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Association between triglyceride-glucose index and incidence risk of gout: a nationwide cohort study

Yoonkyung Chang[1,4], Ju-young Park[2,4] & Tae-Jin Song[3]✉

The global burden of gout is substantial and expected to increase. We investigated the relationship between the triglyceride-glucose (TyG) index, a biomarker of insulin resistance, and gout risk in the general population over time. This study was conducted using data from the National Health Screening Cohort Database of South Korea (2002–2019) among 300,107 participants who had no history of gout and underwent more than three repeated TyG index measurements. During the median of 9.62 years (interquartile range 8.72–10.53), 14,116 individuals (4.72%) developed gout. In a multivariable time-dependent Cox proportional hazards model, a per-unit increase in the TyG index significantly increased gout risk (hazard ratio [HR] 1.150; 95% confidence interval [CI] 1.116–1.184). The multivariate Cox proportional hazards model for average TyG index quartiles was positively associated with the incidence risk of gout, accompanied by a significant trend (HR 1.326, 95% CI 1.260–1.397). This association followed a J-shaped pattern with increased risk. Our findings highlight a strong link between elevated TyG index and gout incidence in the general population, suggesting that the TyG index may serve as a valuable predictor of gout risk.

Keywords Insulin resistance, Triglyceride-glucose index, Gout, Diabetes mellitus

Gout manifests as an inflammatory arthritis characterized by recurring attacks marked by the sudden onset of redness, tenderness, heat, and swelling in the joints. Pain escalates swiftly, often peaking within 12 h[1]. Gout is mainly caused by elevated levels of uric acid in the blood. In hyperuricemic conditions, uric acid crystallization occurs, leading to the deposition of these crystals within joints, tendons, and surrounding tissues[2]. Gout occurs in individuals who consume large amounts of meat, heavy alcohol drinkers, heavy smokers, or those who are overweight[2]. The current global burden of gout is significant and expected to grow in the future. Therefore, identifying and correcting modifiable factors that can increase the risk of gout is considered important[3].

Insulin resistance is a common metabolic disorder usually linked to type 2 diabetes mellitus (DM)[4]. This condition arises when the body's cells exhibit decreased responsiveness to insulin, a crucial hormone responsible for regulating blood sugar levels[5]. The implications of insulin resistance extend beyond diabetes, resulting in various health issues. Insulin resistance is closely related to various diseases and poor prognoses, such as hypertension, dyslipidemia, liver diseases, cardiovascular diseases, neurodegenerative diseases, certain types of cancer, obesity, and inflammatory and infectious diseases[5–9]. The triglyceride-glucose (TyG) index, which is calculated using fasting triglyceride and blood glucose levels, serves as a simple and practical surrogate marker for insulin resistance[10]. The TyG index has gained recognition for its ease of use and cost-effectiveness, especially in settings where more direct and complex measurements of insulin resistance are not readily available. It provides a valuable tool for assessing metabolic health in various clinical settings and identifying individuals at risk of developing insulin resistance-associated complications[7,11].

Previous studies have suggested a correlation and causality between increased insulin resistance and elevated uric acid levels[12,13].

Nevertheless, although hyperuricemia is a pivotal risk factor for initiating gout, it is crucial to note that not all individuals with elevated uric acid levels develop this condition. Therefore, further studies on the association between insulin resistance and the incidence of gout are needed. To date, only a few studies have been conducted to investigate whether the aggravation of insulin resistance increases the incidence of gout. Additionally, despite changes in insulin resistance, studies involving repeatedly measured parameters in the general population are limited. We hypothesized that an increased TyG index is associated with the development of gout. The aim of

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this study was to investigate the association between the TyG index and risk of gout incidence in the general population over time.

Results

Baseline characteristics of participants

The number of measurements repeated during the follow-up period is described in Supplementary Table S1, and the characteristics of the variables for each year are described in Supplementary Table S2.

Table 1 provides the baseline characteristics of the entire cohort, which was divided into four groups based on the quartiles of the average TyG index (Q1 [< 9.017], Q2 [9.017–9.325], Q3 [9.325–9.657], and Q4 [≥ 9.657]). Participants in the Q3 group were older than those in the other groups. The Q4 group was comprised mostly of males and those with obesity. The income level in the Q4 group was lower than that in the other groups. Additionally, the Q4 group had lower rates of smoking, alcohol consumption, and exercise sessions compared with other groups. Regarding laboratory findings, the Q4 group had higher aspartate aminotransferase, alanine aminotransferase, and fasting blood glucose levels than did the other groups, and the proportions of individuals with comorbidities, including DM, hypertension, dyslipidemia, renal disease, and liver disease, and Charlson comorbidity index (CCI) score ≥ 2 were significantly higher in the Q4 group (Table 1).

Relationship of the TyG index with the incidence risk of gout

During the median of 9.62 years (interquartile range 8.72–10.53), 14,116 individuals (4.72%) developed gout. Survival curves depicting the incidence of gout across the quartiles of the average TyG index are shown in Fig. 1. Increased TyG index quartiles were associated with increased gout risk (log-rank test for the entire, DM, and non-DM cohorts: $p < 0.001$).

