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Original Article

Regional variations of cardiovascular risk in gout patients: a nationwide cohort study in Korea

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Objective: The extent of regional variations in cardiovascular risk and associated risk factors in patients with gout in South Korea remains unclear. Therefore, we aimed to investigate the risk of major cardiovascular events in gout patients in different regions.
Methods: This was a nationwide cohort study based on the claims database of the Korean National Health Insurance and the National Health Screening Program. Patients aged 20 to 90 years newly diagnosed with gout after January 2012 were included. After cardiovascular risk profiles before gout diagnosis were adjusted, the relative risks of incident cardiovascular events (myocardial infarction, cerebral infarction, and cerebral hemorrhage) in gout patients in different regions were assessed.
Results: In total, 231,668 patients with gout were studied. Regional differences in cardiovascular risk profiles before the diagnosis were observed. Multivariable analysis showed that patients with gout in Jeolla/Gwangju had a significantly high risk of myocardial infarction (adjusted hazard ratio [aHR], 1.27; 95% confidence interval [CI], 1.02~1.56; p=0.03). In addition, patients with gout in Gangwon (aHR, 1.38; 95% CI, 1.09~1.74; p<0.01), Jeolla/Gwangju (aHR, 1.41; 95% CI, 1.19~1.67; p<0.01), and Gyeongsang/Busan/Daegu/Ulsan (aHR, 1.37; 95% CI, 1.19~1.59; p<0.01) had a significantly high risk of cerebral infarction.
Conclusion: We found there were regional differences in cardiovascular risk and associated risk factors in gout patients. Physicians should screen gout patients for cardiovascular risk profiles in order to facilitate prompt diagnosis and treatment.

Keywords: Regional medical programs, Gout, Cardiovascular diseases

INTRODUCTION

Gout is a common inflammatory arthropathy characterized by chronic hyperuricemia and urate crystal deposition in the joints. While the primary complaints of gout are severe inflammation and joint pain, gout is also closely associated with systemic disorders and cardiovascular (CV) risk profiles, such as hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, alcohol consumption, and obesity [1,2]. In addition, gout has been suggested as a cause of CV diseases via pathogenic mechanisms such as endothelial dysfunction, oxidative metabolism, platelet adhesiveness, and aggregation [3-11]. Accordingly, several epidemiological studies reported that patients with gout had an increased risk for CV events [7-9,12].

Several epidemiological studies investigating the association between gout and CV diseases have been conducted in developed countries, but few studies have been conducted in Korea. Especially, a previous study based on data from the National Health Insurance Service reported that the prevalence of gout increased 2.32-fold from 2001 to 2008 (0.40%), showing a rapid increase in a short period. Given the high association between gout and CV diseases, it is important to investigate the risk fac-

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tors for CV diseases in gout patients due to the growing incidence of gout.

In particular, differences in population characteristics between urban regions and other regions are getting more significant owing to recent rapid industrialization. Accordingly, a survey on regional differences should be conducted; however, there are still few studies on it. Therefore, we aimed to investigate the risk of major CV events, including myocardial infarction, cerebral infarction, and cerebral hemorrhage, in gout patients in different regions using the claims database of the Korean National Health Insurance (NHI) [13].

MATERIALS AND METHODS

Data source

We searched the NHI and the National Health Screening Program (NHSP) databases to obtain information on CV risk profiles and lifestyle factors. The NHI is a government-operated service that provides mandatory insurance to the entire population of more than 50 million people in South Korea and includes data on the use of both inpatient and outpatient healthcare that each medical facility must submit for the purpose of reimbursement.

The NHSP is a screening program through which all insured persons and their dependents are offered cancer screening and biannual health checkups, with the results being recorded in the database thereafter. For the NHSP checkup, each participant must fill out a standardized questionnaire related to their medical and lifestyle habits, including smoking and physical activity. Anthropometric measurements, including blood pressure and body mass index (BMI), are also taken during the checkup, as well as basic tests such as liver enzymes, hepatitis virus status, lipid parameters, chest radiograph, fasting blood sugar (FBS), and creatine.

Study population (gout cohort)

Patients diagnosed with gout between January 2012 and August 2019 were included in this study. Gout patients were defined as those who were assigned with the International Classification of Diseases (ICD) code M10, received a prescription for allopurinol or febuxostat, and visited a clinic more than once in the following year. A 10-year washout period was applied to exclusively select newly diagnosed cases. The exclusion criteria were as follows: (1) unclear cause of death; (2) prescription of allopurinol or febuxostat before 2012; (3) prescription of both allopurinol and febuxostat; (4) known malignancy; (5) prescription of benzbromarone; (6) history of myocardial infarction, cerebral infarction, or cerebral hemorrhage; (7) younger than 20 years or older than 90 years; and (8) failure to participate in the national health screening. This study divided Korea into seven regions, including Seoul, Gyeonggi/Incheon, Gangwon, Chungcheong/Daejeon/Sejong, Jeolla/Gwangju, Gyeongsang/Busan/Daegu, and Jeju, and investigated patients with gout in each of the seven regions.

Verification of the diagnosis

To identify patients with gout using the diagnosis code, we developed several case algorithms based on the frequencies of clinic visits and dosing of allopurinol or febuxostat taken with gout as the principal diagnosis. Although the medical charts of gout patients were only reviewed at Jeju National University Hospital, this allowed us to evaluate the diagnostic accuracy of our algorithm for identifying clinically significant patients with gout. Moreover, to reduce misclassification bias, we also reviewed medical records of control individuals with ambiguous gout status, including those with ICD10 codes for asymptomatic hyperuricemia (E790), pseudogout (M118), septic arthritis (M861, M009), and cellulitis (L039, L0311). These reviews were performed by an experienced rheumatologist. For each combination of algorithms, we determined the diagnostic accuracy, including sensitivity (96.4%) and specificity (98.5%).

