ORIGINAL ARTICLE

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Association of the triglyceride-glucose index with cardiovascular outcomes across cardiovascular-kidney-metabolic syndrome stages

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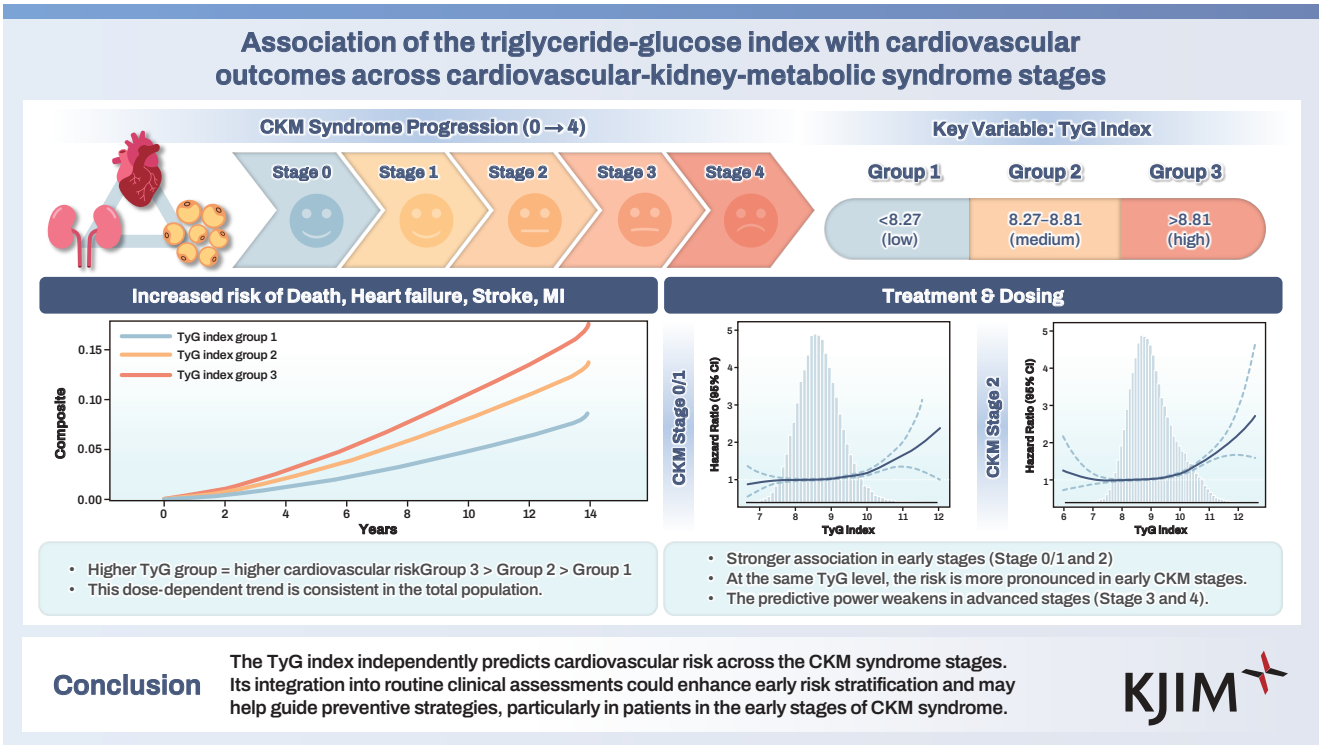

Background/Aims: Cardiovascular-kidney-metabolic (CKM) syndrome reflects the interplay between metabolic dysfunction, chronic kidney disease, and cardiovascular disease. Insulin resistance (IR) is a key driver of CKM and is associated with adverse cardiovascular outcomes. The triglyceride-glucose (TyG) index is a cost-effective surrogate marker of IR; however, its prognostic value across CKM syndrome stages remains unclear.

Methods: We conducted a retrospective cohort study using data of 1,497,913 adults enrolled in the Korean National Health Insurance Database between 2009 and 2012. The participants were stratified into four CKM stages (0/1, 2, 3, and 4) and further categorized into three TyG index tertiles: Group 1 (< 8.27), Group 2 (8.27–8.81), and Group 3 (> 8.81). The primary

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composite outcomes were all-cause mortality, heart failure, stroke, and myocardial infarction.
Results: Over an average follow-up period of 12.6 ± 1.50 years, individuals in the highest TyG tertile demonstrated a significantly higher risk of the composite primary outcome compared to those in the lowest tertile (hazard ratio, 1.116; 95% confidence interval, 1.101–1.131; $p < 0.001$). This dose-dependent relationship was consistent across CKM stages, with the strongest associations observed in the early CKM stages (0/1 and 2). An elevated TyG index is also associated with an increased risk of secondary outcomes, including all-cause death, heart failure, stroke, and myocardial infarction.
Conclusions: The TyG index independently predicted cardiovascular risk across the CKM syndrome stages. Its integration into routine clinical assessments could enhance early risk stratification and guide preventive strategies, particularly for patients in the early stages of CKM syndrome.

Keywords: Triglyceride-glucose index; Cardiovascular disease; Kidney disease; Metabolic syndrome; Insulin resistance

INTRODUCTION

Cardiovascular-kidney-metabolic (CKM) syndrome is a clinically integrated framework that reflects the synergistic pathophysiological interplay between metabolic dysfunction (e.g., obesity, insulin resistance [IR], and dyslipidemia), chronic kidney disease (CKD), and cardiovascular disease (CVD) [1]. The American Heart Association has recently proposed a staging framework, ranging from 0–4, wherein stage 0 indicates no current cardiometabolic or renal risk factors, and extending to stage 4 denotes clinically manifested CVD [2]. This structured approach underscores the need to identify at-risk individuals in the early or subclinical stages before overt cardiovascular or renal complications occur. Advanced CKM syndrome stages (3 and 4) carry a notably heightened burden of morbidity and mortality, necessitating intensive lifestyle interventions and comprehensive guideline-directed pharmacotherapy to curb disease progression and improve clinical outcomes [1-4].

IR plays an integral role in the pathophysiology of CKM syndrome, driving the development of metabolic risk factors, accelerating kidney disease, and ultimately contributing to the development of CVD [2]. It is closely associated with increased cardiovascular risk [5]; however, a practical method for accurately evaluating IR in population-based settings remains elusive [6]. Although the euglycemic–hyperinsulinemic clamp is considered the gold standard, its high cost and complexity limit its widespread use. Similarly, the homeostasis model assessment of IR is commonly employed; however, it relies on measuring circulating insulin, which is not routinely quantified in clinical practice, thus limiting its clinical applicability [7]. The triglyceride-glucose (TyG) index, which is derived from fasting triglyceride and glucose levels, has emerged as a feasible and cost-effective marker of IR. Validation studies have indicated that it offers a performance comparable to or exceeding that of conventional markers and provides a robust prognostic value for type 2 diabetes, a range of CVDs, and mortality [8,9].

Considering the critical role of IR in CKM syndrome and its strong association with CVD, it is essential to understand whether the TyG index offers additional prognostic value beyond CKM staging. Despite its potential, evidence on the association between the TyG index and cardiovascular outcomes within CKM syndrome stages remains scarce. Therefore, this study aimed to assess the relationship between the TyG index and cardiovascular outcomes across all stages of CKM syndrome to enhance risk stratification and inform tailored management strategies.

METHODS

Study populations and data collection

This retrospective cohort study used data from the Korean National Health Insurance Database (NHID), a comprehensive resource that includes the medical claims, demographic data, and health examination records of nearly the entire Korean population. The NHID integrates data from biennial health-screening programs to promote the early detection and management of chronic diseases. These health checkups include measurements of lifestyle behaviors, anthropometric parameters, and laboratory markers, providing a robust dataset for epidemiological research. This dataset has been described in prior publications [10-12].

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This study included 1,500,959 adults who participated in the National Health Screening Program between 2009 and 2012. A total of 3,046 individuals were excluded, including participants aged 90 years or older (n = 374) and participants with missing values for any of the following variables: blood pressure (n = 35), smoking status (n = 166), body mass index (BMI; n = 67), waist circumference (n = 68), fasting glucose (n = 47), lipid profile (n = 1,176), or estimated glomerular filtration rate (eGFR; n = 1,286). The final cohort comprised of 1,497,913 participants. The participants were categorized into four stages: stage 0 or 1 (n = 495,261); stage 2 (n = 862,009); stage 3 (n = 94,864); and stage 4 (n = 45,779). Within each CKM syndrome stage, the participants were divided into three groups based on the TyG index tertiles: Group 1 (TyG index < 8.27), Group 2 (TyG index 8.27–8.81), and Group 3 (TyG index > 8.81). Outcomes were analyzed according to these classifications (Fig. 1). This study was approved by the Institutional Review Board (GURI 2024-12-021), and the requirement for informed consent was waived due to the anonymized and de-identified nature of the NHID dataset. All analyses adhered to relevant ethical guidelines, and the study complied with the tenets of the Declaration of Helsinki.

The key variables collected were demographic factors (age and sex), lifestyle behaviors (smoking status, alcohol consumption, and physical activity), and socioeconomic status (household income categorized into quartiles). Anthropometric measurements included BMI and waist circumference. Laboratory markers included fasting glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein cholesterol, triglycerides, and eGFR. Blood pressure (systolic and diastolic) was measured. Clinical history variables included prior diagnoses of hypertension, diabetes mellitus (DM), and dyslipidemia. Medication use was documented for antihypertensive, glucose-lowering, lipid-lowering, and antiplatelet drugs.

TyG index calculation

The TyG index was calculated using the following formula: TyG index = ln [fasting triglycerides (mg/dL) × fasting glucose (mg/dL)/2] [13]. The participants were classified into three tertiles based on their TyG indices, relative to the distribution of the entire study population: Group 1 (< 8.27), Group 2 (8.27–8.81), and Group 3 (> 8.81), with Group 1

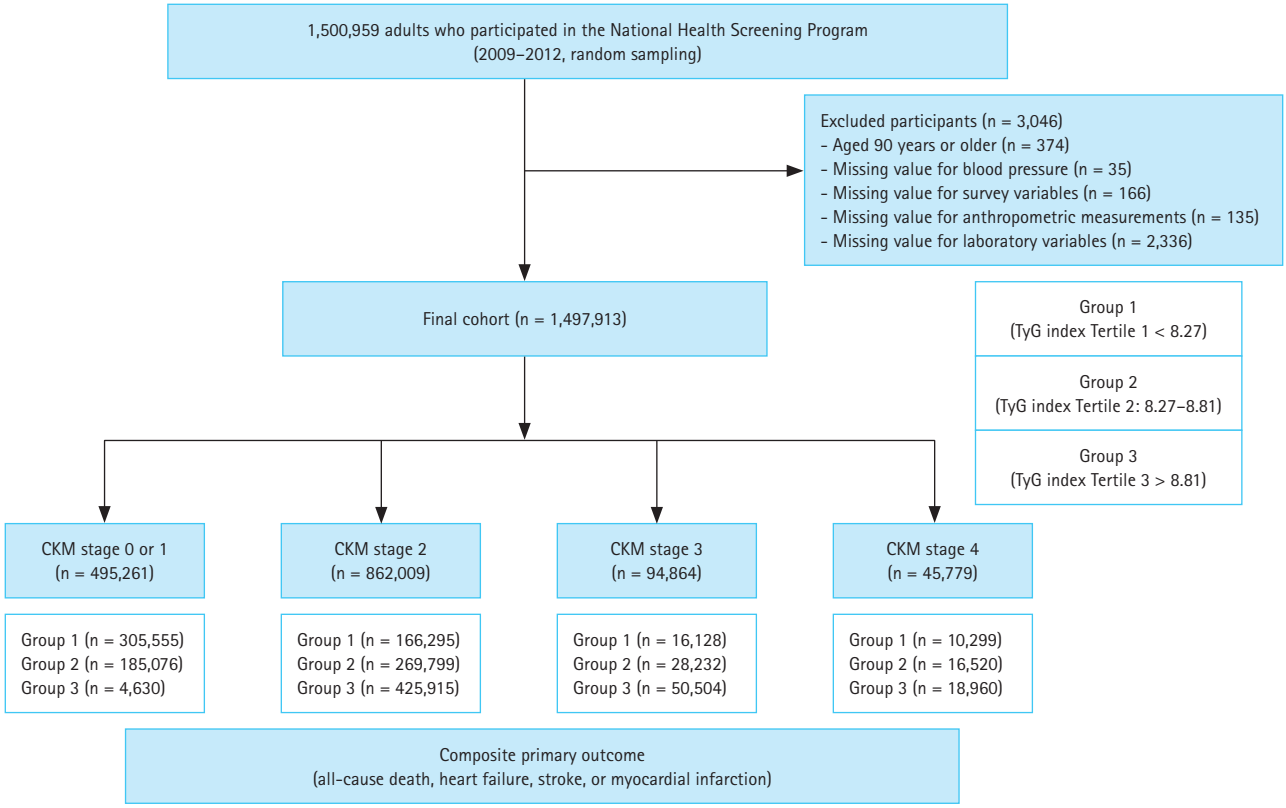

Figure 1. Study flowchart. CKM, cardiovascular-kidney-metabolic; TyG, triglyceride-glucose.

serving as the reference for comparative analysis. In addition, the receiver operating characteristic (ROC) curve analysis for the composite primary outcome was performed in the total population and across the CKM syndrome stages to identify the optimal cutoff values for the TyG index using Youden's index (Supplementary Fig. 1). These cutoffs were subsequently used to dichotomize the participants into high- and low-TyG groups in the supplementary analysis.