Considering the multivariable time-dependent Cox proportional hazard model with repeated TyG index measures, a per-unit increase in the TyG index was significantly associated with increased risk of gout in the entire cohort (hazard ratio [HR] 1.150, 95% confidence interval [CI] 1.116–1.184) and in the DM cohort (HR 1.131; 95% CI 1.072–1.193) and non-DM cohorts (HR 1.162, 95% CI 1.121–1.203) in the fully adjusted multivariate models (Table 2 and Supplementary Table S3).

The results of the multivariate Cox proportional hazards model for the quartiles of the average TyG index during follow-up are detailed in Table 3 and Supplementary Table S4. Compared with the lowest quartile (Q1), the highest quartile (Q4) was positively associated with incidence risk of gout (HR 1.326, 95% CI 1.260–1.397 in the entire cohort; HR 1.228, 95% CI 1.116–1.351 in the DM cohort; HR 1.315, 95% CI 1.243–1.392 in the non-DM cohort) in the well-adjusted multivariable analysis ($p < 0.001$).

Moreover, restricted cubic spline analysis (Fig. 2) showed a clear pattern of non-linear increasing risk (U- or J-shape) of gout with the TyG index in the entire cohort and in the DM and non-DM cohorts. For the entire cohort, the risk of gout increased non-linearly (p-value for non-linearity < 0.001) within the observed range of the TyG index, and the estimated change point was 9.698 (overall p-value of the estimated spinal curve < 0.001). The DM and non-DM cohorts showed significant non-linear patterns (p-value for non-linearity = 0.003 and < 0.001, respectively).

Subgroup analysis of the association of the TyG index with the incidence risk of gout

The association of the TyG index with the incidence risk of gout was more significantly noted in males (p for interaction < 0.001), those with renal disease (p for interaction = 0.038), those with liver disease (p for interaction = 0.003), and those with CCI ≥ 1 (p for interaction < 0.001), compared with their respective counterparts (Fig. 3).

Discussion

Our results showed that the TyG index was associated with gout risk in the general population, using time-dependent and conventional Cox regression analyses of repeatedly measured average TyG index values. In addition, the association of the TyG index with increased gout risk showed non-linearity (J-shape) in the entire, DM, and non-DM cohorts.

The TyG index is linked to several health conditions, including their presence, progression, and adverse events. Elevated TyG index has been associated with increased incidences of cardiovascular and peripheral arterial diseases[14], as well as progression of coronary artery atherosclerosis and calcification[11]. Moreover, it has been associated with severe illness and increased mortality rates in patients with coronavirus disease 2019[15,16]. Moreover, a previous study has revealed a significant association between the TyG index and all-cause and cardiovascular mortality, particularly in young and middle ages[17]. A cross-sectional study revealed a positive correlation between the TyG index and blood uric acid levels in non-obese patients with type 2 DM[18]. Furthermore, a hospital-based cohort study showed a significant independent association between the TyG index and hyperuricemia risk in patients with diabetic nephropathy[19]. Both studies suggest a link between the TyG index and hyperuricemia rather than gout risk. Therefore, our study provides additional information regarding the relationship between the TyG index and gout occurrence in the general population, with a large sample size and a longitudinal setting.

Our study showed a J-shaped relationship between the TyG index and gout risk. In a previous study, the relationship between TyG levels and the onset of atrial fibrillation in a general population without cardiovascular disease revealed a U- or J-shaped phenomenon[20]. In a nationwide cohort study, the TyG index was observed to have a U- or J-shaped relationship with all-cause and cardiovascular mortality in patients with DM[21]. This non-linear relationship suggests non-uniformity in the risk of cardiovascular disease or poor prognosis associated with TyG index levels. The results of these previous studies can be applied to our study regarding the incidence

