that for HOMA-IR, included adjustment for age, body mass index (weight (kg)/height (m)^2), alcohol intake, blood pressure, fasting glucose, estimated glomerular filtration rate (eGFR), high-sensitivity C-reactive protein (hsCRP), total cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, gamma-glutamyltransferase (GGT), and fatty liver. The model for HOMA-IR was adjusted for the same set of variables, except fasting glucose. Dashed lines, 95% confidence interval. (ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDL, low density lipoprotein).

middle-aged South Korean males, which may limit the generalization of the findings to non-Korean populations and/or females.

In conclusion, we observed a very high incidence of hyperuricemia among apparently healthy male workers in South Korea. Among a variety of candidate risk predictors, adiposity-related factors, alcohol intake, blood pressure, low eGFR, elevated hsCRP, elevated GGT, and fatty liver were all independent risk factors for asymptomatic hyperuricemia. The impact of adiposity-related factors is of particular concern, since they are both highly prevalent and strongly associated with incident hyperuricemia. Furthermore, decreasing levels of serum uric acid in overweight or obese subjects may point to an impending risk of diabetes. As a consequence, serum uric acid levels may be added to the list of factors to monitor in overweight or obese participants, and this is an additional reason to achieve and maintain a healthy body weight and control of cardiometabolic risk factors.

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