Study outcomes

The primary outcome was the first occurrence of a CV event after first gout diagnosis, including myocardial infarction, cerebral infarction, and cerebral hemorrhage, which were defined as inpatient hospitalization with ICD-10 codes I21, I63, and I61-62, respectively [14,15].

Categorization of CV risk profiles

From the NHSP database, we acquired data on confounders, including demographic information (age and sex), ICD-10 code, anthropometric information (height, weight, and BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), FBS, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglyceride, and lifestyle factors (physical activity, alcohol consumption, and smoking status).

Table 1. Baseline characteristics of study populations

	Total (n)	Seoul	Gyeonggi/ Incheon	Gangwon	Chungcheong/ Daejeon/ Sejong	Jeolla/ Gwangju	Gyeongsang/ Busan/Daegu/ Ulsan	Jeju	Unknown
Total	231,168	37,136 (100)	63,803 (100)	8,515 (100)	23,285 (100)	26,971 (100)	67,795 (100)	3,583 (100)	80 (100)
Sex (Male)	192,682	31,453 (84.7)	53,762 (84.3)	6,915 (81.2)	19,343 (83.1)	21,847 (81.0)	56,446 (83.3)	2,853 (79.6)	63 (78.8)
Age									
20~29	7,670	1,055 (2.8)	2,203 (3.5)	339 (4.0)	944 (4.1)	729 (2.7)	2,296 (3.4)	103 (2.9)	1 (1.3)
30~39	36,974	6,382 (17.2)	11,582 (18.2)	1,050 (12.3)	3,922 (16.8)	3,366 (12.5)	10,208 (15.1)	459 (12.8)	5 (6.3)
40~49	53,090	8,549 (23.0)	16,364 (25.7)	1,746 (20.5)	5,225 (22.4)	5,713 (21.2)	14,613 (21.6)	864 (24.1)	16 (20.0)
50~59	57,408	8,943 (24.1)	15,929 (25.0)	2,171 (25.5)	5,693 (24.5)	6,843 (25.4)	16,928 (25.0)	878 (24.5)	23 (28.8)
60~69	43,066	7,150 (19.3)	10,326 (16.2)	1,637 (19.2)	4,133 (17.8)	5,467 (20.3)	13,677 (20.2)	658 (18.4)	18 (22.5)
70~79	26,230	4,109 (11.1)	5,936 (9.3)	1,201 (14.1)	2,584 (11.1)	3,812 (14.1)	8,085 (11.9)	490 (13.7)	13 (16.3)
80~89	6,730	948 (2.6)	1,463 (2.3)	371 (4.4)	784 (3.4)	1,041 (3.9)	1,988 (2.9)	131 (3.7)	4 (5.0)
Body mass index (BMI) (kg/m^2)									
<18.5	2,434	353 (1.0)	600 (0.9)	77 (0.9)	272 (1.2)	361 (1.3)	744 (1.1)	27 (0.8)	0 (0.0)
18.5≤BMI<23.0	44,791	6,746 (18.2)	11,702 (18.3)	1,540 (18.1)	4,566 (19.6)	5,439 (20.2)	14,184 (20.9)	590 (16.5)	24 (30.0)
23≤BMI<25	53,454	8,608 (23.2)	14,244 (22.3)	1,936 (22.7)	5,224 (22.4)	6,336 (23.5)	16,374 (24.2)	715 (20.0)	17 (21.3)
≥25	130,489	21,429 (57.7)	37,257 (58.4)	4,962 (58.3)	13,223 (56.8)	14,835 (55.0)	36,493 (53.8)	2,251 (62.8)	39 (48.8)
Blood pressure categories by the American Heart Association (mmHg)									
SBP<120 & DBP<80	54,007	8,120 (21.9)	14,413 (22.6)	1,764 (20.7)	5,074 (21.8)	6,560 (24.3)	17,360 (25.6)	703 (19.6)	13 (16.3)
120≤SBP<130 or DBP <80	26,927	4,815 (13.0)	7,498 (11.8)	979 (11.5)	2,390 (10.3)	2,798 (10.4)	8,100 (12.0)	336 (9.4)	11 (13.8)
130≤SBP<140 or 80≤DBP<90	96,495	14,670 (39.5)	26,637 (41.8)	3,419 (40.2)	10,124 (43.5)	11,694 (43.4)	28,379 (41.9)	1,540 (43.0)	32 (40.0)
140≤SBP<180 or 90≤DBP<120	52,064	9,250 (24.9)	14,748 (23.1)	2,273 (26.7)	5,501 (23.6)	5,745 (21.3)	13,544 (20.0)	980 (27.4)	23 (28.8)
180≤SBP or 120≤DBP	1,664	280 (0.8)	503 (0.8)	79 (0.9)	195 (0.8)	173 (0.6)	409 (0.6)	24 (0.7)	1 (1.3)
Missing	11	1 (0.0)	4 (0.0)	1 (0.0)	1 (0.0)	1 (0.0)	3 (0.0)	0 (0.0)	0 (0.0)
Pulse pressure (PP) (mmHg)									
<40	29,080	5,294 (14.3)	8,864 (13.9)	946 (11.1)	3,106 (13.3)	3,349 (12.4)	6,977 (10.3)	532 (14.9)	12 (15.0)
40≤PP<60	167,543	26,111 (70.3)	45,896 (71.9)	6,002 (70.5)	16,762 (72.0)	19,543 (72.5)	50,706 (74.8)	2,475 (69.1)	48 (60.0)
≥60	34,534	5,730 (15.4)	9,039 (14.2)	1,566 (18.4)	3,416 (14.7)	4,078 (15.1)	10,109 (14.9)	576 (16.1)	20 (25.0)
Missing	11	1 (0.0)	4 (0.0)	1 (0.0)	1 (0.0)	1 (0.0)	3 (0.0)	0 (0.0)	0 (0.0)