Variables	Total	TyG index quartile				
		Q1 (< 9.017)	Q2 (9.017–9.325)	Q3 (9.325–9.657)	Q4 (≥ 9.657)	
		Mean ± SD, N (%)	Mean ± SD, N (%)	Mean ± SD, N (%)	Mean ± SD, N (%)	p-value
Number	300,107	75,027 (25.0)	75,027 (25.0)	75,026 (25.0)	75,027 (25.0)	
Age, years						< 0.001
< 65	237,743 (79.2)	61,707 (82.2)	58,471 (77.9)	57,716 (76.9)	59,849 (79.8)	
≥ 65	62,364 (20.8)	13,320 (17.8)	16,556 (22.1)	17,310 (23.1)	15,178 (20.2)	
Sex						< 0.001
Female	141,061 (47.0)	41,390 (55.2)	38,183 (50.9)	34,517 (46.0)	26,971 (35.9)	
Male	159,046 (53.0)	33,637 (44.8)	36,844 (49.1)	40,509 (54.0)	48,056 (64.1)	
Body mass index (kg/m^2)						< 0.001
< 25	196,712 (65.5)	60,236 (80.3)	51,713 (68.9)	45,703 (60.9)	39,060 (52.1)	
≥ 25	103,395 (34.5)	14,791 (19.7)	23,314 (31.1)	29,323 (39.1)	35,967 (47.9)	
Waist circumference (cm)						< 0.001
Male < 90, female < 85	242,151 (80.7)	68,113 (90.8)	62,842 (83.8)	58,314 (77.7)	52,882 (70.5)	
Male ≥ 90, female ≥ 85	57,956 (19.3)	6914 (9.2)	12,185 (16.2)	16,712 (22.3)	22,145 (29.5)	
Household income						0.004
Low	191,763 (63.9)	47,679 (63.5)	47,841 (63.8)	47,916 (63.9)	48,327 (64.4)	
High	108,344 (36.1)	27,348 (36.5)	27,186 (36.2)	27,110 (36.1)	26,700 (35.6)	
Smoking status						< 0.001
Never	194,918 (64.9)	55,689 (74.2)	51,502 (68.6)	47,533 (63.4)	40,194 (53.6)	
Former	55,622 (18.5)	11,870 (15.8)	13,383 (17.8)	14,329 (19.1)	16,040 (21.4)	
Current	49,567 (16.6)	7468 (10.0)	10,142 (13.6)	13,164 (17.5)	18,793 (25.0)	
Alcohol consumption (days/week)						< 0.001
None	180,970 (60.3)	49,191 (65.5)	47,685 (63.6)	45,174 (60.2)	38,920 (51.9)	
1–2 times	78,781 (26.3)	18,384 (24.5)	18,704 (24.9)	19,680 (26.2)	22,013 (29.3)	
3–4 times	26,536 (8.8)	4782 (6.4)	5759 (7.7)	6651 (8.9)	9344 (12.5)	
≥ 5 times	13,820 (4.6)	2670 (3.6)	2879 (3.8)	3521 (4.7)	4750 (6.3)	
Regular physical activity (days/week)						< 0.001
None	74,194 (24.7)	17,539 (23.4)	18,656 (24.8)	19,067 (25.4)	18,932 (25.2)	
1–4 days	133,808 (44.6)	32,867 (43.8)	33,219 (44.3)	33,144 (44.2)	34,578 (46.1)	
≥ 5 days	92,105 (30.7)	24,621 (32.8)	23,152 (30.9)	22,815 (30.4)	21,517 (28.7)	
Laboratory findings						
AST (U/L)	26.2 ± 16.1	25.0 ± 16.0	25.4 ± 15.9	26.1 ± 14.4	28.2 ± 17.8	< 0.001
ALT (U/L)	25.0 ± 18.6	21.5 ± 17.3	23.3 ± 17.5	25.5 ± 18.3	29.7 ± 20.2	< 0.001
Total-C (mg/dL)	200.2 ± 37.1	190.3 ± 33.4	198.9 ± 35.4	203.8 ± 37.1	207.9 ± 39.7	< 0.001
HDL-C (mg/dL)	54.8 ± 23.7	60.3 ± 20.3	56.1 ± 23.3	53.2 ± 25.9	49.3 ± 23.6	< 0.001
LDL-C (mg/dL)	119.0 ± 35.7	115.0 ± 32.1	121.8 ± 33.7	123.1 ± 35.9	116.1 ± 39.8	< 0.001
Triglyceride (mg/dL)	136.4 ± 82.7	75.9 ± 28.7	108.2 ± 39.9	142.7 ± 55.3	218.8 ± 103.0	< 0.001
FBG (mg/dL)	100.5 ± 24.1	91.9 ± 12.8	96.2 ± 15.9	100.7 ± 20.6	113.1 ± 35.1	< 0.001
Comorbidities						
Hypertension	90,097 (30.0)	15,319 (20.4)	20,901 (27.9)	25,036 (33.4)	28,841 (38.4)	< 0.001
Diabetes mellitus	36,674 (12.2)	2415 (3.2)	5198 (6.9)	9121 (12.2)	19,940 (26.6)	< 0.001
Dyslipidemia	47,249 (15.7)	7326 (9.8)	10,443 (13.9)	13,029 (17.4)	16,451 (21.9)	< 0.001
Renal disease	38,679 (12.9)	8241 (11.0)	9458 (12.6)	10,114 (13.5)	10,866 (14.5)	< 0.001
Liver disease	49,343 (16.4)	10,609 (14.1)	11,539 (15.4)	12,618 (16.8)	14,577 (19.4)	< 0.001
Stroke	2790 (0.9)	533 (0.7)	758 (1.0)	736 (1.0)	763 (1.0)	< 0.001
Charlson comorbidity index						< 0.001
0	156,676 (52.2)	42,304 (56.4)	40,071 (53.4)	38,237 (51.0)	36,064 (48.1)	
1	123,739 (41.2)	28,644 (38.2)	30,612 (40.8)	31,890 (42.5)	32,593 (43.4)	
2 or more	19,692 (6.6)	4079 (5.4)	4344 (5.8)	4899 (6.5)	6,370 (8.5)	
Use of statin	39,911 (13.3)	5732 (7.6)	8804 (11.7)	11,379 (15.2)	13,996 (18.7)	< 0.001
Use of diuretics	48,012 (16.0)	8191 (10.9)	11,094 (14.8)	13,278 (17.7)	15,449 (20.6)	< 0.001

Table 1. Baseline characteristics of study participants. Q, quartile; SD, standard deviation; N, number; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Total-C, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBS, fasting blood glucose.