Staging of CKM syndrome

The participants were stratified into CKM syndrome stages (0–4) based on previously established criteria incorporating metabolic, cardiovascular, and renal parameters [1,2]. Stage 0 represented individuals without cardiometabolic risk factors or CKD. Stage 1 included those with overweight or dysfunctional adiposity, but no additional metabolic or renal dysfunction. Stage 2 included participants with metabolic risk factors, such as hypertriglyceridemia, hypertension, metabolic syndrome, or diabetes, as well as patients with CKD, who exhibited eGFRs ranging from 30–59 mL/min/1.73 m^2. Stage 3 included individuals with subclinical CVD, defined by either very high-risk CKD (eGFR < 30 mL/min/1.73 m^2) or an elevated 10-year cardiovascular risk, as indicated by a Predicting Risk of Cardiovascular Disease EVENTs (PREVENT) score ≥ 20% [14]. The PREVENT score—a cardiovascular risk model recently developed by the American Heart Association—is derived and validated using data from over six million individuals across 46 U.S.-based datasets. In this study, we used a base model, which incorporated variables, such as age, non-HDL cholesterol levels, HDL cholesterol levels, systolic blood pressure, diabetes, smoking status, BMI, eGFR, and use of antihypertensive or statin medications. The detailed formula is available at: https://professional.heart.org/prevent [14]. Stage 4 represented individuals clinically diagnosed with CVD. A detailed description of the CKM staging is provided in Supplementary Table 1.

Study outcomes

The primary outcome of the study was a composite endpoint comprising all-cause death, heart failure, stroke (both ischemic and hemorrhagic), and myocardial infarction during the follow-up period, which concluded on December 31, 2022. The average follow-up duration was 12.60 ± 1.50 years. Secondary outcomes included the individual components of the primary composite outcomes. Heart failure was identified based on hospitalization records using the International Classification of Diseases, Tenth Revision (ICD-10) codes I50, I42.0, I11.0, or I13.0–I13.2. Myocardial infarction was defined as hospitalization with coronary revascularization and a discharge diagnosis coded I21 or I22. Stroke was confirmed in hospitalized individuals using brain imaging and discharge diagnoses of ICD-10 codes I63–I64 for ischemic stroke and I60–I62 for hemorrhagic stroke. Supplementary Table 2 provides a detailed list of diagnostic and procedural definitions, including the ICD-10 codes used to classify the comorbidities, CKM syndrome stages, and clinical outcomes.

Statistical analyses

Baseline characteristics according to the TyG index tertiles were compared using the chi-square test for categorical variables and one-way analysis of variance (ANOVA) for continuous variables. The incidence rates of cardiovascular outcomes were calculated as the total number of events divided by the cumulative person-years of follow-up and expressed per 1,000 person-years. Kaplan–Meier survival curves were constructed for each CKM syndrome stage to compare event-free survival across TyG tertiles. Statistical differences between survival curves were tested using the log-rank test. Cox proportional hazards regression models were used to assess the association between the TyG index tertiles and outcomes within each CKM syndrome stage. Hazard ratios (HRs) and 95% confidence intervals (CIs) were adjusted for confounders including age, sex, smoking status, alcohol consumption, physical activity, household income, and medication use (antihypertensive, glucose-lowering, lipid-lowering, and antiplatelet drugs). Model 1 included adjustments for age and sex, whereas Model 2 included additional lifestyle and socioeconomic variables. Model 3 was further adjusted for medication use (antihypertensive, glucose-lowering, lipid-lowering, and antiplatelet drugs); eGFR category (≥ 90, 60–89, 30–59, 15–30, < 15); and dipstick proteinuria. To assess the continuous relationship between the TyG index and cardiovascular outcomes, restricted cubic spline regression models were applied using Model 3 adjustments across all CKM syndrome stages. All analyses were performed using complete case data, excluding participants with missing data. Statistical significance was set at a two-tailed p value < 0.05. All the analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC, USA) and R (version 4.2.1; R Foundation for Statistical Computing).

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Table 1. Baseline characteristics

Total patients (N = 1,497,913)	TyG index tertile groups			*p* value
	Group 1 (TyG index < 8.27) (n = 498,277)	Group 2 (TyG index 8.27–8.81) (n = 499,627)	Group 3 (TyG index > 8.81) (n = 500,009)	
Age (yr)	43.57 ± 13.86	49.16 ± 13.90	50.83 ± 13.17	< 0.001
Sex				< 0.001
Male	194,201 (38.97)	268,562 (53.75)	334,503 (66.90)	
Female	304,076 (61.03)	231,065 (46.25)	165,506 (33.10)	
Blood pressure (mmHg)				
SBP	117.37 ± 13.95	122.62 ± 14.53	126.88 ± 14.80	< 0.001
DBP	73.12 ± 9.47	76.32 ± 9.67	79.06 ± 9.90	< 0.001
Smoking				< 0.001
Never	362,541 (72.76)	308,371 (61.72)	247,855 (49.57)	
Past	52,517 (10.54)	74,312 (14.87)	91,968 (18.39)	
Current	83,219 (16.70)	116,944 (23.41)	160,186 (32.04)	
Physical activity (times/week)				< 0.001
0	308,284 (61.87)	304,060 (60.86)	298,517 (59.70)	
1–2	112,796 (22.64)	116,493 (23.32)	124,635 (24.93)	
3–4	47,471 (9.53)	48,088 (9.62)	47,754 (9.55)	
5–6	20,740 (4.16)	20,419 (4.09)	18,522 (3.70)	
7	8,986 (1.80)	10,567 (2.11)	10,581 (2.12)	
Alcohol consumption (times/week)				< 0.001
0	279,591 (56.11)	270,982 (54.24)	234,183 (46.84)	
1–2	174,997 (35.12)	167,960 (33.62)	176,395 (35.28)	
3–4	32,319 (6.49)	43,266 (8.66)	62,911 (12.58)	
≥ 5	11,370 (2.28)	17,419 (3.49)	26,520 (5.30)	
Body mass index (kg/m^2)	22.33 ± 2.88	23.79 ± 3.04	25.08 ± 3.05	< 0.001
< 18.5	34,975 (7.02)	13,157 (2.63)	4,118 (0.82)	< 0.001
18.5–22.9	273,744 (54.94)	191,107 (38.25)	115,255 (23.05)	
23.0–24.9	104,679 (21.01)	133,702 (26.76)	135,315 (27.06)	
≥ 25	84,879 (17.03)	161,661 (32.36)	245,321 (49.06)	
Waist circumference (cm)	75.47 ± 8.35	80.49 ± 8.37	84.72 ± 8.01	< 0.001
Fasting glucose (mg/dL)	88.48 ± 10.74	94.79 ± 13.93	108.20 ± 31.45	< 0.001
< 100	436,169 (87.54)	361,114 (72.28)	245,131 (49.03)	< 0.001
100–125.9	59,447 (11.93)	124,696 (24.96)	180,868 (36.17)	
≥ 126	2,661 (0.53)	13,817 (2.77)	74,010 (14.80)	
Total cholesterol (mg/dL)	181.62 ± 31.88	195.70 ± 34.56	207.75 ± 38.03	< 0.001
< 200	367,309 (73.72)	286,605 (57.36)	218,761 (43.75)	< 0.001
200–239.9	108,772 (21.83)	161,665 (32.36)	187,638 (37.53)	
≥ 240	22,196 (4.45)	51,357 (10.28)	93,610 (18.72)	
LDL (mg/dL)	107.97 ± 29.54	118.23 ± 32.72	115.01 ± 36.84	< 0.001
HDL (mg/dL)	60.55 ± 13.63	55.05 ± 12.74	49.20 ± 11.94	< 0.001

Table 1. Continued

Total patients (N = 1,497,913)	TyG index tertile groups			*p* value
	Group 1 (TyG index < 8.27) (n = 498,277)	Group 2 (TyG index 8.27–8.81) (n = 499,627)	Group 3 (TyG index > 8.81) (n = 500,009)	
< 40 for men or < 50 for women	57,832 (11.61)	93,217 (18.66)	154,876 (30.97)	< 0.001
Triglyceride (mg/dL)	63.68 ± 16.12	110.86 ± 21.35	219.87 ± 101.16	< 0.001
≥ 150	6 (0.00)	22,292 (4.46)	411,027 (82.20)	< 0.001
Estimated glomerular filtration rate (mL/min/1.73 m^2)	84.97 ± 20.85	83.43 ± 21.54	84.29 ± 22.32	< 0.001
≥ 90	183,773 (36.88)	171,606 (34.35)	181,663 (36.33)	< 0.001
60–89	272,998 (54.79)	273,146 (54.67)	262,316 (52.46)	
30–59	38,609 (7.75)	52,143 (10.44)	53,369 (10.67)	
15–29	401 (0.08)	838 (0.17)	1,078 (0.22)	
< 15	2,496 (0.5)	1,894 (0.38)	1,583 (0.32)	
Dipstick proteinuria				< 0.001
Negative	477,123 (95.75)	477,676 (95.61)	469,555 (93.91)	
Trace	10,694 (2.15)	10,295 (2.06)	12,382 (2.48)	
1+	6,341 (1.27)	6,907 (1.38)	10,384 (2.08)	
2+	1,873 (0.38)	2,438 (0.49)	4,512 (0.90)	
3+	423 (0.08)	610 (0.12)	1,338 (0.27)	
4+	73 (0.01)	121 (0.02)	276 (0.06)	
Household income, quartile				< 0.001
First	118,907 (23.86)	106,946 (21.41)	98,961 (19.79)	
Second	115,782 (23.24)	100,053 (20.03)	95,065 (19.01)	
Third	127,434 (25.57)	130,117 (26.04)	136,214 (27.24)	
Fourth	136,154 (27.32)	162,511 (32.53)	169,769 (33.95)	
Hypertension	150,902 (30.28)	219,917 (44.02)	270,517 (54.10)	< 0.001
Diabetes mellitus	12,436 (2.50)	33,067 (6.62)	99,786 (19.96)	< 0.001
Dyslipidemia	51,449 (10.33)	109,975 (22.01)	184,780 (36.96)	< 0.001
Use of antihypertensive drugs	122,480 (24.6)	178,233 (35.7)	214,046 (42.8)	
Use of glucose-lowering drugs	11,003 (2.21)	26,502 (5.30)	66,537 (13.31)	< 0.001
Use of lipid-lowering drugs	33,872 (6.80)	71,808 (14.37)	121,764 (24.35)	< 0.001
Use of antiplatelet drugs	65,508 (13.15)	100,175 (20.05)	127,224 (25.44)	< 0.001
PREVENT score	3.10 ± 6.08	5.42 ± 7.55	8.72 ± 9.59	< 0.001
TyG index	7.90 ± 0.28	8.54 ± 0.16	9.28 ± 0.39	< 0.001
CKM stage				< 0.001
Stage 0	189,661 (38.06)	70,873 (14.19)	0 (0.00)	
Stage 1	115,894 (23.26)	114,203 (22.86)	4,630 (0.93)	
Stage 2	166,295 (33.37)	269,799 (54.00)	425,915 (85.18)	
Stage 3	16,128 (3.24)	28,232 (5.65)	50,504 (10.10)	
Stage 4	10,299 (2.07)	16,520 (3.31)	18,960 (3.79)	

Values are presented as mean ± standard deviation or number (%).
CKM, cardiovascular kidney metabolic; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PREVENT, Predicting Risk of cardiovascular disease EVENTs; SBP, systolic blood pressure; TyG index, triglyceride-glucose index.