Table 1. Continued 1

	Total (n)	Seoul	Gyeonggi/ Incheon	Gangwon	Chungcheong/ Daejeon/ Sejong	Jeolla/ Gwangju	Gyeongsang/ Busan/ Daegu/Ulsan	Jeju	Unknown
Fasting blood sugar (FBS) (mg/dL)									
<100	176,137	28,490 (76.7)	49,199 (77.1)	6,373 (74.8)	17,832 (76.6)	19,577 (72.6)	51,912 (76.6)	2,702 (75.4)	52 (65.0)
100≤FBS<126	32,565	5,096 (13.7)	8,735 (13.7)	1,229 (14.4)	3,230 (13.9)	4,320 (16.0)	9,400 (13.9)	544 (15.2)	11 (13.8)
126≤FBS	22,441	3,542 (9.5)	5,866 (9.2)	910 (10.7)	2,218 (9.5)	3,072 (11.4)	6,481 (9.6)	335 (9.4)	17 (21.3)
Missing	25	8 (0.0)	3 (0.0)	3 (0.0)	5 (0.0)	2 (0.0)	2 (0.0)	2 (0.1)	0 (0.0)
Protein in urine analysis									
≤1+	214,555	34,122 (91.9)	59,223 (92.8)	7,935 (93.2)	21,619 (92.9)	25,184 (93.4)	63,115 (93.1)	3,286 (91.71)	71 (88.8)
≥2+	15,123	2,794 (7.5)	4,214 (6.6)	529 (6.2)	1,460 (6.3)	1,571 (5.8)	4,279 (6.3)	268 (7.48)	8 (10.0)
Missing	1,490	220 (0.6)	366 (0.6)	51 (0.6)	206 (0.9)	216 (0.8)	401 (0.6)	29 (0.81)	1 (1.3)
Total cholesterol (mg/dL)									
Total cholesterol<200	119,095	19,067 (51.3)	32,279 (50.6)	4,728 (55.5)	12,409 (53.3)	14,119 (52.4)	34,703 (51.2)	1,738 (48.5)	52 (65.0)
200≤total cholesterol<240	75,247	12,197 (32.8)	21,236 (33.3)	2,579 (30.3)	7,249 (31.1)	8,392 (31.1)	22,322 (32.9)	1,253 (35.0)	19 (23.8)
≥240	36,801	5,864 (15.8)	10,285 (16.1)	1,205 (14.2)	3,622 (15.56)	4,458 (16.5)	10,768 (15.9)	590 (16.5)	9 (11.3)
Missing	25	8 (0.0)	3 (0.0)	3 (0.0)	5 (0.0)	2 (0.0)	2 (0.0)	2 (0.1)	0 (0.0)
High-density lipoprotein (HDL) cholesterol (mg/dL)									
HDL<40	41,594	6,485 (17.5)	11,740 (18.4)	1,603 (18.8)	4,081 (17.5)	5,272 (19.6)	11,742 (17.3)	656 (18.3)	15 (18.3)
40≤HDL	189,547	30,643 (82.5)	52,060 (81.6)	6,908 (81.1)	19,199 (82.5)	21,696 (80.4)	56,051 (82.7)	2,925 (81.6)	65 (81.3)
Missing	27	8 (0.0)	3 (0.0)	4 (0.1)	5 (0.0)	3 (0.0)	2 (0.0)	2 (0.1)	0 (0.0)
Low-density lipoprotein (LDL) cholesterol (mg/dL)									
LDL<100	80,692	13,166 (35.5)	22,275 (34.9)	3,242 (38.1)	8,582 (36.9)	9,530 (35.3)	22,774 (33.6)	1,089 (30.4)	34 (42.5)
100≤LDL<130	73,974	11,920 (32.1)	20,499 (32.1)	2,716 (31.9)	7,433 (31.9)	8,399 (31.1)	21,828 (32.2)	1,151 (32.1)	28 (35.0)
130≤LDL<160	49,130	7,868 (21.2)	13,591 (21.3)	1,673 (19.7)	4,677 (20.1)	5,576 (20.7)	14,858 (21.9)	875 (24.4)	12 (15.0)
160≤LDL<190	18,318	2,832 (7.6)	4,940 (7.7)	587 (6.9)	1,695 (7.3)	2,273 (8.4)	5,678 (8.4)	309 (8.6)	4 (5.0)
≥190	6,098	879 (2.4)	1,655 (2.6)	199 (2.3)	573 (2.5)	824 (3.1)	1,858 (2.7)	108 (3.0)	2 (2.5)
Missing	2,956	471 (1.3)	843 (1.3)	98 (1.2)	325 (1.4)	369 (1.4)	799 (1.2)	51 (1.4)	0 (0.0)
Triglyceride (TG) (mg/dL)									
TG<150	113,930	18,259 (49.2)	29,991 (47.0)	4,243 (49.8)	11,081 (47.6)	13,475 (50.0)	34,859 (51.4)	1,978 (55.2)	44 (55.0)
150≤TG<200	42,762	6,934 (18.7)	11,971 (18.8)	1,657 (19.5)	4,353 (18.7)	4,928 (18.3)	12,338 (18.2)	569 (15.9)	12 (15.0)
200≤TG<500	66,707	10,714 (28.9)	19,490 (30.6)	2,350 (27.6)	7,002 (30.1)	7,641 (28.3)	18,567 (27.4)	925 (25.8)	18 (22.5)
≥500	7,743	1,221 (3.3)	2,348 (3.7)	262 (3.1)	844 (3.6)	924 (3.4)	2,029 (3.0)	109 (3.0)	6 (7.5)
Missing	26	8 (0.0)	3 (0.0)	3 (0.0)	5 (0.0)	3 (0.0)	2 (0.0)	2 (0.1)	0 (0.0)