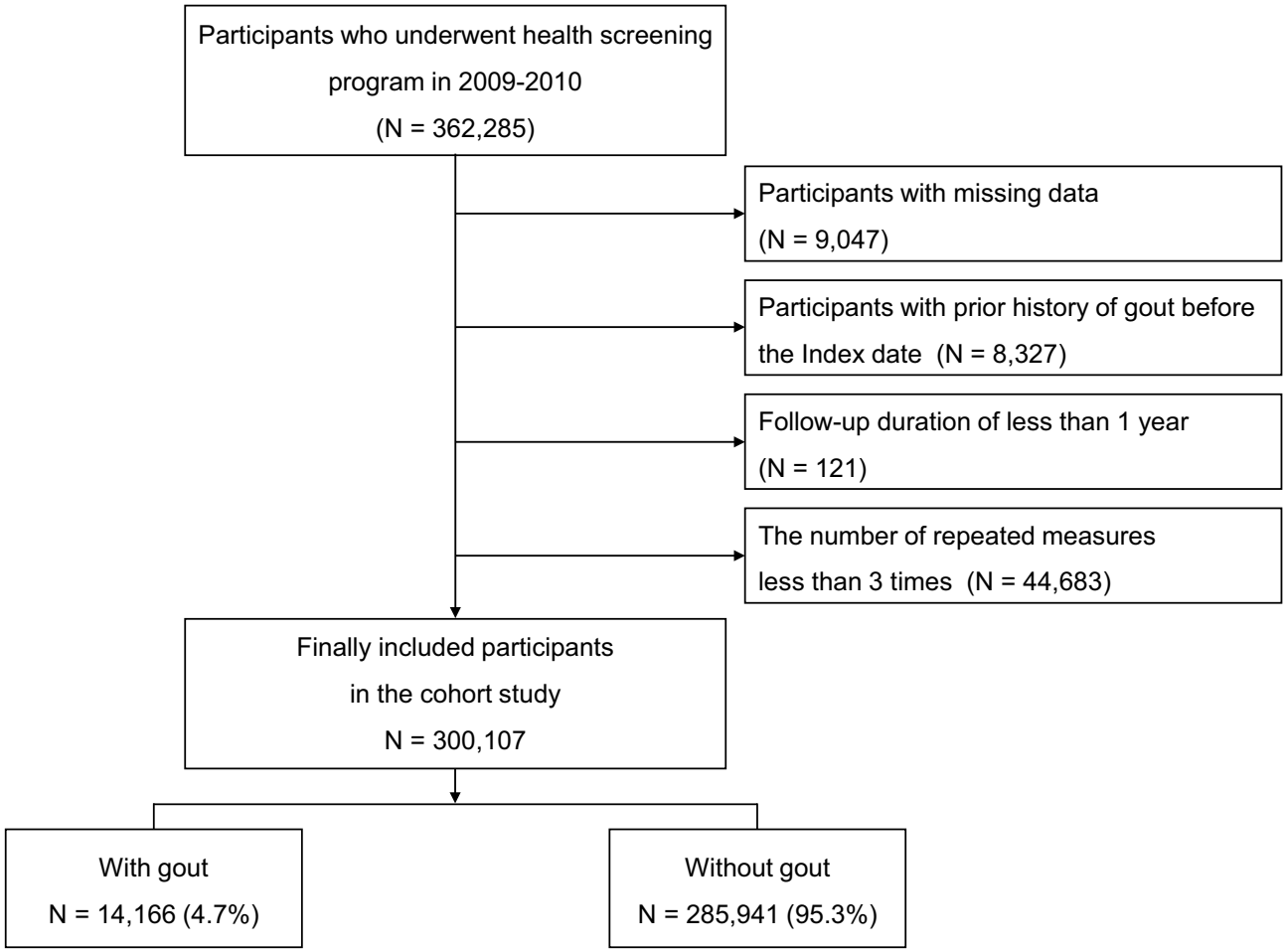


Fig. 1. Kaplan–Meier survival curves of gout outcome according to TyG index quartiles. (**A**) Total cohort, (**B**) diabetic mellitus cohort, and (**C**) non-diabetic mellitus cohort.

Groups	N	Events	Person-years	Incidence rate (per 1000 person-years)	Unadjusted HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Total	300,107	14,166	2,877,847	4.922	1.273 (1.239, 1.309)	1.230 (1.197, 1.264)	1.150 (1.116, 1.184)
DM	67,370	3477	644,680	5.393	1.226 (1.163, 1.292)	1.155 (1.096, 1.218)	1.125 (1.067, 1.186)
Non-DM	232,737	10,689	2,233,166	4.786	1.289 (1.245, 1.334)	1.235 (1.193, 1.278)	1.163 (1.123, 1.205)

Table 2. Risk of gout considering the TyG index as a time-dependent covariate. N, number; HR, hazard ratio; CI, confidence interval; DM, diabetes mellitus. The estimated HR (95% confidence interval [CI]) was calculated using a time-dependent Cox regression model. Model 1 is adjusted for age and sex. Model 2 was adjusted for age, sex, body mass index, household income, smoking status, alcohol consumption, regular physical activity, hypertension, diabetes mellitus, dyslipidemia, renal disease, liver disease, stroke, Charlson Comorbidity Index, statin use, and diuretic use.

of gout. Because the TyG index comprises triglyceride and glucose levels, it is difficult to rule out the possibility that a very low TyG index is associated with poor health. Low TyG index levels may signify optimal metabolic health characterized by robust insulin sensitivity and reduced lipid levels. However, excessively low TyG index levels could indicate underlying health issues such as malnutrition or genetic predispositions, which might paradoxically elevate cardiovascular risk.

Our subgroup analysis showed a strong link between the TyG index and gout, particularly in populations with comorbidities such as renal and liver diseases. These results suggest an association between insulin resistance and gout risk in populations with kidney or liver disease. Therefore, awareness of the risk of developing gout is important in patients with renal or liver disease with relatively high TyG index.