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RESULTS

Baseline characteristics

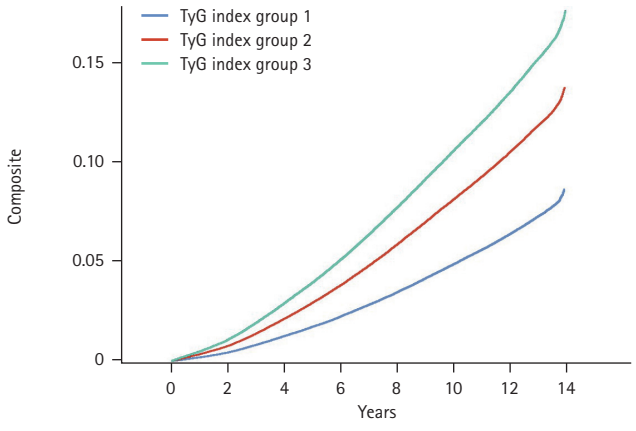
Table 1 presents the baseline characteristics of the study population stratified by TyG index tertiles. Participants in the higher TyG tertiles were older, with Group 3 having the highest mean age (50.83 ± 13.17 years) and a greater proportion of men (66.9% vs. 53.8% vs. 38.9%, Group 3 vs. 2 vs. 1). A higher TyG index was associated with increased metabolic risk factors, including an elevated BMI; waist circumference; and fasting glucose, triglyceride, and total cholesterol levels. The prevalence of hypertension, DM, and dyslipidemia increased progressively across the TyG tertiles, with Group 3 exhibiting the highest prevalence of these conditions. Similarly, the use of antihypertensive, glucose-lowering, lipid-lowering, and antiplatelet medications was most frequent in Group 3 ($p < 0.001$). In addition, the mean PREVENT score increased progressively across TyG tertiles (3.10 ± 6.08 in Group 1, 5.42 ± 7.55 in Group 2, and 8.72 ± 9.59 in Group 3; $p < 0.001$). The distribution of CKM syndrome stages differed notably across TyG tertiles ($p < 0.001$). In Group 1, a higher proportion of participants were classified as stage 0 or 1, whereas Group 3 was predominantly composed of individuals with stage 2 or higher. The proportions of participants in stages 3 and 4 were significantly higher in Group 3 (10.1% and 3.8%, respectively) than in Group 1 (3.2% and 2.1%, respectively).

Clinical outcomes according to TyG index across CKM syndrome stages

Figure 2 illustrates the Kaplan–Meier survival curves for the composite primary outcomes (all-cause death, heart failure, stroke, or myocardial infarction) and the secondary outcomes across the TyG index tertiles in the total population. Individuals in the highest TyG tertile (Group 3) exhibited a significantly higher cumulative incidence of the composite primary outcome than those in the lower tertiles, demonstrating a clear dose–response relationship (Fig. 2A, log-rank $p < 0.001$). A similar pattern was observed for the secondary outcomes: all-cause death (Fig. 2B), heart failure (Fig. 2C), stroke (Fig. 2D), and myocardial infarction (Fig. 2E). Overall, these trends were consistent with the primary outcome, showing a higher cumulative incidence in the highest TyG tertile with a dose–response relationship (all log-rank $p < 0.001$).

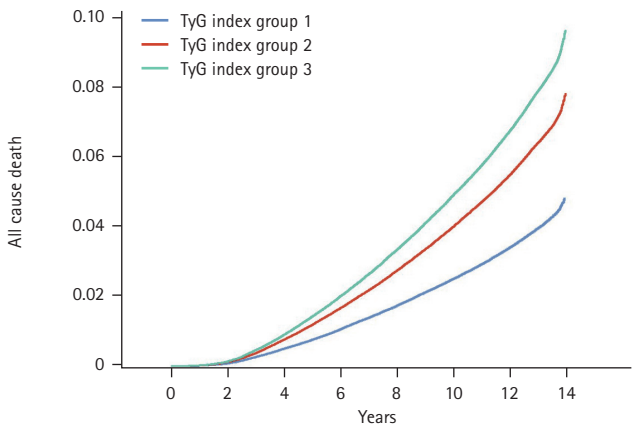
Table 2 shows the association between the TyG index tertiles and the composite primary outcome after adjusting for potential confounders in both the total population and across the CKM syndrome stages. In the fully adjusted model (Model 3), the individuals in Group 3 exhibited a significantly higher risk of the composite primary outcome than those in Group 1 (HR, 1.116; 95% CI, 1.101–1.131; $p < 0.001$), showing a dose-dependent relationship. Group 2 showed a modest increase in risk (HR, 1.035; 95% CI, 1.021–1.049; $p < 0.001$). When stratified by CKM syndrome stage (interaction $p < 0.001$), a stronger association was observed in the earlier stages, with the highest HRs observed in Group 3 at stage 0/1 (HR, 1.166; 95% CI, 1.036–1.312; $p = 0.011$) and stage 2 (HR, 1.090; 95% CI, 1.069–1.111, $p < 0.001$). The effect remained significant in stage 3, although it was attenuated compared to that of the earlier stages (HR, 1.055; 95% CI, 1.025–1.085; $p < 0.001$). However, in Stage 4, the association between Group 3 and the composite outcome was no longer statistically significant after adjustment (HR, 1.040; 95% CI, 0.999–1.083; $p = 0.055$). Group 2 followed a similar trend, with a moderate increase in risk across all CKM syndrome stages. However, only the increased risk for stage 2 was significant (HR, 1.023; 95% CI, 1.004–1.044; $p = 0.019$). In addition, when the participants were dichotomized using the optimal TyG cutoff values identified by the ROC curve analysis for the composite outcome in the total population and CKM stages (8.489 for the total population, 8.097 for Stage 0/1, 8.132 for Stage 2, 9.571 for Stage 3, and 8.509 for Stage 4), those with a high TyG index had a higher risk of the primary composite outcome than those with a low TyG index relative to the total population and all CKM stages. For secondary outcomes (Supplementary Tables 3–6), Group 3 showed significantly higher risks for all-cause death (HR, 1.061; 95% CI, 1.042–1.081; $p < 0.001$); heart failure (HR, 1.054; 95% CI, 1.032–1.078; $p < 0.001$); stroke (HR, 1.209; 95% CI, 1.179–1.239; $p < 0.001$); and myocardial infarction (HR, 1.736; 95% CI, 1.647–1.829; $p < 0.001$) in the total population. The relative risks of myocardial infarction and stroke were higher than those of all-cause death and heart failure. Across CKM stages, the association showed a similar pattern to that of the primary outcome, with stronger effects observed in the earlier stages than in the later stages.

Furthermore, Figure 3 presents the RCS curves illustrating the association between the TyG index and composite primary outcome based on the fully adjusted model across the total population (Fig. 3A) and CKM syndrome stages (Fig.



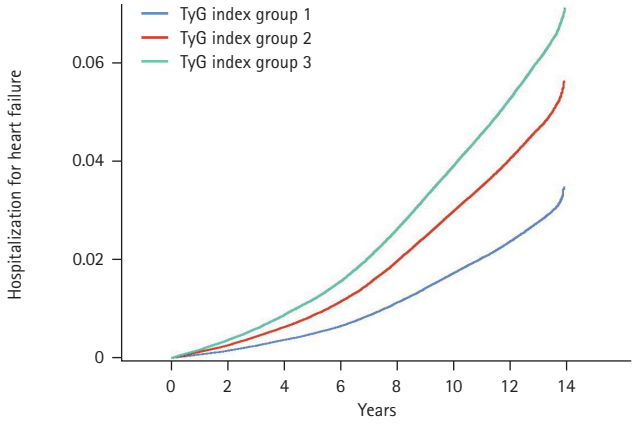
TyG index group 1	498277	496107	492013	487068	481004	473912	431488
TyG index group 2	499627	495819	489011	480556	470326	458956	418996
TyG index group 3	500009	494666	485488	474527	461387	446983	402608

A



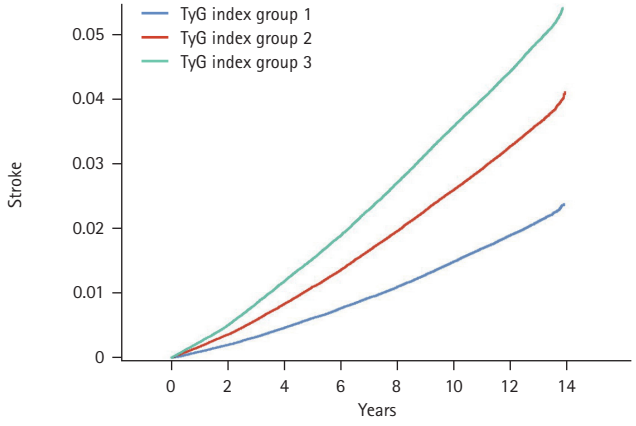
TyG index group 1	498277	497904	495788	492991	489635	485711	445497
TyG index group 2	499627	499072	495834	491288	485916	479520	442672
TyG index group 3	500009	499338	495499	489950	483311	475262	434210

B



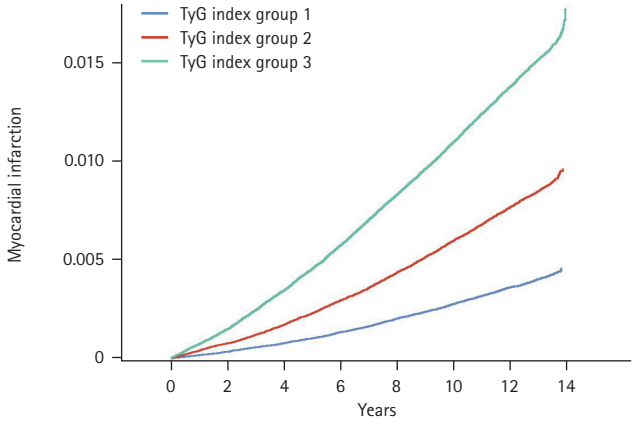
TyG index group 1	498277	497173	494199	490416	485385	479461	437802
TyG index group 2	499627	497813	493083	486666	478360	468708	429745
TyG index group 3	500009	497554	491622	483533	473139	461048	417530

C



TyG index group 1	498277	496917	493727	489798	485321	480103	439071
TyG index group 2	499627	497302	492093	485574	478168	469832	431815
TyG index group 3	500009	496894	490169	481964	472538	461985	419877

D



TyG index group 1	498277	497731	495425	492398	488761	484560	444123
TyG index group 2	499627	498687	495023	489952	484028	477052	439796
TyG index group 3	500009	498602	493853	487337	479663	470673	429081

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Figure 2. Kaplan–Meier curves illustrating the cumulative incidence of the composite primary outcome (all-cause death, heart failure, stroke, and myocardial infarction) and secondary outcomes across the TyG index tertiles in the total population. Curves for (A) composite primary outcomes (all-cause death, heart failure, stroke, and myocardial infarction); (B) all-cause death; (C) heart failure; (D) stroke; and (E) myocardial infarction. TyG, triglyceride-glucose.