Table 1. Continued 2

	Total (n)	Seoul	Gyeonggi/ Incheon	Gangwon	Chungcheong/ Daejeon/ Sejong	Jeolla/ Gwangju	Gyeongsang/ Busan/Daegu/ Ulsan	Jeju	Unknown
Physical activity									
No	100,729	14,743 (39.7)	26,877 (42.1)	4,023 (47.3)	10,802 (46.4)	12,574 (46.6)	29,934 (44.2)	1,744 (48.7)	32 (40.0)
1~4 day/week	110,661	19,115 (51.5)	31,905 (50.0)	3,706 (43.5)	10,615 (45.6)	12,201 (45.2)	31,484 (46.4)	1,594 (44.5)	41 (51.3)
5~7 day/week	19,677	3,251 (8.8)	4,973 (7.8)	782 (9.2)	1,861 (8.0)	2,193 (8.1)	6,366 (9.4)	244 (6.8)	7 (8.8)
Missing	101	27 (0.1)	48 (0.1)	4 (0.1)	7 (0.0)	3 (0.01)	11 (0.0)	1 (0.0)	0 (0.0)
Smoking									
Non-smoker	91,443	14,024 (37.8)	23,399 (36.7)	3,651 (42.9)	9,399 (40.4)	12,628 (46.8)	26,798 (39.5)	1,502 (41.9)	42 (52.5)
Ever smoker	64,123	11,297 (30.4)	18,163 (28.5)	2,142 (25.2)	6,386 (27.4)	6,507 (24.1)	18,690 (27.6)	915 (25.5)	23 (28.8)
Current smoker	75,516	11,789 (31.8)	22,205 (34.8)	2,718 (31.9)	7,492 (32.2)	7,835 (29.1)	22,298 (32.9)	1,165 (32.5)	14 (17.5)
Missing	86	26 (0.1)	36 (0.1)	4 (0.1)	8 (0.0)	1 (0.0)	9 (0.0)	1 (0.0)	1 (1.3)
Drinking/week									
None	83,604	12,186 (32.8)	21,327 (33.4)	3,274 (38.5)	8,604 (37.0)	11,374 (42.2)	25,471 (37.6)	1,334 (37.2)	34 (42.5)
1/week	69,585	12,141 (32.7)	20,192 (31.7)	2,424 (28.5)	6,803 (29.2)	7,254 (26.9)	19,780 (29.2)	969 (27.0)	22 (27.5)
2 or more/week	77,746	12,739 (34.3)	22,185 (34.8)	2,810 (33.0)	7,862 (33.8)	8,334 (30.9)	22,517 (33.2)	1,276 (35.6)	23 (28.8)
Missing	233	70 (0.2)	99 (0.7)	7 (0.1)	16 (0.1)	9 (0.0)	27 (0.0)	4 (0.1)	1 (1.3)

Values are presented as number (%).
SBP: systolic blood pressure, DBP: diastolic blood pressure.

Statistical analysis

All variables were categorized and presented as frequencies and percentages. Chi-squared test was used to compare the standardized differences in categorical variables between the two cohorts. Follow-up started on the index date and patients were censored on the date of outcome occurrence, death, or last follow-up. Crude incidence rates (IRs) for myocardial infarction, cerebral infarction, and cerebral hemorrhage were separately calculated as the number of CV events per 10,000 person-days. Kaplan-Meier curves were used to describe the cumulative incidence of each cardio-cerebrovascular event between the two cohorts. The Cox-proportional hazard model was used to examine the independent association of gout with the risk of CV events, and the results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). The independent variables were gout and the following confounding risk factors that were chosen based on existing studies and their known association with CV events: blood pressure categories suggested by the American Heart Association, pulse pressure, BMI, FBS, cholesterol, positive urine dipstick results for proteinuria, smoking, and drinking before the diagnosis of gout. Multivariable adjustments for SBP, DBP, pulse pressure, BMI, FBS, lipid profiles, smoking/drinking status, and proteinuria were conducted.

p-values ≤0.05 were considered as indicating statistical significance and all statistical tests were two-sided. Stata version 15.0 (Stata Corp., College Station, TX, USA) was used for all statistical analyses. Personal details were protected, and all data were anonymized. This study was approved by the Institutional Review Board of Jeju National University Hospital (2018-12-003).

RESULTS

Characteristics and CV risk profiles of the study population

The study population comprised 231,668 individuals in the gout cohort. The baseline characteristics of the gout cohorts are summarized in Table 1. In the gout cohort, 192,682 (83.4%) were male, and the peak age at the incidence of gout was between 50 and 59 years (24.8%).

Among all regions, the proportions of older adult patients with gout aged ≥60 years were highest in Jeolla/Gwangju (38.3%) and Gangwon (37.7%). In contrast, the proportion of older adult patients was lowest in Gyeonggi/Incheon (27.8%).