Although our study was not mechanistic, several plausible hypotheses exist regarding the association between the TyG index and incidence risk of gout. The TyG index, derived from fasting plasma glucose and triglyceride

Average TyG index	N	Events	Person-years	Incidence rate (per 1000 person-years)	Unadjusted	Model 1	Model 2
					HR (95% CI)	HR (95% CI)	HR (95% CI)
Total							
Q1 (< 9.017)	75,027	2907	721,031	4.032	Ref	Ref	Ref
Q2 (9.017–9.325)	75,027	3272	720,858	4.539	1.125 (1.070, 1.183)	1.144 (1.089, 1.203)	1.090 (1.036, 1.146)
Q3 (9.325–9.657)	75,026	3495	720,358	4.852	1.203 (1.145, 1.263)	1.215 (1.156, 1.276)	1.122 (1.066, 1.180)
Q4 (≥ 9.657)	75,027	4492	715,600	6.277	1.567 (1.495, 1.642)	1.506 (1.437, 1.579)	1.334 (1.267, 1.405)
p-value for trend					< 0.0001	< 0.0001	< 0.0001
DM							
Q1 (< 9.359)	16,843	762	161,025	4.732	ref	ref	ref
Q2 (9.359–9.665)	16,842	814	161,713	5.034	1.059 (0.96, 1.169)	1.043 (0.945, 1.151)	1.023 (0.926, 1.130)
Q3 (9.665–9.993)	16,842	800	161,733	4.946	1.041 (0.943, 1.150)	0.998 (0.904, 1.102)	0.975 (0.882, 1.078)
Q4 (≥ 9.993)	16,843	1101	160,209	6.872	1.462 (1.333, 1.603)	1.308 (1.191, 1.436)	1.225 (1.114, 1.348)
p-value for trend					< 0.0001	< 0.0001	< 0.0001
Non-DM							
Q1 (< 8.953)	58,184	2204	559,623	3.938	Ref	Ref	Ref
Q2 (8.953–9.237)	58,184	2473	559,379	4.421	1.122 (1.059, 1.188)	1.139 (1.075, 1.206)	1.081 (1.020, 1.145)
Q3 (9.237–9.537)	58,184	2633	559,050	4.71	1.195 (1.130, 1.265)	1.203 (1.137, 1.274)	1.109 (1.047, 1.175)
Q4 (≥ 9.537)	58,185	3379	555,114	6.087	1.556 (1.474, 1.641)	1.481 (1.403, 1.564)	1.318 (1.246, 1.395)
p-value for trend					< 0.0001	< 0.0001	< 0.0001

Table 3. Risk of gout based on average TyG index quartile during the follow-up period. HR, hazard ratio; CI, confidence interval; Q, quartile; DM, diabetes mellitus. Data are expressed as HR (95% CI) derived using the conventional Cox regression model. Model 1 is adjusted for age and sex. Model 2 was adjusted for age, sex, body mass index, household income, smoking status, alcohol consumption, regular physical activity, hypertension, diabetes mellitus, dyslipidemia, renal disease, liver disease, stroke, Charlson Comorbidity Index, statin use, and diuretic use.

levels, is suggested as an easy and dependable clinical substitute indicator for metabolic syndrome and insulin resistance[10]. Consequently, the link between the TyG index and gout could be due to a mechanism involving insulin resistance. During insulin resistance, intermediates of glycolysis are converted into 5-phosphoribose and ribose phosphate pyrophosphate, resulting in a boost in serum uric acid production[22]. Furthermore, elevated insulin levels due to insulin resistance promote Na+–H+ exchange in the renal tubules, leading to enhanced H+ elimination and increased reabsorption of uric acid[23]. Additionally, activation of the renin-angiotensin system triggered by hyperinsulinemia reduces renal blood flow and augments urate reabsorption. This process generates xanthine oxidase, which subsequently increases uric acid production[24]. This increased blood uric acid level could increase the risk of gout. An additional possible mechanism may involve changes in blood glucose levels and dyslipidemia. In addition, high blood glucose and dyslipidemia can reduce the activity of glyceraldehyde 3-phosphate dehydrogenase, leading to an increase in uric acid synthesis[25]. Furthermore, TG can cause stenosis or occlusion of small arteries in the kidneys via long-term dyslipidemia, eventually leading to disorders in urate excretion. A previous study showed that TG level is an independent and significant risk factor for elevated uric acid levels[26].

Our study has certain limitations. First, its generalizability may be limited, as it was exclusively focused on the Korean population. Second, despite using multiple TyG index measures to improve reliability, the retrospective design prevented the establishment of a causal relationship between the TyG index and gout incidence. Third, key gout-related biomarkers, such as uric acid levels, were not included because of dataset limitations. Additionally, alcohol consumption and physical activity were self-reported, introducing potential recall bias, and dietary factors, which may influence the TyG index and gout risk, were not considered in the analysis. While the TyG index served as a surrogate marker for insulin resistance, more direct and validated measures, such as HOMA-IR (Homeostatic Model Assessment of Insulin Resistance), were not incorporated, potentially limiting the accuracy of metabolic risk assessment. Although the TyG index may serve as a predictive indicator for gout, it may not fully reflect the complex metabolic pathways involved in its pathogenesis. Furthermore, in this study, TyG index values were derived from random time points rather than during acute gout episodes, which may have introduced measurement bias. Given that TyG index levels may differ between acute and intermittent phases of gout, further investigation is warranted. Finally, participant data were drawn from a health screening database, which may introduce selection bias and limit the applicability of the findings to a broader population. Future prospective studies and randomized controlled trials are required to confirm these findings.