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Table 2. Association between TyG index and composite primary outcome across CKM syndrome stages

	Events (N)	Person-years	IR	Model 1			Model 2			Model 3		
				HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Total population												
Group 1 (n = 498,227)	35,782	6,220,082	5.75	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
Group 2 (n = 499,627)	58,657	6,130,946	9.57	1.086	1.072–1.101	< 0.001	1.063	1.049–1.077	< 0.001	1.035	1.021–1.049	< 0.001
Group 3 (n = 500,009)	75,236	6,035,328	12.47	1.284	1.267–1.300	< 0.001	1.227	1.211–1.243	< 0.001	1.116	1.101–1.131	< 0.001
TyG < 8.489 (n = 703,588)	57,456	8,751,493	6.57	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
TyG ≥ 8.489 (n = 794,325)	112,219	9,634,864	11.65	1.199	1.187–1.211	< 0.001	1.091	1.080–1.103	< 0.001	1.084	1.072–1.095	< 0.001
Stage 0 or 1												
Group 1 (n = 305,555)	8,294	3,881,692	2.14	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
Group 2 (n = 185,076)	7,515	2,346,625	3.20	1.045	1.012–1.078	< 0.001	1.025	0.993–1.059	0.129	1.026	0.994–1.060	0.112
Group 3 (n = 4,630)	290	58,319	4.97	1.219	1.084–1.372	< 0.001	1.164	1.034–1.309	0.012	1.166	1.036–1.312	0.011
TyG < 8.097 (n = 226,940)	5,652	2,883,997	1.96	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
TyG ≥ 8.097 (n = 268,321)	10,447	3,402,639	3.07	1.056	1.022–1.092	0.001	1.033	0.999–1.068	0.054	1.035	1.001–1.070	0.042
Stage 2												
Group 1 (n = 166,295)	15,990	2,064,360	7.75	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)		
Group 2 (n = 269,799)	29,614	3,330,212	8.89	1.049	1.029–1.069	< 0.001	1.018	0.998–1.038	0.073	1.023	1.004–1.044	0.019
Group 3 (n = 425,915)	44,298	5,259,701	8.42	1.144	1.123–1.165	< 0.001	1.076	1.057–1.097	< 0.001	1.090	1.069–1.111	< 0.001
TyG < 8.132 (n = 119,751)	10,995	1,489,067	7.38	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
TyG ≥ 8.132 (n = 742,258)	78,907	9,165,206	8.61	1.109	1.087–1.131	< 0.001	1.052	1.031–1.073	< 0.001	1.060	1.038–1.082	< 0.001
Stage 3												
Group 1 (n = 16,128)	7,728	165,889	46.59	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)		
Group 2 (n = 28,232)	14,636	284,921	51.37	1.037	1.009–1.066	0.009	1.049	1.021–1.079	< 0.001	1.012	0.984–1.041	0.389
Group 3 (n = 50,504)	22,297	527,443	42.27	1.129	1.100–1.159	< 0.001	1.163	1.132–1.195	< 0.001	1.055	1.025–1.085	< 0.001
TyG < 9.571 (n = 74,708)	37,865	757,770	49.97	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
TyG ≥ 9.571 (n = 20,156)	6,796	220,484	30.82	1.176	1.143–1.210	< 0.001	1.202	1.168–1.237	< 0.001	1.129	1.096–1.163	< 0.001
Stage 4												
Group 1 (n = 10,299)	3,770	108,141	34.86	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)		
Group 2 (n = 16,520)	6,892	169,189	40.74	1.023	0.983–1.065	0.259	1.025	0.984–1.066	0.236	0.999	0.960–1.040	0.975
Group 3 (n = 18,960)	8,351	189,865	43.98	1.141	1.098–1.186	< 0.001	1.143	1.099–1.189	< 0.001	1.040	0.999–1.083	0.055
TyG < 8.509 (n = 17,017)	6,484	177,289	36.57	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
TyG ≥ 8.509 (n = 28,762)	12,529	289,906	43.22	1.108	1.076–1.142	< 0.001	1.111	1.077–1.145	< 0.001	1.043	1.011–1.076	0.007

CI, confidence interval; CKM, cardiovascular-kidney-metabolic; HR, hazard ratio; IR, incidence rate; Ref., reference; TyG index, triglyceride-glucose index; eGFR, estimated glomerular filtration rate.
The primary outcome was defined as a composite of all-cause death, heart failure, stroke (both ischemic and hemorrhagic), and myocardial infarction.
Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, smoking status, alcohol consumption, physical activity, and household income. Model 3: adjusted for age, sex, smoking status, alcohol consumption, physical activity, household income, use of antihypertensive drugs, use of glucose-lowering drugs, use of lipid-lowering drugs, use of antiplatelet drugs, eGFR category, and dipstick proteinuria.

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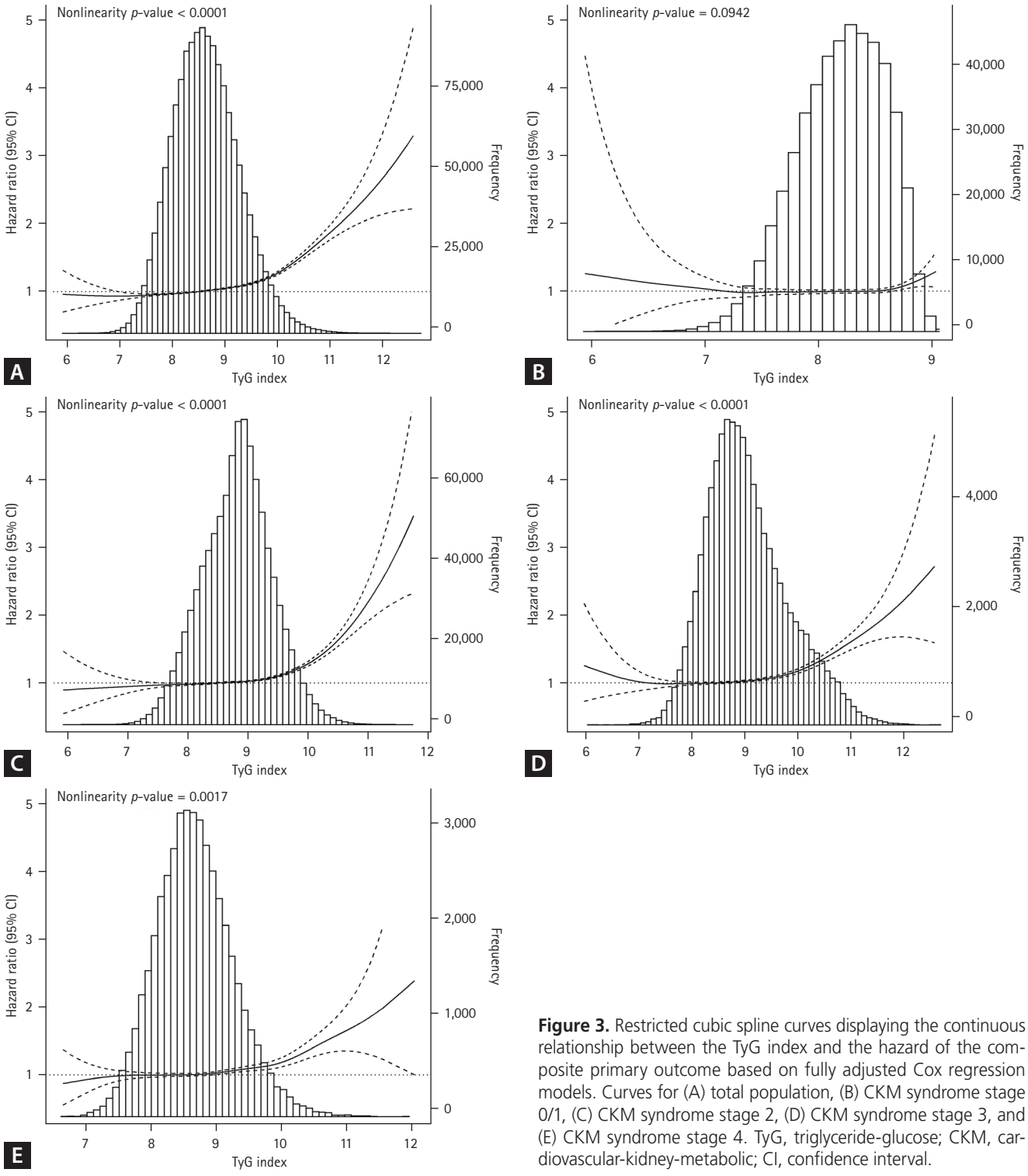

Figure 3. Restricted cubic spline curves displaying the continuous relationship between the TyG index and the hazard of the composite primary outcome based on fully adjusted Cox regression models. Curves for (A) total population, (B) CKM syndrome stage 0/1, (C) CKM syndrome stage 2, (D) CKM syndrome stage 3, and (E) CKM syndrome stage 4. TyG, triglyceride-glucose; CKM, cardiovascular-kidney-metabolic; CI, confidence interval.

3B–E). The analysis demonstrated a nonlinear, dose-dependent relationship, with a notable increase in HRs at higher TyG index levels. Excluding Stage 0/1, in which the TyG index distribution was concentrated at lower values, earlier CKM syndrome stages exhibited a greater increase in HRs at higher TyG index levels than later stages.

To assess the potential effect of lipid-lowering therapy, we conducted a subgroup analysis stratified by baseline

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statin use. Although the association between a higher TyG index and clinical outcomes remained generally consistent across the statin user and non-user groups, the magnitude of the association appeared slightly more pronounced among non-users. The interaction *p* values were statistically significant for heart failure and myocardial infarction (Supplementary Table 7).

DISCUSSION

This study investigated the association between TyG index and cardiovascular outcomes across CKM syndrome stages in a large nationwide cohort. Our findings suggested that the TyG index serves as an independent predictor of adverse outcomes beyond the CKM staging. This is the first large-scale study to evaluate the prognostic value of the TyG index across all stages of CKD. In this study, CKM Stages 0 and 1 were combined into a single reference category (Stage 0/1) because of their low event rates, and the distribution of the TyG index in Stage 0 was heavily skewed towards the lower values, such that no participants qualified for the highest TyG tertile (Group 3). CKM Stage 0 is defined as the absence of any metabolic risk factors, whereas stage 1 includes individuals with overweight or dysfunctional adiposity, but without metabolic or renal dysfunction [2]. Both groups represented populations at relatively low cardiometabolic risk, where the primary drivers of future disease are subclinical metabolic disturbances, such as IR. A separate analysis of Stages 0 and 1 for the primary composite outcomes is shown in Supplementary Table 8. The key findings were as follows: (1) the individuals in the highest TyG tertile (Group 3, TyG index > 8.81) had a significantly higher risk of the composite primary outcome than those in the lowest tertile (Group 1, TyG index < 8.27), with a dose-dependent relationship observed both in the total population and across most CKM syndrome stages, although the association was not statistically significant in Stage 4 after full adjustment; (2) this association was stronger in earlier CKM syndrome stages, particularly in Stages 0/1 and 2, and attenuated in advanced stages; and (3) similar trends were observed for secondary outcomes, including all-cause death, heart failure, stroke, and myocardial infarction. These findings indicated that the TyG index may serve as a valuable marker to enhance the prognostic utility of the CKM syndrome staging system, particularly for facilitating early risk stratification before the development of overt CVD.