Table 2. Incidence of myocardial infarction, cerebral infarction, and cerebral hemorrhage per 10,000 person-years in patients with gout according to region in Korea

	Seoul			Gyeonggi/Incheon			Gangwon			Chungcheong/Daejeon/Sejong			Jeolla/Gwangju			Gyeongsang/Busan/Daegu/Ulsan			Jeju		
	Person-time	Failures	Rate (95% CI)	Person-time	Failures	Rate (95% CI)	Person-time	Failures	Rate (95% CI)	Person-time	Failures	Rate (95% CI)	Person-time	Failures	Rate (95% CI)	Person-time	Failures	Rate (95% CI)	Person-time	Failures	Rate (95% CI)
Myocardial infarction	128,250	171	13.3 (11.5~15.5)	214,802	293	13.6 (12.2~15.3)	28,550	48	16.8 (12.7~22.31)	79,810	111	13.9 (11.6~16.8)	92,239	178	19.3 (16.7~22.4)	228,274	362	15.9 (14.3~17.6)	11,750	16	13.6 (8.3~22.2)
Cerebral infarction	128,094	255	19.9 (17.6~22.5)	214,392	426	19.9 (18.1~21.9)	28,430	94	33.1 (27.0~40.5)	79,586	199	25.0 (21.8~28.7)	91,883	304	33.1 (29.6~37.0)	227,612	661	29.0 (26.9~31.3)	11,710	30	25.6 (17.9~36.6)
Cerebral hemorrhage	128,477	98	7.6 (6.3~9.3)	215,121	152	7.1 (6.0~8.3)	28,630	17	5.9 (3.7~9.6)	79,938	73	9.1 (7.3~11.5)	92,450	95	10.3 (8.4~12.6)	228,781	188	8.2 (7.1~9.5)	11,766	10	8.5 (4.6~15.8)

CI: confidence interval.

In terms of CV risk profiles at the health checkup before diagnosis of gout, the proportion of patients with gout whose BMI was at least 25 was highest in Jeju (62.8%), and was lowest in Gyeongsang/Busan/Daegu/Ulsan (53.8%).The proportions of gout patients with SBP ≥140 mmHg or DBP ≥90 mmHg were highest in Jeju (28.1%) and Gangwon (27.6%), and were lowest in Gyeongsang/Busan/Daegu/Ulsan (20.6%) and Jeolla/Gwangju (21.9%). The highest proportion of gout patients with FBS ≥126 mg/dL was found in Jeolla/Gwangju (11.4%). The highest proportion of gout patients with LDL-cholesterol ≥160 mg/dL was observed in Jeju (11.6%), followed by Jeolla/Gwangju (11.5%) and Gyeongsang/Busan/Daegu/Ulsan (11.1%).

The proportions of gout patients with no physical activity were highest in Jeju (48.7%) and Gangwon (47.3%), and was lowest in Seoul (39.7%). Most of gout patients who were current smokers resided in Gyeonggi/Incheon (34.8%), whereas least of patients resided in Jeolla/Gwangju (29.1%). The proportion of gout patients who drank at least two times a week was highest in Jeju (35.6%) and lowest in Jeolla/Gwangju (30.9%).

Incidence of CV events

The number of events, IRs, and IR ratios for CV events are shown in Table 2. In total, there were 1,179, 1,970, and 633 newly diagnosed cases of myocardial infarction, cerebral infarction, and cerebral hemorrhage, respectively.

The IR for myocardial infarction was higher in Jeolla/Gwangju (19.30 per 10,000 person-years; 95% CI, 16.7~22.4) than in other areas. The IR for cerebral infarction was higher in Jeolla/Gwangju (33.1 per 10,000 person-years; 95% CI, 29.6~37.0) and Gangwon (33.1 per 10,000 person-years; 95% CI, 27.0~40.5) than in other areas. The IR for cerebral hemorrhage was higher in Jeolla/Gwangju (10.3 per 10,000 person-years; 95% CI, 8.4~12.6) than in other areas.

The risk of CV events

The associations between CV risk profiles and the risk of CV events are shown in Figure 1. The risk of CV events was significantly lower in women than in men. Age was significantly associated with significant CV events. Higher BP, FBS, and urine protein were associated with higher risks of cerebral hemorrhage, cerebral infarction, and myocardial infarction. Higher LDL-cholesterol was associated with significantly higher risks of myocardial infarction and cerebral infarction. However, higher LDL-cholesterol was associated with significantly lower risks of cerebral hemorrhage. In addition, higher physical activity was associated with lower risks of cerebral hemorrhage, cerebral infarction, and myocardial infarction. Current smoker was associated with significantly higher risks of myocardial infarction and cerebral infarction.

In the Cox-proportional hazard model adjusted for baseline CV risk profiles, the risk of myocardial infarction was significantly high in gout patients residing in Jeolla/Gwangju (HR 1.27; 95% CI, 1.02~1.56, p=0.029). Furthermore, a significantly high risk of cerebral infarction was observed in gout patients residing in Gangwon (HR 1.38; 95% CI, 1.09~1.74; p=0.008), Jeolla/Gwangju (HR 1.41; 95% CI, 1.19~1.67; p<0.001), and Gyeongsang/Busan/Daegu/Ulsan (HR 1.37; 95% CI, 1.19~1.59; p<0.001). A significantly high risk of cerebral hemorrhage was not observed in any region.

DISCUSSION

In this nationwide population-based cohort study from the NHI and NHSP databases in South Korea, we found real-world evidence of regional differences in CV risk profiles in gout patients. In addition, we found that gout patients in different regions had various risks of incident myocardial infarction and cerebral infarction after adjusting for CV risk profiles measured before the diagnosis of gout. To our knowledge, this is the first study to address regional disparities in CV risk in gout patients.