In conclusion, our study demonstrates that increased TyG index levels are associated with the incidence of gout in the general population. Additionally, this association showed a non-linear increasing risk (J-shape) in the entire cohort and in the DM and non-DM cohorts. Thus, the TyG index may be an important parameter for predicting the incidence of gout.

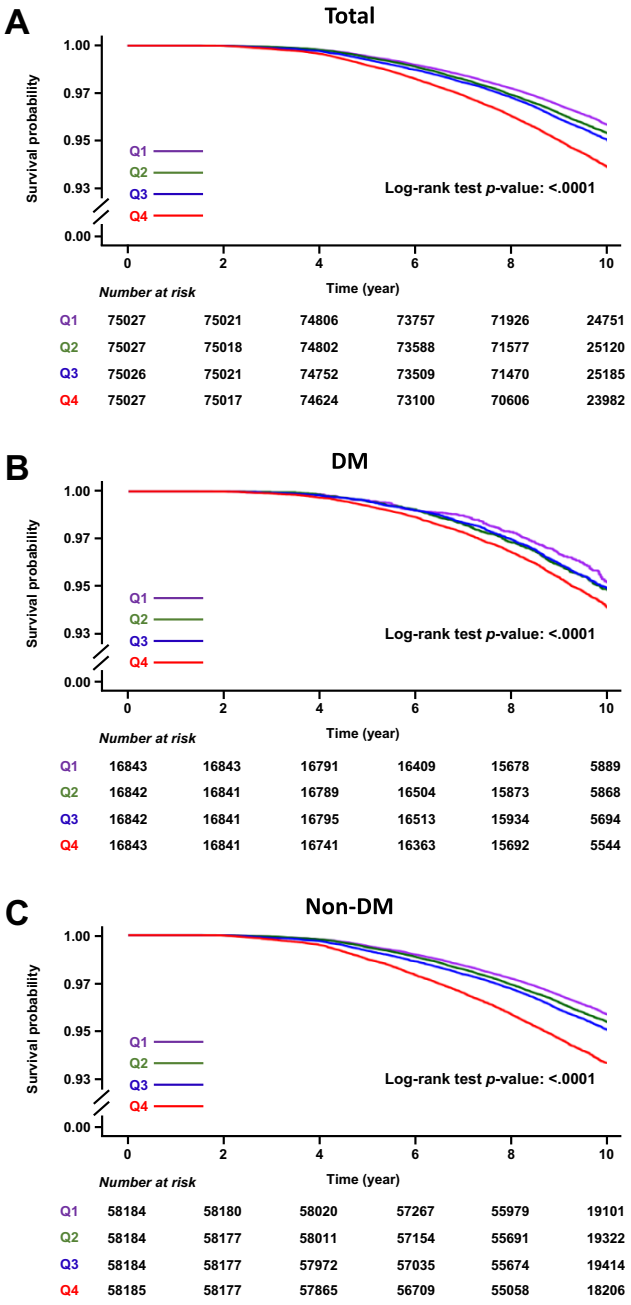


Fig. 2. Spline curve for incidence risk of gout according to average TyG index. (**A**) Total cohort, (**B**) diabetic mellitus cohort, and (**C**) non-diabetic mellitus cohort.

Methods

Data source

This study was conducted using data from the National Health Insurance Service Health Screening Cohort (NHIS-HEALS) database, which is a subset of the Korean NHIS, a government program that provides health insurance to approximately 97% of the Korean population. The Medical Aid Program, an affiliate of the NHIS, covers 3% of the population not covered by the NHIS. Our study was conducted based on the NHIS-HEALS cohort database of South Korea (2002–2019)[27]. The NHIS provides a nationwide free health screening program every 2 years for all South Korean adults aged 40 and over.

The NHIS-HEALS encompasses measurements of blood pressure, body mass index, blood biochemistry, medical history, and lifestyle factors. Additionally, health claims data covering all hospital visits, diagnoses, procedures, surgeries, and participant prescriptions from 2002 to 2019 were included. The diagnoses at each visit were recorded according to the International Classification of Diseases, Tenth Revision (ICD-10). Demographic information such as sex, age, and household income were included, and data regarding participants' health claims, insurance coverage maintenance, and death were available up to December 31, 2019.