CKM syndrome represents a complex, multidirectional interplay between metabolic risk factors, CKD, and the cardiovascular system, which contributes to adverse clinical outcomes [3]. IR is the fundamental driver of this syndrome and accelerates the progression of metabolic disturbances, CKD, and CVD [2,15-17]. The TyG index, a simple and cost-effective marker of IR, is associated with cardiovascular risk [8,18]. In previous cross-sectional studies, an elevated TyG index was associated with advanced CKM syndrome [19]. Moreover, a recent study in China demonstrated that a high TyG index was associated with kidney function deterioration in patients with CKM syndrome [20]. However, its prognostic significance in cardiovascular outcomes within the CKM staging framework remains largely unknown. While a modified version of the TyG index, the triglyceride glucose-BMI , previously correlated with cardiovascular risk in populations with CKM syndrome stages 0–3 [21], the study relied on survey-based self-reports for outcome assessment and had a relatively small sample size, limiting the consistency of findings across CKM subgroups. Our study extended these previous observations [19-21] by utilizing a large, comprehensive, and nationwide cohort data to accurately capture a range of outcomes, including all-cause death, across the entire CKM syndrome spectrum, thereby providing more robust evidence of the prognostic value of the TyG index for cardiovascular events across CKM syndrome stages.

Intriguingly, the cardiovascular risk in the highest TyG tertile (group 3, TyG > 8.81) was most pronounced in the earlier stages of CKM syndrome. Several mechanisms may explain these observations. In the early stages of CKM (particularly Stages 0/1 and 2), the predominant pathology involves IR, low-grade inflammation, and early vascular dysfunction, rather than irreversible organ damage [2]. Consequently, the TyG index may capture the subclinical metabolic disturbances that precede overt CVD, underscoring its role as an important early risk marker [22]. This suggests that, in populations with a relatively low baseline risk, the TyG index may serve as an early warning marker, identifying individuals who might benefit from timely lifestyle interventions to prevent progression to more advanced, high-risk stages. Furthermore, we observed that the impact of the TyG index on myocardial infarction and stroke was greater than its effect on heart failure or all-cause death, suggesting that IR may drive atherosclerotic processes more strongly [23]. These findings warrant further prospective studies to

confirm and expand upon these observations.

These findings have important clinical implications. Incorporating the TyG index into routine clinical assessments can enhance early risk stratification in patients with CKM syndrome, particularly during the initial stages. This straightforward and cost-effective measure enables clinicians to identify individuals at an elevated risk of progressing to advanced CKM syndrome stages and developing CVD, before the overt disease manifests [19]. Early detection using the TyG index may help inform early lifestyle modification strategies, such as dietary changes, increased physical activity, and weight management, aimed at reducing IR and mitigating disease progression [24,25]. Specifically, individuals with elevated TyG levels in the early stages of CKM syndrome may benefit from structured lifestyle interventions combined with regular evaluations of IR and CKM stage progression, enabling the timely identification of candidates for pharmacological therapy. Ultimately, the integration of the TyG index into current screening protocols can refine patient management by providing a more nuanced understanding of cardiometabolic risk across the CKM spectrum.

The strengths of our study include its large, nationally representative sample size and long follow-up period of > 12 years, which allowed for a robust assessment of long-term outcomes. Furthermore, the comprehensive nature of the Korean NHID enabled detailed adjustment for potential confounders, including demographic, lifestyle, and pharmacological factors. By stratifying participants according to both the CKM syndrome stage and TyG index tertiles, we were able to delineate a clear, graded relationship between IR and adverse outcomes across different stages of cardiometabolic and renal health. Despite these strengths, this study had several limitations that warrant consideration. First, the retrospective observational design precluded definitive causal inferences regarding the relationship between TyG index and cardiovascular outcomes. Second, our reliance on claims data and health-screening records might have led to the misclassification or underestimation of some clinical events despite rigorous coding protocols. Third, although the homogeneity of the Korean population provided a consistent dataset, it may limit the generalizability of our findings to other ethnic groups and healthcare settings. Furthermore, the PREVENT risk score used in this study was developed based on U.S.-based cohorts. Therefore, its applicability to Koreans should be interpreted with caution. Fourth, unmeasured confounding factors, such as dietary habits, genetic predisposition, and socioeconomic status may have influenced both the TyG index and clinical outcomes. These factors were not fully accounted for in this study. Fifth, while the TyG index is a dynamic biomarker reflecting the ongoing metabolic status, our study was restricted to baseline measurements, which limited our ability to assess the impact of temporal changes on cardiovascular outcomes. Future longitudinal studies with more frequent measurements are essential for a better understanding of their prognostic roles. Finally, although the TyG index demonstrated an independent prognostic value across CKM stages, its applicability and method of integration into existing cardiovascular risk models remain unclear and requires further investigation. Future research should validate these findings in diverse populations and explore the mechanisms linking IR to CKM syndrome progression, including the potential role of longitudinal changes in the TyG index and the effects stratified by age and sex, which may inform personalized management strategies across the CKM stages. Prospective studies or randomized controlled trials evaluating whether aggressive lifestyle interventions and close monitoring in the early stages of CKM syndrome, specifically in individuals with a high TyG index, can effectively reduce the incidence of cardiovascular events would be particularly valuable.

In conclusion, our study demonstrated that the TyG index is a valuable prognostic marker for cardiovascular outcomes across the CKM syndrome stages. Individuals with a high TyG index, particularly those in the early stages of CKM syndrome, are at an increased risk of progressing to advanced CKM syndrome stages and developing adverse cardiovascular events. Integrating the TyG index into routine clinical assessments could enhance early risk stratification, enabling timely lifestyle interventions to mitigate the progression of cardiometabolic and renal dysfunctions. Future prospective studies in diverse populations are warranted to validate these findings and to elucidate the underlying mechanisms linking IR to CKM syndrome progression.

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KEY MESSAGE

1. The TyG index is independently associated with dose-dependent adverse cardiovascular outcomes.
2. Its prognostic value is consistent across all CKM syndrome stages, with the highest risk in early stages.
3. Incorporating the TyG index into clinical assessments may enable early, targeted management of CKM syndrome and prevent its progression.

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Byung Sik Kim: conceptualization, data curation, formal analysis, investigation, writing - original draft, writing - review & editing; Hyun-Jin Kim: conceptualization, data curation, formal analysis, investigation, writing - original draft, writing - review & editing; Shinje Moon: writing - review & editing; Hasung Kim: investigation, methodology, validation, visualization; Jungkuk Lee: investigation, methodology, software, validation; Jeong-Hun Shin: conceptualization, data curation, formal analysis, supervision, writing - review & editing

Conflicts of interest
The authors disclose no conflicts.

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Supplementary Table 1. Definitions of cardiovascular-kidney-metabolic syndrome stages

Stage	Definition
Stage 0: no CKM risk factors	Individuals without overweight/obesity, hypertension, hypertriglyceridemia, metabolic syndrome, diabetes mellitus, CKD, or any clinical or subclinical CVD
Stage 1: excess or dysfunctional adiposity	Individuals with overweight/obesity, abdominal obesity, or dysfunctional adipose tissue, but no additional metabolic risk factors or CKD - BMI ≥ 23 kg/m^2 (for Asian cutoff) - Waist circumference ≥ 80 cm (women) or ≥ 90 cm (men) (for Asian cutoff) - Fasting glucose between 100 and 125 mg/dL
Stage 2: metabolic risk factors and CKD	Individuals with at least one metabolic risk factors (hypertriglyceridemia, hypertension, metabolic syndrome, diabetes), or CKD - Triglyceride levels ≥ 135 mg/dL - Hypertension, defined as blood pressure ≥ 140/90 mmHg, prior diagnosis of hypertension, or use of antihypertensive drugs - Metabolic syndrome (defined as at least three of the following): 1) Abdominal obesity (waist circumference ≥ 80 cm for women, ≥ 90 cm for men) 2) Fasting glucose ≥ 100 mg/dL, prior diagnosis of diabetes mellitus, or use of glucose-lowering drugs 3) Blood pressure ≥ 130/85 mmHg, prior diagnosis of hypertension, or use of antihypertensive drugs 4) Triglyceride levels ≥ 150 mg/dL 5) HDL cholesterol levels < 40 mg/dL (men) or < 50 mg/dL (women) - Diabetes mellitus, defined as fasting glucose ≥ 126 mg/dL or prior diagnosis of diabetes mellitus or use of glucose-lowering drugs - CKD, defined as an eGFR of 30–59 mL/min/1.73 m^2
Stage 3: subclinical CVD	Individuals with subclinical ASCVD coexisting with excess/dysfunctional adiposity, other metabolic risk factors, or CKD - Very high-risk CKD, defined as an eGFR < 30 mL/min/1.73 m^2 - High 10-year CVD risk (PREVENT score ≥ 20%)
Stage 4: clinical CVD	Individuals with clinical CVD (coronary heart disease, heart failure, stroke, peripheral artery disease, atrial fibrillation) coexisting with excess/dysfunctional adiposity, other metabolic risk factors, or CKD

ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CKD, chronic kidney disease; CKM, cardiovascular-kidney-metabolic syndrome; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; PREVENT, Predicting Risk of cardiovascular disease EVENTs.

Supplementary Table 2. Definitions of comorbidities and clinical outcomes based on ICD-10 codes

Diagnosis	Definition
Hypertension	Blood pressure ≥ 140/90 mmHg, prior history of hypertension (ICD-10 codes I10–I15), or the use of antihypertensive drugs
Diabetes mellitus	Fasting glucose ≥ 126 mg/dL, prior history of diabetes mellitus (ICD-10 codes E10–E14), or the use of glucose-lowering drugs
Dyslipidemia	Total cholesterol ≥ 240 mg/dL, prior history of dyslipidemia (ICD-10 code E78), or the use of lipid-lowering drugs
Heart failure	Hospitalization with ICD-10 codes I50, I42.0, I11.0, or I13.0–I13.2
Myocardial infarction	Hospitalization with ICD-10 codes I21–I22, with documented coronary revascularization (e.g., PCI or CABG) using corresponding procedural codes
Coronary artery disease	History of myocardial infarction or coronary revascularization
Coronary artery bypass graft surgery	Procedure codes O1640–O1642, O1647–O1649, OA640–OA642, or OA647–OA649
Percutaneous coronary intervention	Procedure codes M6551–M6554, M6561–M6567, M6571, M6572, or O1876–O1877
Stroke	Hospitalization with primary diagnosis ICD-10 codes I63–I64 (ischemic stroke) or I60–I62 (hemorrhagic stroke), combined with brain imaging procedure codes
Brain imaging	Procedure codes HA441, HA451, HA461, HA851, HE101, HE201, HE301, HE401, HE501, HE102, HE135, HE136, HE202, HE235, HE236, HE301, HE302, HE501, HE502, HE535, HE536, HI101, HI135, HI136, HI201, HI235, HI236, HI301, HI401, HI501, HI535, HI536, HJ101, HJ135, HJ136, HJ201, HJ235, HJ236, HJ301, HJ401, HJ501, HJ535, or HJ536
Peripheral artery disease	Hospitalization with ICD-10 codes I70–71, I73.1, I73.8–9, I77.1, I79.0, I79.2, K55.1, K55.8–9, or Z95.8–9, with evidence of peripheral artery revascularization.
Peripheral artery revascularization	Procedure codes M6597, M6605, M6620, M6613, M6632, O0161~70, O1645, O1646, O2064, O2065, O2067, or O2068
Atrial fibrillation	Defined as ICD-10 code I48

CABG, coronary artery bypass grafting; ICD, International Classification of Diseases; PCI, percutaneous coronary intervention.