The regional disparities of health between populations have long been recognized as a problem of public health that remains unresolved. Health care, particularly that for CV diseases, is influenced by many factors, including race/ethnicity, urban versus rural location, and socioeconomic status [16-18]. The prevalence of CV diseases varies geographically depending on the region, and the prognosis of patients is poor in regions where disease management is difficult [19]. Access to health care is an important factor contributing to widening the health disparity between urban and rural areas, further exacerbating the disparity of CV risk factors [20]. Residents in urban areas have more opportunities to visit health care services than those in rural areas, resulting in lower mortality and morbidity, as well as exacerbated health disparities [21]. In addition, in this study, the risks of cerebral hemorrhage, cerebral infarction, and myocardial infarction tend to be low in Seoul and Gyeonggi.

A previous study found that the risk of CV events was highest in regions with low population densities, especially in those

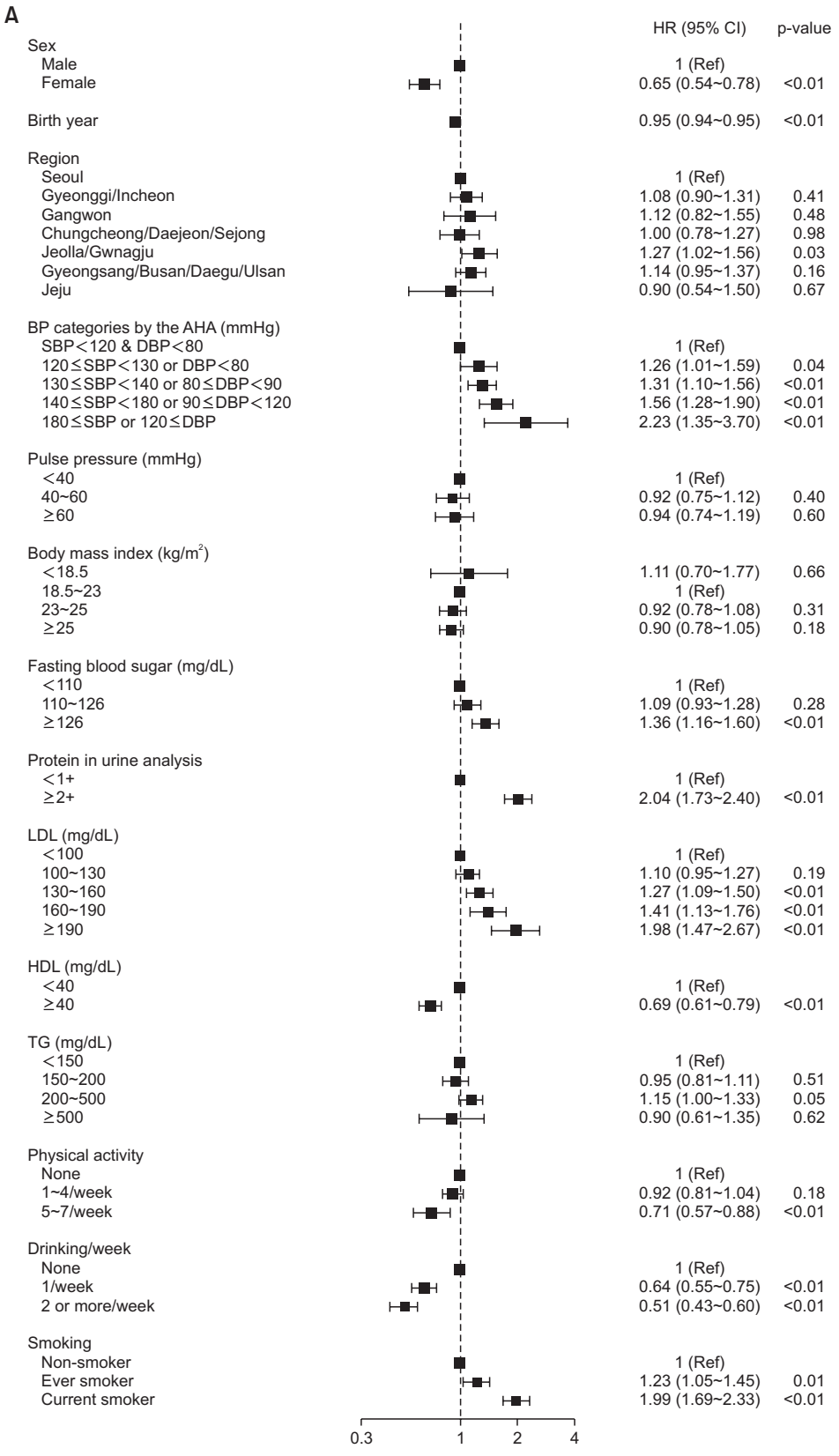

Figure 1. Forest plot of the risk of myocardial infarction (A), cerebral infarction (B), and cerebral hemorrhage (C). BP: blood pressure, DBP: diastolic blood pressure, HDL: High-density lipoprotein cholesterol, LDL: low-density lipoprotein cholesterol, SBP: systolic blood pressure, TG: triglyceride.