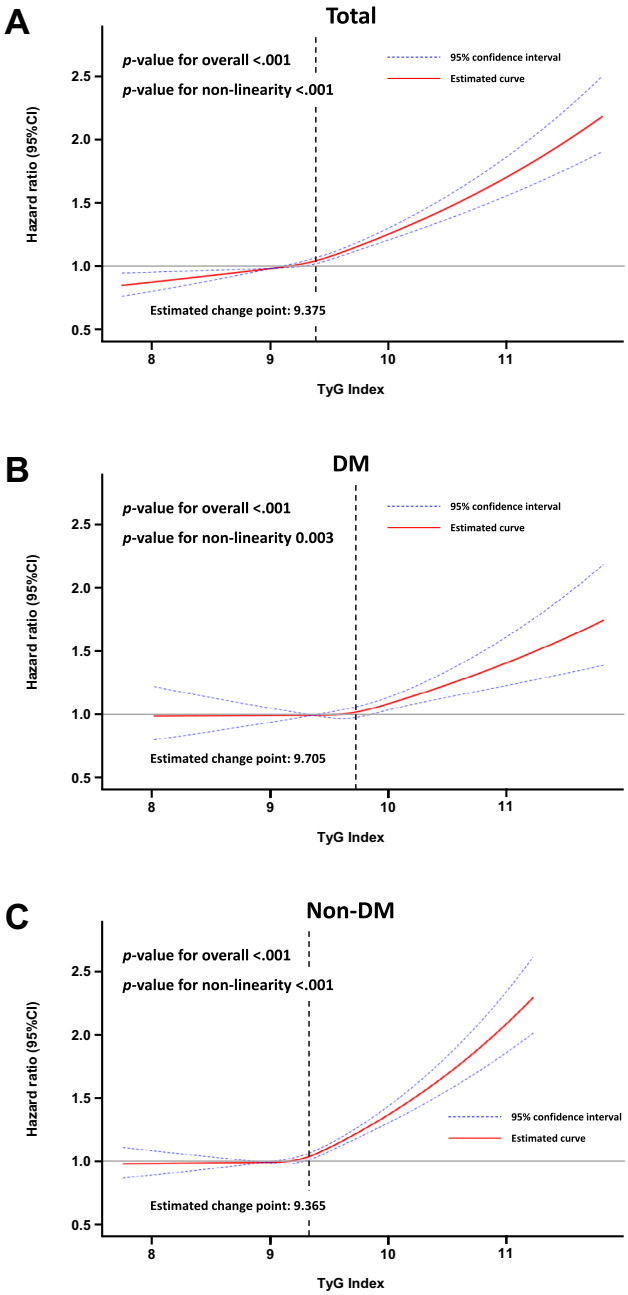


Fig. 3. Forest plots of incidence risk of gout according to demographic data and comorbidities.

Study population

From the NHIS-HEALS database, we included 362,285 participants aged 40 and above who underwent health screening programs during the baseline years of 2009–2010. Among 362,285 participants, those with missing demographic information, lifestyle information, or laboratory findings were excluded (n = 9047). The washout period was extended from 2002 to the index date, during which patients with a history of gout were excluded (n = 8327). Participants with a follow-up duration of less than one year (n = 121) were excluded to avoid possible reverse causality or association, as well as participants with less than three repeated measurements (n = 44,683). After applying the inclusion and exclusion criteria, the final cohort comprised 300,107 individuals (Fig. 4).

Data collection and definitions

Using health claims data from the NHIS-HEALS, demographic information (age, sex, body mass index (BMI), waist circumference, and income) and lifestyle details (self-reported questionnaires) were extracted. Details can be obtained in the Supplementary Methods.