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Supplementary Table 3. Association between TyG index and all-cause death across CKM syndrome stages

		Events (N)	Person-years	IR	Model 1			Model 2			Model 3		
					HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Total population	Group 1 (n = 498,227)	19,504	6,313,169	3.09	1 (Ref.)			1 (Ref.)			1 (Ref.)		
	Group 2 (n = 499,627)	31,769	6,294,545	5.05	1.017	0.999–1.035	0.072	1.037	1.019–1.056	< 0.001	1.008	0.990–1.026	0.413
	Group 3 (n = 500,009)	39,129	6,262,664	6.25	1.138	1.119–1.158	< 0.001	1.179	1.158–1.200	< 0.001	1.061	1.042–1.081	< 0.001
	TyG < 8.489 (n = 703,588)	31,286	8,904,193	3.51	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
	TyG ≥ 8.489 (n = 794,325)	59,116	9,966,185	5.93	1.103	1.088–1.118	< 0.001	1.130	1.115–1.147	< 0.001	1.050	1.035–1.065	< 0.001
Stage 0 or 1	Group 1 (n = 305,555)	3,944	3,901,223	1.01	1 (Ref.)			1 (Ref.)			1 (Ref.)		
	Group 2 (n = 185,076)	3,539	2,365,706	1.50	0.976	0.932–1.022	0.298	0.988	0.943–1.035	0.622	0.991	0.946–1.038	0.691
	Group 3 (n = 4,630)	147	59,098	2.49	1.159	0.982–1.367	0.081	1.147	0.972–1.354	0.105	1.150	0.975–1.358	0.098
	TyG < 8.097 (n = 226,940)	2,685	2,897,245	0.93	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
	TyG ≥ 8.097 (n = 268,321)	4,945	3,428,782	1.44	0.986	0.94–1.034	0.566	0.995	0.948–1.045	0.850	0.998	0.951–1.048	0.944
Stage 2	Group 1 (n = 166,295)	7,446	2,110,050	3.53	1 (Ref.)			1 (Ref.)			1 (Ref.)		
	Group 2 (n = 269,799)	13,344	3,419,839	3.90	0.998	0.970–1.026	0.872	1.005	0.977–1.034	0.731	1.006	0.977–1.035	0.698
	Group 3 (n = 425,915)	18,942	5,400,504	3.51	1.049	1.022–1.078	< 0.001	1.052	1.023–1.081	< 0.001	1.046	1.017–1.076	0.002
	TyG < 8.132 (n = 119,751)	5,140	1,520,241	3.38	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
	TyG ≥ 8.132 (n = 742,258)	34,592	9,410,151	3.68	1.027	0.997–1.057	0.0805	1.029	0.999–1.060	0.0604	1.026	0.995–1.057	0.010

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Supplementary Table 3. Continued

		Events (N)	Person-years	IR	Model 1			Model 2			Model 3		
					HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Stage 3	Group 1 (n = 16,128)	5,920	180,688	32.76	1 (Ref.)			1 (Ref.)			1 (Ref.)		
	Group 2 (n = 28,232)	10,975	315,423	34.79	1.020	0.989–1.053	0.210	1.058	1.025–1.092	< 0.001	1.018	0.986–1.051	0.269
	Group 3 (n = 50,504)	15,380	582,012	26.43	1.079	1.046–1.112	< 0.001	1.171	1.134–1.208	< 0.001	1.060	1.026–1.094	< 0.001
	TyG < 9.571 (n = 74,708)	28,085	838,698	33.49	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
	TyG ≥ 9.571 (n = 20,156)	4,190	239,425	17.50	1.142	1.103–1.183	< 0.001	1.206	1.164–1.250	< 0.001	1.119	1.079–1.160	< 0.001
Stage 4	Group 1 (n = 10,299)	2,194	121,208	18.10	1 (Ref.)			1 (Ref.)			1 (Ref.)		
	Group 2 (n = 16,520)	3,911	193,577	20.20	0.970	0.920–1.022	0.246	1.001	0.949–1.055	0.975	0.971	0.921–1.024	0.279
	Group 3 (n = 18,960)	4,660	221,050	21.08	1.075	1.021–1.131	0.006	1.137	1.079–1.198	< 0.001	1.008	0.955–1.063	0.782
	TyG < 8.509 (n = 17,017)	3,706	200,191	18.51	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
	TyG ≥ 8.509 (n = 28,762)	7,059	335,644	21.03	1.091	1.048–1.135	< 0.001	1.138	1.093–1.186	< 0.001	1.047	1.004–1.091	0.032

CI, confidence interval; CKM, cardiovascular-kidney-metabolic; HR, hazard ratio; IR, incidence rate; Ref., reference; TyG index, triglyceride-glucose index; eGFR, estimated glomerular filtration rate.

Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, smoking status, alcohol consumption, physical activity, and household income. Model 3: adjusted for age, sex, smoking status, alcohol consumption, physical activity, household income, use of antihypertensive drugs, use of glucose-lowering drugs, use of lipid-lowering drugs, use of antiplatelet drugs, eGFR category, and dipstick proteinuria.

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Supplementary Table 4. Association between TyG index and heart failure across CKM syndrome stages

		Events (N)	Person-years	IR	Model 1			Model 2			Model 3		
					HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Total population	Group 1 (n = 498,227)	13,408	6,266,340	2.14	1 (Ref.)			1 (Ref.)			1 (Ref.)		
	Group 2 (n = 499,627)	22,589	6,213,446	3.64	1.110	1.086–1.134	< 0.001	1.054	1.032–1.077	< 0.001	1.012	0.990–1.034	0.273
	Group 3 (n = 500,009)	29,080	6,154,681	4.72	1.327	1.300–1.354	< 0.001	1.202	1.177–1.228	< 0.001	1.054	1.032–1.078	< 0.001
	TyG < 8.489 (n = 703,588)	21,652	8,828,103	2.45	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
	TyG ≥ 8.489 (n = 794,325)	43,425	9,806,365	4.43	1.231	1.211–1.252	< 0.001	1.146	1.127–1.165	< 0.001	1.045	1.027–1.063	< 0.001
Stage 0 or 1	Group 1 (n = 305,555)	2,638	3,892,809	0.68	1 (Ref.)			1 (Ref.)			1 (Ref.)		
	Group 2 (n = 185,076)	2,317	2,357,893	0.98	1.049	0.992–1.111	0.095	1.024	0.967–1.085	0.410	1.025	0.968–1.086	0.393
	Group 3 (n = 4,630)	81	58,792	1.38	1.147	0.919–1.432	0.226	1.095	0.877–1.368	0.424	1.098	0.879–1.371	0.412
	TyG < 8.097 (n = 226,940)	1,799	2,891,361	0.62	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
	TyG ≥ 8.097 (n = 268,321)	3,237	3,418,132	0.95	1.070	1.010–1.135	0.023	1.042	0.982–1.106	0.173	1.044	0.983–1.108	0.158
Stage 2	Group 1 (n = 166,295)	6,093	2,087,847	2.92	1 (Ref.)			1 (Ref.)			1 (Ref.)		
	Group 2 (n = 269,799)	11,331	3,377,946	3.35	1.062	1.029–1.095	< 0.001	1.005	0.974–1.037	0.767	1.013	0.981–1.045	0.429
	Group 3 (n = 425,915)	16,208	5,339,254	3.04	1.144	1.111–1.179	< 0.001	1.034	1.003–1.066	0.029	1.060	1.028–1.093	< 0.001
	TyG < 8.132 (n = 119,751)	4,143	1,505,188	2.75	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
	TyG ≥ 8.132 (n = 742,258)	29,489	9,299,859	3.17	1.130	1.094–1.168	< 0.001	1.035	1.001–1.070	0.041	1.051	1.016–1.086	0.004

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Supplementary Table 4. Continued

		Events (N)	Person-years	IR	Model 1			Model 2			Model 3		
					HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Stage 3	Group 1 (n = 16,128)	2,730	172,667	15.81	1 (Ref.)			1 (Ref.)			1 (Ref.)		
	Group 2 (n = 28,232)	5,412	298,962	18.10	1.060	1.012–1.110	0.013	1.04	0.993–1.090	0.094	0.992	0.947–1.040	0.749
	Group 3 (n = 50,504)	8,442	554,299	15.23	1.170	1.120–1.223	< 0.001	1.132	1.082–1.184	< 0.001	1.002	0.956–1.050	0.938
	TyG < 9.571 (n = 74,708)	13,981	795,652	17.57	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
	TyG ≥ 9.571 (n = 20,156)	2,603	230,276	11.30	1.21	1.156–1.268	< 0.001	1.19	1.135–1.247	< 0.001	1.109	1.057–1.164	< 0.001
Stage 4	Group 1 (n = 10,299)	1,947	113,018	17.23	1 (Ref.)			1 (Ref.)			1 (Ref.)		
	Group 2 (n = 16,520)	3,529	178,646	19.75	1.000	0.947–1.057	0.987	0.98	0.927–1.036	0.478	0.953	0.901–1.007	0.089
	Group 3 (n = 18,960)	4,349	202,336	21.49	1.118	1.060–1.180	< 0.001	1.076	1.019–1.137	0.009	0.969	0.916–1.024	0.265
	TyG < 8.509 (n = 17,017)	3,324	186,096	17.86	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
	TyG ≥ 8.509 (n = 28,762)	6,501	307,904	21.11	1.100	1.055–1.147	< 0.001	1.073	1.028–1.119	0.001	1.001	0.959–1.045	0.956

CI, confidence interval; CKM, cardiovascular-kidney-metabolic; HR, hazard ratio; IR, incidence rate; Ref., reference; TyG index, triglyceride-glucose index; eGFR, estimated glomerular filtration rate.

Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, smoking status, alcohol consumption, physical activity, and household income. Model 3: adjusted for age, sex, smoking status, alcohol consumption, physical activity, household income, use of antihypertensive drugs, use of glucose-lowering drugs, use of lipid-lowering drugs, use of antiplatelet drugs, eGFR category, and dipstick proteinuria.

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Supplementary Table 5. Association between TyG index and stroke across CKM syndrome stages

		Events (N)	Person-years	IR	Model 1			Model 2			Model 3		
					HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Total population	Group 1 (n = 498,227)	10,247	6,267,377	1.63	1 (Ref.)			1 (Ref.)			1 (Ref.)		
	Group 2 (n = 499,627)	17,558	6,214,311	2.83	1.150	1.122–1.179	< 0.001	1.111	1.084–1.138	< 0.001	1.084	1.058–1.111	< 0.001
	Group 3 (n = 500,009)	23,624	6,152,521	3.84	1.423	1.391–1.457	< 0.001	1.326	1.294–1.358	< 0.001	1.209	1.179–1.239	< 0.001
	TyG < 8.489 (n = 703,588)	16,754	8,828,394	1.90	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
	TyG ≥ 8.489 (n = 794,325)	34,675	9,805,815	3.54	1.280	1.256–1.304	< 0.001	1.212	1.189–1.236	< 0.001	1.134	1.113–1.156	< 0.001
Stage 0 or 1	Group 1 (n = 305,555)	2,328	3,890,962	0.60	1 (Ref.)			1 (Ref.)			1 (Ref.)		
	Group 2 (n = 185,076)	2,208	2,355,677	0.94	1.122	1.057–1.190	< 0.001	1.075	1.013–1.142	0.018	1.075	1.012–1.141	0.019
	Group 3 (n = 4,630)	87	58,678	1.48	1.369	1.104–1.697	0.004	1.262	1.017–1.566	0.034	1.263	1.018–1.566	0.034
	TyG < 8.097 (n = 226,940)	1,587	2,890,301	0.55	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
	TyG ≥ 8.097 (n = 268,321)	3,036	3,415,017	0.89	1.124	1.056–1.195	< 0.001	1.073	1.008–1.143	0.027	1.073	1.008–1.143	0.027
Stage 2	Group 1 (n = 166,295)	4,815	2,087,292	2.31	1 (Ref.)			1 (Ref.)			1 (Ref.)		
	Group 2 (n = 269,799)	9,306	3,375,077	2.76	1.097	1.059–1.136	< 0.001	1.062	1.025–1.100	< 0.001	1.068	1.031–1.107	< 0.001
	Group 3 (n = 425,915)	14,186	5,331,969	2.66	1.230	1.190–1.271	< 0.001	1.151	1.113–1.190	< 0.001	1.163	1.124–1.203	< 0.001
	TyG < 8.132 (n = 119,751)	3,293	1,504,678	2.19	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
	TyG ≥ 8.132 (n = 742,258)	25,014	9,289,661	2.69	1.182	1.140–1.226	< 0.001	1.115	1.075–1.57	< 0.001	1.122	1.082–1.165	< 0.001

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Supplementary Table 5. Continued

		Events (N)	Person-years	IR	Model 1			Model 2			Model 3		
					HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Stage 3	Group 1 (n = 16,128)	1,927	173,234	11.12	1 (Ref.)			1 (Ref.)			1 (Ref.)		
	Group 2 (n = 28,232)	3,773	300,331	12.56	1.060	1.004–1.120	0.037	1.055	0.999–1.115	0.056	1.015	0.960–1.073	0.594
	Group 3 (n = 50,504)	6,402	554,599	11.54	1.206	1.145–1.270	< 0.001	1.198	1.136–1.263	< 0.001	1.079	1.021–1.140	0.007
	TyG < 9.571 (n = 74,708)	10,024	798,250	12.56	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
	TyG ≥ 9.571 (n = 20,156)	2,078	229,914	9.04	1.17	1.109–1.233	< 0.001	1.160	1.100–1.224	< 0.001	1.079	1.020–1.141	0.008
Stage 4	Group 1 (n = 10,299)	1,177	115,888	10.16	1 (Ref.)			1 (Ref.)			1 (Ref.)		
	Group 2 (n = 16,520)	2,271	183,225	12.39	1.086	1.012–1.165	0.023	1.081	1.007–1.160	0.032	1.057	0.984–1.134	0.130
	Group 3 (n = 18,960)	2,949	207,276	14.23	1.276	1.193–1.365	< 0.001	1.264	1.179–1.355	< 0.001	1.161	1.082–1.246	< 0.001
	TyG < 8.509 (n = 17,017)	2,074	190,706	10.88	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
	TyG ≥ 8.509 (n = 28,762)	4,323	315,684	13.69	1.186	1.125–1.249	< 0.001	1.177	1.116–1.241	< 0.001	1.112	1.054–1.174	< 0.001

CI, confidence interval; CKM, cardiovascular-kidney-metabolic; HR, hazard ratio; IR, incidence rate; Ref., reference; TyG index, triglyceride-glucose index; eGFR, estimated glomerular filtration rate.

Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, smoking status, alcohol consumption, physical activity, and household income. Model 3: adjusted for age, sex, smoking status, alcohol consumption, physical activity, household income, use of antihypertensive drugs, use of glucose-lowering drugs, use of lipid-lowering drugs, use of antiplatelet drugs, eGFR category, and dipstick proteinuria.

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Supplementary Table 6. Association between TyG index and myocardial infarction across CKM syndrome stages

		Events (N)	Person-years	IR	Model 1			Model 2			Model 3		
					HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Total population	Group 1 (n = 498,227)	1,962	6,304,029	0.31	1 (Ref.)			1 (Ref.)			1 (Ref.)		
	Group 2 (n = 499,627)	4,140	6,274,810	0.66	1.450	1.374–1.531	< 0.001	1.344	1.273–1.419	< 0.001	1.303	1.234–1.376	< 0.001
	Group 3 (n = 500,009)	7,334	6,225,536	1.18	2.236	2.127–2.351	< 0.001	1.952	1.854–2.056	< 0.001	1.736	1.647–1.829	< 0.001
	TyG < 8.489 (n = 703,588)	3,363	8,888,379	0.38	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
	TyG ≥ 8.489 (n = 794,325)	10,073	9,915,996	1.02	1.817	1.747–1.890	< 0.001	1.632	1.567–1.699	< 0.001	1.496	1.436–1.558	< 0.001
Stage 0 or 1	Group 1 (n = 305,555)	477	3,899,084	0.12	1 (Ref.)			1 (Ref.)			1 (Ref.)		
	Group 2 (n = 185,076)	608	2,363,037	0.26	1.321	1.171–1.491	< 0.001	1.208	1.069–1.366	0.003	1.209	1.070–1.367	0.002
	Group 3 (n = 4,630)	24	58,985	0.41	1.438	0.954–2.169	0.083	1.301	0.862–1.965	0.211	1.304	0.864–1.969	0.207
	TyG < 8.097 (n = 226,940)	5,652	2,883,997	1.96	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
	TyG ≥ 8.097 (n = 268,321)	10,447	3,402,639	3.07	1.056	1.022–1.092	0.001	1.033	0.999–1.068	0.054	1.035	1.001–1.070	0.042
Stage 2	Group 1 (n = 166,295)	940	2,105,536	0.45	1 (Ref.)			1 (Ref.)			1 (Ref.)		
	Group 2 (n = 269,799)	2,348	3,408,360	0.69	1.352	1.253–1.458	< 0.001	1.264	1.172–1.364	< 0.001	1.265	1.172–1.365	< 0.001
	Group 3 (n = 425,915)	4,962	5,374,593	0.92	1.814	1.691–1.946	< 0.001	1.627	1.514–1.748	< 0.001	1.639	1.524–1.762	< 0.001
	TyG < 8.132 (n = 119,751)	619	1,517,321	0.41	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
	TyG ≥ 8.132 (n = 742,258)	7,631	9,371,168	0.81	1.676	1.544–1.820	< 0.001	1.497	1.378–1.627	< 0.001	1.493	1.373–1.623	< 0.001

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Supplementary Table 6. Continued

		Events (N)	Person-years	IR	Model 1			Model 2			Model 3		
					HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Stage 3	Group 1 (n = 16,128)	292	179,528	1.63	1 (Ref.)			1 (Ref.)			1 (Ref.)		
	Group 2 (n = 28,232)	691	312,368	2.21	1.325	1.155–1.519	< 0.001	1.288	1.123–1.478	< 0.001	1.192	1.038–1.368	0.013
	Group 3 (n = 50,504)	1,597	574,556	2.78	1.730	1.526–1.963	< 0.001	1.665	1.462–1.895	< 0.001	1.336	1.168–1.529	< 0.001
	TyG < 9.571 (n = 74,708)	1,902	830,338	2.29	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
	TyG ≥ 9.571 (n = 20,156)	678	236,113	2.87	1.445	1.306–1.509	< 0.001	1.438	1.297–1.595	< 0.001	1.221	1.094–1.364	< 0.001
Stage 4	Group 1 (n = 10,299)	253	119,881	2.11	1 (Ref.)			1 (Ref.)			1 (Ref.)		
	Group 2 (n = 16,520)	493	191,045	2.58	1.135	0.976–1.321	0.101	1.099	0.943–1.281	0.226	1.035	0.889–1.206	0.656
	Group 3 (n = 18,960)	751	217,402	3.45	1.516	1.315–1.748	< 0.001	1.442	1.245–1.670	< 0.001	1.200	1.034–1.392	0.017
	TyG < 8.509 (n = 17,017)	445	197,833	2.25	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
	TyG ≥ 8.509 (n = 28,762)	1,052	330,495	3.18	1.351	1.209–1.510	< 0.001	1.299	1.160–1.455	< 0.001	1.143	1.019–1.283	0.022

CI, confidence interval; CKM, cardiovascular-kidney-metabolic; HR, hazard ratio; IR, incidence rate; Ref., reference; TyG index, triglyceride-glucose index; eGFR, estimated glomerular filtration rate.

Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, smoking status, alcohol consumption, physical activity, and household income. Model 3: adjusted for age, sex, smoking status, alcohol consumption, physical activity, household income, use of antihypertensive drugs, use of glucose-lowering drugs, use of lipid-lowering drugs, use of antiplatelet drugs, eGFR category, and dipstick proteinuria.

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Supplementary Table 7. Association between TyG index tertiles and primary and secondary outcomes according to baseline statin use

		Events (N)	Person-years	IR	Model 1			Model 2			Model 3		
					HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Composite primary outcome						Interaction *p* value	0.061		Interaction *p* value	0.068		Interaction *p* value	0.067
Statin non-users	Group 1 (n = 466,442)	29,438	5,845,825	5.04	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
	Group 2 (n = 432,577)	43,818	5,349,428	8.19	1.079	1.063–1.095	< 0.001	1.059	1.043–1.075	< 0.001	1.041	1.026–1.057	< 0.001
	Group 3 (n = 391,417)	49,690	4,783,070	10.39	1.247	1.229–1.265	< 0.001	1.198	1.180–1.217	< 0.001	1.120	1.103–1.137	< 0.001
Stain users	Group 1 (n = 31,835)	6,344	374,258	16.95	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
	Group 2 (n = 67,050)	14,839	781,518	18.99	1.045	1.014–1.076	0.004	1.027	0.997–1.058	0.079	1.009	0.979–1.039	0.563
	Group 3 (n = 108,592)	25,546	1,252,259	20.40	1.226	1.193–1.260	< 0.001	1.183	1.150–1.216	< 0.001	1.095	1.064–1.126	< 0.001
All-cause death						Interaction *p* value	< 0.001		Interaction *p* value	0.010		Interaction *p* value	0.360
Statin non-users	Group 1 (n = 466,442)	16,198	5,919,332	2.74	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
	Group 2 (n = 432,577)	24,014	5,466,370	4.39	1.012	0.992–1.033	0.237	1.035	1.015–1.056	< 0.001	1.012	0.991–1.032	0.261
	Group 3 (n = 391,417)	26,111	4,926,445	5.30	1.108	1.086–1.130	< 0.001	1.156	1.133–1180	< 0.001	1.061	1.039–1.083	< 0.001
Stain users	Group 1 (n = 31,835)	3,306	393,837	8.39	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
	Group 2 (n = 67,050)	7,755	828,175	9.36	1.034	0.992–1.077	0.110	1.039	0.998–1.083	0.066	1.008	0.967–1.050	0.713
	Group 3 (n = 108,592)	13,018	1,336,219	9.74	1.209	1.164–1.256	< 0.001	1.21	1.164–1.258	< 0.001	1.079	1.037–1.122	< 0.001

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Supplementary Table 7. Continued

		Events (N)	Person-years	IR	Model 1			Model 2			Model 3		
					HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Heart failure						Interaction *p* value	0.002		Interaction *p* value	0.001		Interaction *p* value	0.014
Statin non-users	Group 1 (n = 466,442)	10,492	5,883,594	1.78	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
	Group 2 (n = 432,577)	15,920	5,411,107	2.94	1.100	1.073–1.127	< 0.001	1.052	1.026–1.079	< 0.001	1.028	1.003–1.054	0.028
	Group 3 (n = 391,417)	17,722	4,862,913	3.64	1.265	1.235–1.296	< 0.001	1.158	1.129–1.188	< 0.001	1.064	1.037–1.092	< 0.001
Stain users	Group 1 (n = 31,835)	2,916	382,746	7.62	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
	Group 2 (n = 67,050)	6,669	802,339	8.31	1.016	0.972–1.061	0.484	0.981	0.939–1.025	0.385	0.962	0.921–1.005	0.080
	Group 3 (n = 108,592)	11,358	1,291,768	8.79	1.185	1.138–1.234	< 0.001	1.11	1.065–1.157	< 0.001	1.019	0.978–1.063	0.366
Stroke						Interaction *p* value	0.053		Interaction *p* value	0.072		Interaction *p* value	0.081
Statin non-users	Group 1 (n = 466,442)	8,389	5,881,870	1.43	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
	Group 2 (n = 432,577)	13,086	5,406,581	2.42	1.149	1.118–1.181	< 0.001	1.107	1.076–1.138	< 0.001	1.090	1.060–1.121	< 0.001
	Group 3 (n = 391,417)	15,481	4,854,277	3.19	1.39	1.354–1.428	< 0.001	1.285	1.249–1.321	< 0.001	1.205	1.172–1.240	< 0.001
Stain users	Group 1 (n = 31,835)	1,858	385,507	4.82	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
	Group 2 (n = 67,050)	4,472	807,730	5.54	1.075	1.018–1.134	0.009	1.06	1.004–1.119	0.035	1.044	0.989–1.102	0.123
	Group 3 (n = 108,592)	8,143	1,298,244	6.27	1.32	1.255–1.388	< 0.001	1.281	1.217–1.349	< 0.001	1.185	1.125–1.248	< 0.001

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Supplementary Table 7. Continued

		Events (N)	Person-years	IR	Model 1			Model 2			Model 3		
					HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Myocardial infarction						Interaction *p* value	< 0.001		Interaction *p* value	< 0.001		Interaction *p* value	< 0.001
Statin non-users	Group 1 (n = 466,442)	1,527	5,912,503	0.26	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
	Group 2 (n = 432,577)	3,006	5,452,392	0.55	1.452	1.365–1.545	< 0.001	1.337	1.256–1.423	< 0.001	1.320	1.240–1.405	< 0.001
	Group 3 (n = 391,417)	4,768	4,902,339	0.97	2.192	2.068–2.323	< 0.001	1.884	1.774–2.001	< 0.001	1.777	1.672–1.888	< 0.001
Stain users	Group 1 (n = 31,835)	435	391,526	1.11	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
	Group 2 (n = 67,050)	1,134	822,419	1.38	1.171	1.049–1.308	0.005	1.149	1.028–1.284	0.014	1.136	1.017–1.270	0.024
	Group 3 (n = 108,592)	2,566	1,323,197	1.94	1.601	1.446–1.773	< 0.001	1.555	1.402–1.725	< 0.001	1.453	1.309–1.613	< 0.001

CI, confidence interval; HR, hazard ratio; IR, incidence rate; Ref., reference; TyG index, triglyceride-glucose index; eGFR, estimated glomerular filtration rate.
Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, smoking status, alcohol consumption, physical activity, and household income. Model 3: adjusted for age, sex, smoking status, alcohol consumption, physical activity, household income, use of antihypertensive drugs, use of glucose-lowering drugs, use of lipid-lowering drugs, use of antiplatelet drugs, eGFR category, and dipstick proteinuria.