B

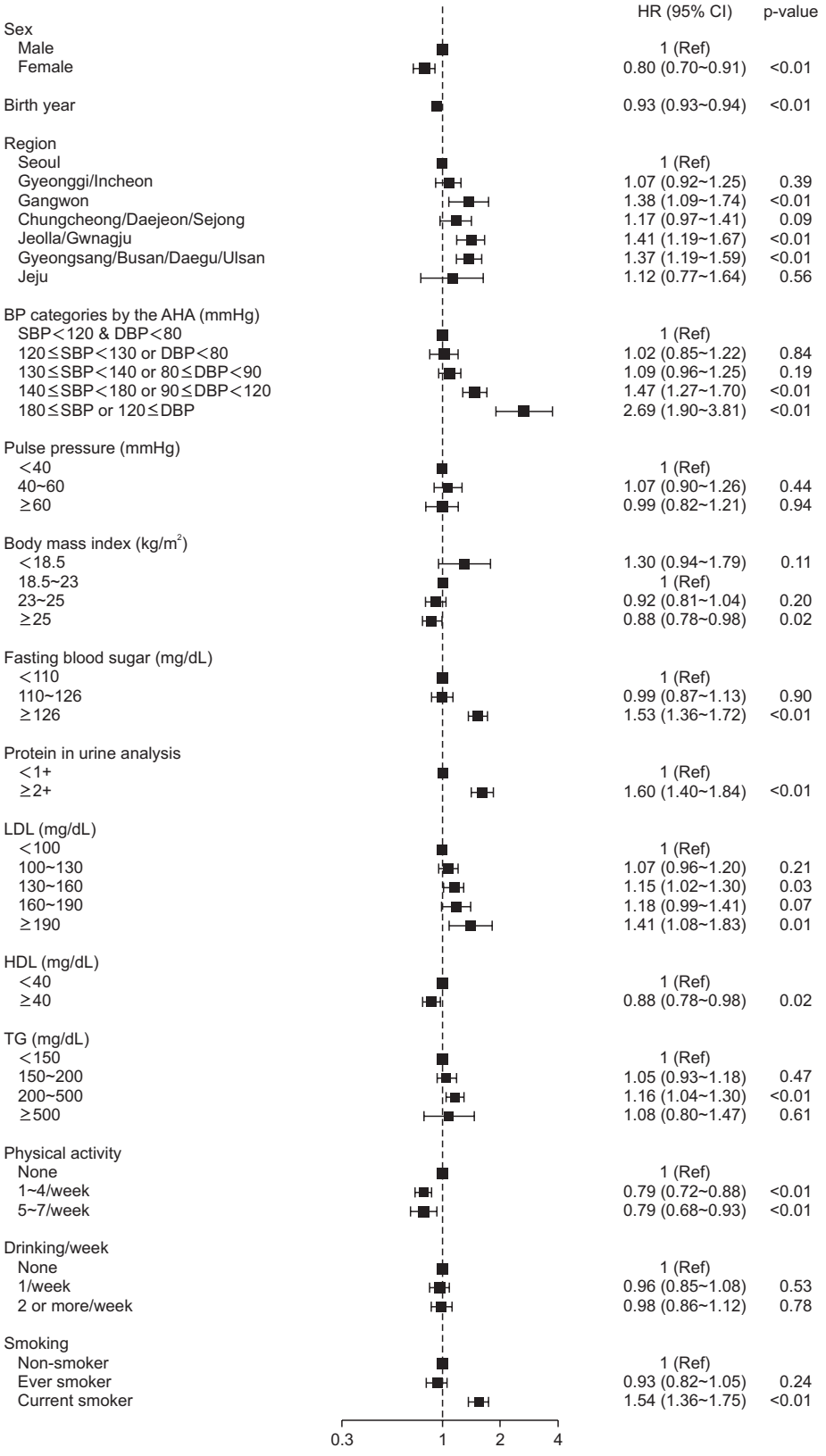

Figure 1. Continued 1

C

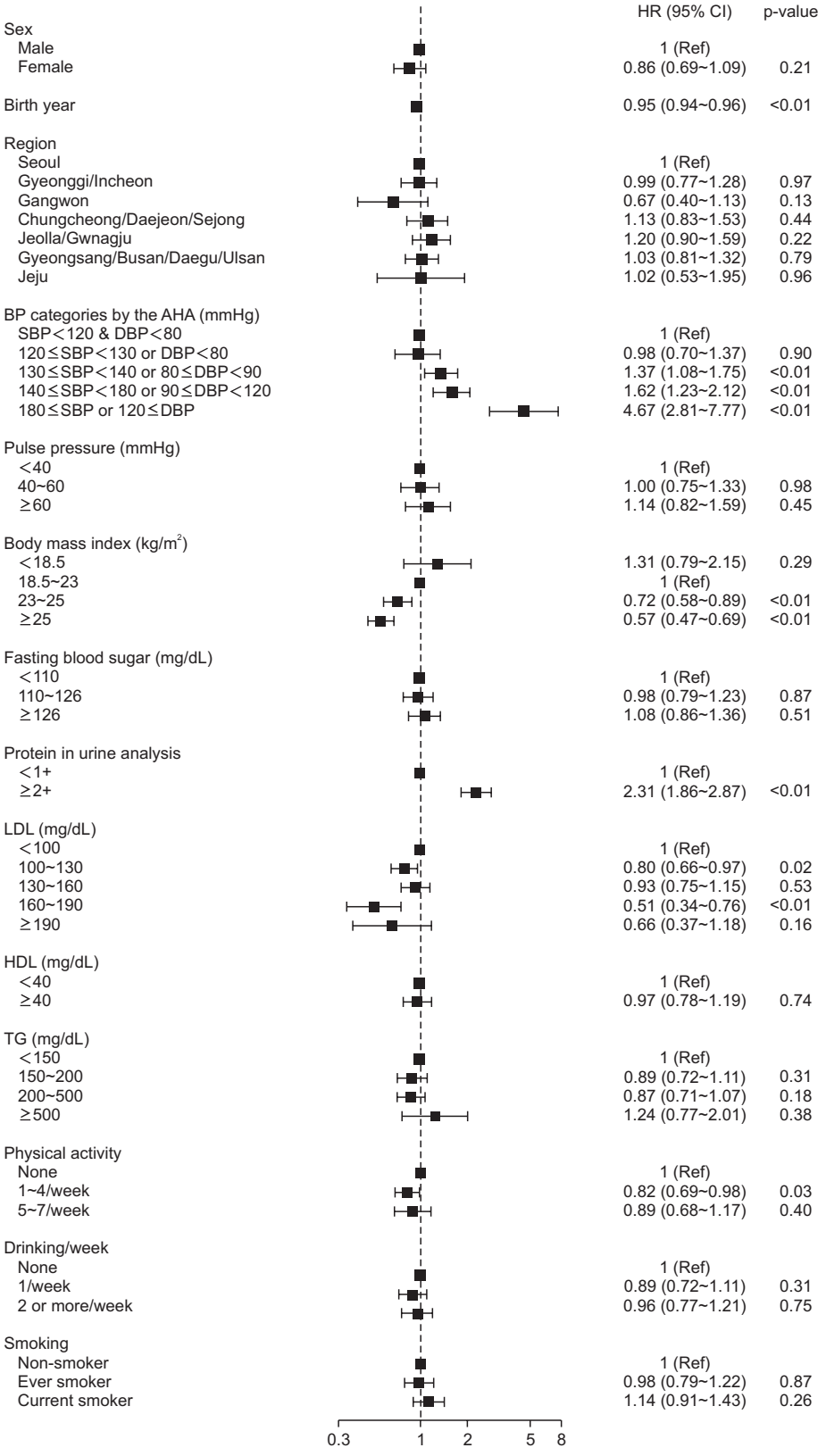

Figure 1. Continued 2

with populations under 100,000, compared to regions with high population densities [22]. These results were interpreted as differences in the quality of healthcare between regions. Access to care is one of the most important factors for preventing disease and having better patient outcomes. However, the risk of cerebral hemorrhage, cerebral infarction, and myocardial infarction in Jeju or Chungcheong was similar to or lower than that in Seoul and Gyeonggi. In particular, although the known specific values of CV risk profiles were adjusted, the risk of CV events in gout patients was different by region. This may result from the differences in the treatment of gout patients. A recent study reported that discontinuation of febuxostat or allopurinol could increase the risks of CV events [23]. In addition, according to another study, sufficient time for controlling uric acid levels and appropriate management of uric acid levels could reduce the risks of CV events [24]. Accordingly, compliance with urate-lowering therapy might affect CV events. Additional regional differences other than these may affect the onset of CV events. Therefore, it is necessary to conduct additional research on regional differences in the risks of CV events.

Elevated LDL-cholesterol increased the risk of myocardial infarction and atherosclerotic CV diseases [25]. In a previous study including non-gout patients, the difference between the regions with the highest and lowest proportions of patients with LDL-cholesterol was approximately 3%. The difference was approximately 2% in the current study, which is similar to that of the previous study conducted on non-gout patients. In this study, low LDL-cholesterol levels were observed in Seoul/Gyeonggi/Incheon and Gangwon. The possible explanations for differences in serum cholesterol distributions may be the regional variations in socioeconomic status, dietary habits, physical activity, and the quality of available healthcare [18,26]. Differences in various CV risk factors other than these were observed. Nevertheless, there were some regions where risk factors for CV events were much better than those in Seoul and Gyeonggi.

As gout is a very common disease, even a small increase in the CV risk induced by gout may result in a substantial increase in the number of new CV events and deaths. Therefore, physicians should consider the risk of CV events in gout patients. In particular, diabetic patients or high-risk groups for CV diseases require early intervention or management, such as regular exercise and improvement of eating habits, to lower the risk of CV diseases, making the role of primary care providers important. Long-term monitoring and management of CV risk profiles would be important for reducing the risks of myocardial infarction, and cerebral infarction, as well as cerebral hemorrhage, should also be considered in gout patients.