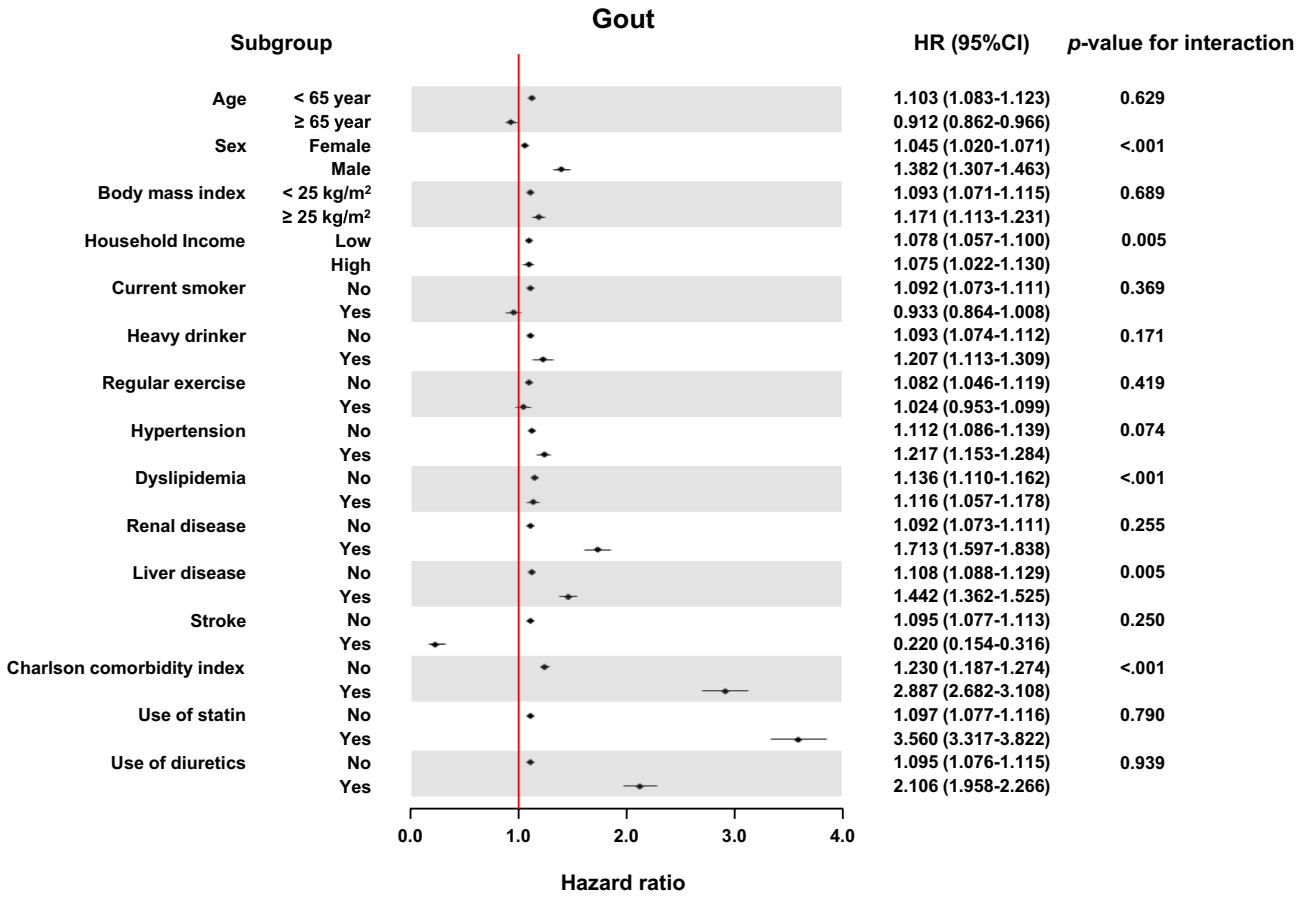


Fig. 4. Flow chart of inclusion and exclusion criteria.

Calculation of TyG index

The TyG index was calculated as ln (TG [mg/dL] × FBG [mg/dL]/2)[7,28] and considered a time-dependent covariate throughout the follow-up period. For further analysis, the average of at least three repeated TyG index measurements was used to reduce bias.

Outcome

The population was identified as having gout at least two times, with the initial date of diagnosis noted. The diagnosis of gout was determined using the M10 code from the ICD-10[29]. A follow-up was conducted until December 31, 2019, death, or the first occurrence of gout.

Statistical analysis

We conducted group comparisons based on quartiles of the TyG index using one-way analysis of variance for continuous variables and the chi-squared test (or Fisher's exact test) for categorical variables. Survival curves for time-to-event outcomes were plotted using Kaplan–Meier curves, and a log-rank test was used to compare survival curves across TyG index groups. To explore the linear relationship between the TyG index and gout incidence, restricted cubic splines with three knots (at the 25th, 50th, and 75th percentiles) were used. The optimal change point in the spline curve analysis was estimated using a regression model with piecewise linear relationships.

To evaluate the incidence of gout in relation to the repeatedly measured TyG index, a time-dependent Cox proportional hazards model was used. Furthermore, the participants were allocated into four quartile groups (Q1, Q2, Q3, and Q4) based on the average TyG index during follow-up. To ascertain the risk of gout according to the quartile groups, a conventional Cox proportional hazards model was used. The proportionality of the hazard assumption was evaluated using the Grambsch–Therneau test of the Schoenfeld residuals, which yielded satisfactory results.

The results of the time-dependent and conventional Cox regression analyses are represented as HR and 95% CI for an unadjusted model, Model 1 and Model 2, depending on the adjustment of covariates. Model 1 was adjusted for age and sex, whereas Model 2 was adjusted for Model 1 + BMI, household income, smoking status, alcohol consumption, regular physical activity, hypertension, DM, renal disease, liver disease, and CCI score. Liver enzyme levels and liver disease were not additionally adjusted for in multivariable Model 2 owing to multicollinearity. Considering the covariates, in cases where participants underwent multiple health checkups between 2009 and 2019, data from their latest examinations were used for statistical analysis. For sensitivity

analysis, because insulin resistance is closely associated with DM, further analyses were performed according to the presence of DM. Subgroup analyses of the association of the TyG index with gout were performed according to demographics, lifestyle, and covariates, yielding p-values for interaction. All statistical analyses were performed using SAS version 9.4 (SAS Inc., Cary, NC, USA) and R software version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria), with statistical significance defined as two-sided p-values < 0.05. The NHIS-HEALS data were analyzed using SAS. For the Cox regression model, the "coxph" function from the survival package in R was used, and the Kaplan–Meier survival curve was drawn using the "survfit" function. Additionally, the restricted cubic spline curve was created using the "rcsplot" function from the plotRCS package in R.

Data availability

The data used in this study were available from the National Health Insurance Service-National Health Screening Cohort (NHIS-HEALS) database. However, restrictions apply to the public availability of data used under the license for this study. Requests for access to the NHIS data can be made through the National Health Insurance Sharing Service homepage (http://nhiss.nhis.or.kr/bd/ab/bdaba021eng.do). To access the database, a comp leted application form, research proposal, and application for approval from the Institutional Review Board were submitted to the Inquiry Committee of Research Support at the NHIS for review.

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Author contributions
T.-J.S. designed the study. Y.C. and J.P. extracted, collected, and analyzed the data. J.P. and T.-J.S. prepared tables and figures. T.-J.S., Y.C., and J.P. reviewed the results and interpreted the data. T.-J.S. and Y.C. prepared the manuscript. All authors have approved the submission of the manuscript.

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Declarations

Competing interests
The authors declare no competing interests.

Ethics statement
This study was approved by the Institutional Review Board of the Ewha Womans University Seoul Hospital (EUMC-2022-02-018). Given that the data are accessible to the public through the NHIS database, the need for ethical approval and informed consent was waived.

Additional information
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