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Supplementary Table 8. Association between TyG index and composite primary outcome in CKM stage 0 and stage 1 analyzed separately

		Events (N)	Person-years	IR	Model 1			Model 2			Model 3		
					HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Total population	Group 1 (n = 498,227)	35,782	6,220,082	5.75	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
	Group 2 (n = 499,627)	58,657	6,130,946	9.57	1.086	1.072–1.101	< 0.001	1.063	1.049–1.077	< 0.001	1.035	1.021–1.049	< 0.001
	Group 3 (n = 500,009)	75,236	6,035,328	12.47	1.284	1.267–1.300	< 0.001	1.227	1.211–1.243	< 0.001	1.116	1.101–1.131	< 0.001
	TyG < 8.489 (n = 703,588)	57,456	8,751,493	6.57	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
	TyG ≥ 8.489 (n = 794,325)	112,219	9,634,864	11.65	1.199	1.187–1.211	< 0.001	1.091	1.080–1.103	< 0.001	1.084	1.072–1.095	< 0.001
Stage 0	Group 1 (n = 189,661)	4,367	2,410,980	1.81	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
	Group 2 (n = 70,873)	2,479	899,972	2.75	1.016	0.966–1.068	0.535	1.012	0.962–1.064	0.647	1.013	0.964–1.066	0.607
	Group 3 (n = 0)	–	–	–	–	–	–	–	–	–	–	–	–
	TyG < 8.111 (n = 152,612)	3,261	1,940,345	1.68	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
	TyG ≥ 8.111 (n = 107,922)	3,585	1,370,607	2.62	1.037	0.989–1.088	0.136	1.029	0.981–1.080	0.244	1.032	0.983–1.083	0.210
Stage 1	Group 1 (n = 115,894)	3,927	1,470,712	2.67	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
	Group 2 (n = 114,203)	5,036	1,446,653	3.48	1.061	1.017–1.107	0.006	1.035	0.993–1.080	0.106	1.036	0.994–1.081	0.097
	Group 3 (n = 4,630)	290	58,319	4.97	1.242	1.102–1.400	< 0.001	1.172	1.039–1.322	0.010	1.174	1.041–1.324	0.009
	TyG < 8.336 (n = 131,904)	4,550	1,673,774	2.72	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
	TyG ≥ 8.336 (n = 102,823)	4,703	1,301,910	3.61	1.079	1.036–1.125	< 0.001	1.052	1.010–1.097	0.015	1.054	1.011–1.098	0.013

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Supplementary Table 8. Continued

		Events (N)	Person-years	IR	Model 1			Model 2			Model 3		
					HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Stage 0 or 1	Group 1 (n = 305,555)	8,294	3,881,692	2.14	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
	Group 2 (n = 185,076)	7,515	2,346,625	3.20	1.045	1.012–1.078	< 0.001	1.025	0.993–1.059	0.129	1.026	0.994–1.060	0.112
	Group 3 (n = 4,630)	290	58,319	4.97	1.219	1.084–1.372	< 0.001	1.164	1.034–1.309	0.012	1.166	1.036–1.312	0.011
	TyG < 8.097 (n = 226,940)	5,652	2,883,997	1.96	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
	TyG ≥ 8.097 (n = 268,321)	10,447	3,402,639	3.07	1.056	1.022–1.092	0.001	1.033	0.999–1.068	0.054	1.035	1.001–1.070	0.042
Stage 2	Group 1 (n = 166,295)	15,990	2,064,360	7.75	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)		
	Group 2 (n = 269,799)	29,614	3,330,212	8.89	1.049	1.029–1.069	< 0.001	1.018	0.998–1.038	0.073	1.023	1.004–1.044	0.019
	Group 3 (n = 425,915)	44,298	5,259,701	8.42	1.144	1.123–1.165	< 0.001	1.076	1.057–1.097	< 0.001	1.090	1.069–1.111	< 0.001
	TyG < 8.132 (n = 119,751)	10,995	1,489,067	7.38	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
	TyG ≥ 8.132 (n = 742,258)	78,907	9,165,206	8.61	1.109	1.087–1.131	< 0.001	1.052	1.031–1.073	< 0.001	1.060	1.038–1.082	< 0.001
Stage 3	Group 1 (n = 16,128)	7,728	165,889	46.59	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)		
	Group 2 (n = 28,232)	14,636	284,921	51.37	1.037	1.009–1.066	0.009	1.049	1.021–1.079	< 0.001	1.012	0.984–1.041	0.389
	Group 3 (n = 50,504)	22,297	527,443	42.27	1.129	1.100–1.159	< 0.001	1.163	1.132–1.195	< 0.001	1.055	1.025–1.085	< 0.001
	TyG < 9.571 (n = 74,708)	37,865	757,770	49.97	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
	TyG ≥ 9.571 (n = 20,156)	6,796	220,484	30.82	1.176	1.143–1.210	< 0.001	1.202	1.168–1.237	< 0.001	1.129	1.096–1.163	< 0.001

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Supplementary Table 8. Continued

		Events (N)	Person-years	IR	Model 1			Model 2			Model 3		
					HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Stage 4	Group 1 (n = 10,299)	3,770	108,141	34.86	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)		
	Group 2 (n = 16,520)	6,892	169,189	40.74	1.023	0.983–1.065	0.259	1.025	0.984–1.066	0.236	0.999	0.960–1.040	0.975
	Group 3 (n = 18,960)	8,351	189,865	43.98	1.141	1.098–1.186	< 0.001	1.143	1.099–1.189	< 0.001	1.040	0.999–1.083	0.055
	TyG < 8.509 (n = 17,017)	6,484	177,289	36.57	1 (Ref.)	–	–	1 (Ref.)	–	–	1 (Ref.)	–	–
	TyG ≥ 8.509 (n = 28,762)	12,529	289,906	43.22	1.108	1.076–1.142	< 0.001	1.111	1.077–1.145	< 0.001	1.043	1.011–1.076	0.007

CI, confidence interval; CKM, cardiovascular-kidney-metabolic; HR, hazard ratio; IR, incidence rate; Ref., reference; TyG index, triglyceride-glucose index; eGFR, estimated glomerular filtration rate.

The primary outcome was defined as a composite of all-cause death, heart failure, stroke (both ischemic and hemorrhagic), and myocardial infarction.

Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, smoking status, alcohol consumption, physical activity, and household income. Model 3: adjusted for age, sex, smoking status, alcohol consumption, physical activity, household income, use of antihypertensive drugs, use of glucose-lowering drugs, use of lipid-lowering drugs, use of antiplatelet drugs, eGFR category, and dipstick proteinuria.

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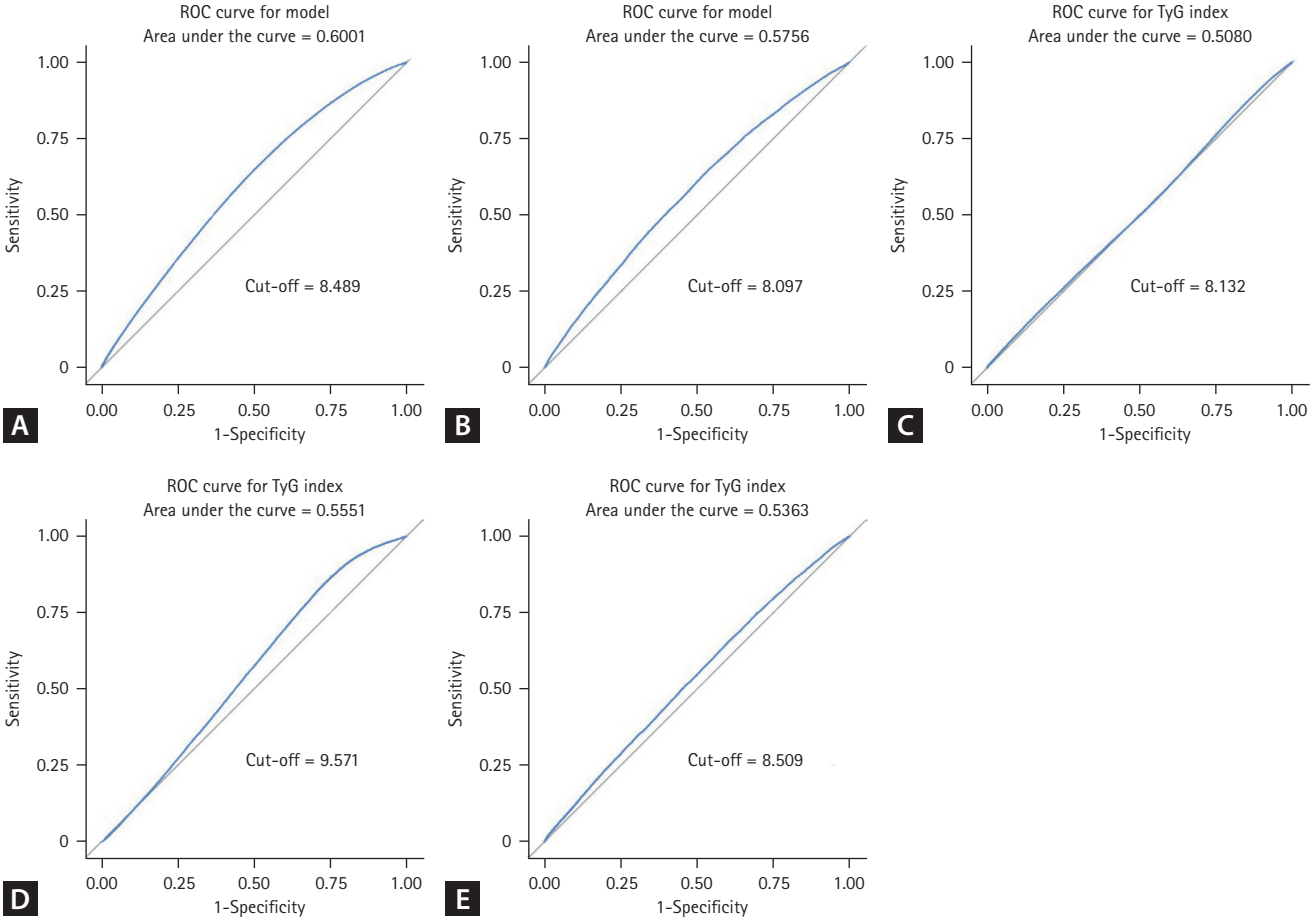

Supplementary Figure 1. Receiver operating characteristic (ROC) curves of the TyG index for predicting composite primary outcome across CKM Stages. Curves for (A) total population, (B) CKM syndrome stage 0/1, (C) CKM syndrome stage 2, (D) CKM syndrome stage 3, and (E) CKM syndrome stage 4. CKM, cardiovascular-kidney-metabolic; TyG, triglyceride-glucose.