Our study has several limitations. First, the diagnosis of gout was primarily based on the administrative claims data reported by physicians or hospitals. While this method had been employed in other registry-based studies, we attempted to maximize the diagnostic accuracy by developing case algorithms based on the number of hospital visits and prescription of hypouricemic agents and selected a combination of algorithms that offered sensitivity and specificity of >95%. Second, the present study lacked information on serum uric acid levels, which is an intrinsic limitation of the Korean administrative claims data. Nevertheless, as the focus of our study was gout rather than serum uric acid levels, we assume that the absence of this information would not have significantly influenced the main outcome of this study. Third, the data were obtained from the National Health Insurance Service database in our study. However, this database was not primarily intended for research purposes, which may raise concerns about the quality and completeness of the data. Consequently, the accuracy of our findings may be affected by the limitations and shortcomings of the available data. Therefore, although we analyzed and adjusted the physical activity, smoking, and drinking data, we were unable to investigate and analyze other significant risk factors, such as family history, socioeconomic status, other lifestyle factors, and medications, that can contribute to the development of CV disease. These factors could have an impact on the interpretation of our findings. Therefore, even though we found differences in the risk of CV disease among patients with gout based on geographic regions, it is essential to acknowledge these limitations when interpreting our results. Nevertheless, to overcome the limitations of previous studies and to minimize residual confounding effects, we performed multiple adjustments for specific values of various CV risk profiles to take into account the differences between the exposed and unexposed groups.

CONCLUSION

We found there were regional differences in CV risk factors in gout patients. Moreover, using specific values of CV risk profiles before the diagnosis of gout from approximately all Korean gout patients, we found that gout patients in different regions had various risks of incident myocardial infarction and cerebral

infarction. Hence, the presence of gout should alert physicians to screen for CV risk profiles so that they can be promptly diagnosed and treated.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conception and design of study: B.G., H.J.K. Acquisition of data: H.J.K. Analysis and/or interpretation of data: B.G., H.J.K. Drafting the manuscript: B.G. Revising the manuscript critically for important intellectual content: J.K., H.S.A. All authors read and approved the final manuscript.

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