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Original Article

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Triglyceride-Glucose Index Is a Useful Marker for Predicting Future Cardiovascular Disease and Mortality in Young Korean Adults: A Nationwide Population-Based Cohort Study

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ABSTRACT

Objective: The triglyceride-glucose (TyG) index, the product of fasting triglycerides and glucose, is a useful and cost-effective marker of insulin resistance (IR). Furthermore, the TyG index is a known IR screening tool in healthy young adults but not in those with atherosclerotic cardiovascular disease (CVD). Thus, this study aimed to evaluate the TyG index as a predictor of CVD in healthy young adults.
Methods: This study enrolled 6,675,424 adults aged 20–39 years without CVD from the National Health Information Database. We categorized them by TyG index quartile from 2009–2017. The study outcomes were stroke, myocardial infarction (MI), and mortality. All outcomes were analyzed by Cox proportional hazards regression analysis while controlling for baseline covariates.
Results: During a mean 7.4 years of follow-up, 8,506 cases of stroke, 12,312 cases of MI, and 22,667 deaths were recorded. Multivariable-adjusted hazard ratios (HRs) for participants in the highest TyG index quartile demonstrated that they were at higher risk for stroke (HR, 1.253; 95% confidence interval [CI], 1.167–1.346), MI (HR, 1.258; 95% CI, 1.187–1.334), and mortality (HR, 1.151; 95% CI, 1.104–1.200) than those in the lowest TyG index quartile independent of age, sex, smoking, alcohol consumption, physical activity, income, body mass index, blood pressure, and total cholesterol. The HRs for outcomes in the highest quartiles were higher when the TyG index was applied than when triglyceride or fasting glucose alone was applied.
Conclusion: TyG index, a simple measure reflecting IR, can predict CVD and mortality in young and healthy populations.

Keywords: Cardiovascular diseases; Mortality; Triglyceride; Glucose; Young adult

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Conflict of Interest

The authors have no conflicts of interest to declare.

Author Contributions

Conceptualization: Cho YK, Lee WJ. Data curation: Han KD. Formal analysis: Han KD. Funding acquisition: Cho YK. Investigation: Cho YK, Han KD, Kim HS, Jung CH, Park JY, Lee WJ. Methodology: Cho YK, Han KD. Project administration: Cho YK, Lee WJ. Resources: Han KD. Software: Han KD. Supervision: Lee WJ. Writing - original draft: Cho YK. Writing - review & editing: Han KD, Kim HS, Jung CH, Park JY, Lee WJ.

INTRODUCTION

Insulin resistance (IR) is a major risk factor for cardiovascular disease (CVD).[1,2] IR is not only linked to the conventional risk factors including type 2 diabetes (T2D), hypertension, dyslipidemia, and obesity, it is also an independent risk factor for CVD.[3] The triglyceride-glucose (TyG) index, a product of triglyceride and fasting plasma glucose (FPG), is currently being studied as a surrogate marker for IR.[4-6] Previous research found a link between IR and major CVD risk factors including T2D and hypertension.[7,8] A higher plasma TyG index level was reportedly associated with an increased incidence of CVD irrespective of other conventional CVD risk factors.[2] Korean researchers recently demonstrated that a higher TyG index was significantly associated with an increased risk of future myocardial infarction (MI) and stroke in a study on 7,183,262 persons aged 40 years and older who participated in the national health screening program.[9]

Furthermore, the TyG index has been established in healthy young adults as an effective screening tool for IR. Guerrero-Romero et al.[10] demonstrated that the TyG index had high diagnostic concordance with the homeostasis model assessment for IR (HOMA-IR), the most widely used method for assessing IR, suggesting that TyG may be useful for screening IR in young adults. They found that, in young adults aged 18–23 years, the diagnostic concordance between the TyG index and HOMA-IR was high - approximately 0.9 regardless of body weight and sex.[10] Nonetheless, to the best of our knowledge, the prognostic value of the TyG index for estimating cardiovascular risk has not previously been evaluated in young adults. Accordingly, here, we aimed to evaluate the TyG index's predictive value for CVD risk and mortality in young adults using a large-scale population dataset from the National Health Information Database (NHID). We hypothesized that TyG index would predict CVD and mortality in young and healthy Korean populations.

MATERIALS AND METHODS

1. Study population

This is a large-population based prospective study that utilized data from the NHID, a public healthcare utilization and health screening database that contains sociodemographic and mortality information for the entire population of South Korea. The entire structure and function of the Korean NHID are described in the relevant literatures.[11,12] A total of 6,819,845 young adults aged 20–39 years participated in the national health screening program in 2009–2012 and were in the NHID database. Of them, 78,436 individuals who took antidiabetic or lipid-lowering medications, 57,261 for whom complete data were lacking, and 8,724 with a history of CVD were excluded. Therefore, the final study cohort included 6,675,424 subjects; a flowchart of the study population inclusion is shown in **Fig. 1**. This study was approved by the Institutional Review Board of Hallym University Sacred Heart Hospital (HALLYM 2020-05-007). The study was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

2. TyG index

TyG index was calculated using the following formula: ln (fasting TG [mg/dL]×FPG [mg/dL]/2).[13] The TyG index from the first measurement was used as the baseline TyG index. The study population was divided into TyG index quartile groups (**Supplementary Table 1**). The study outcomes were newly diagnosed MI, stroke, or death. Stroke was defined as International

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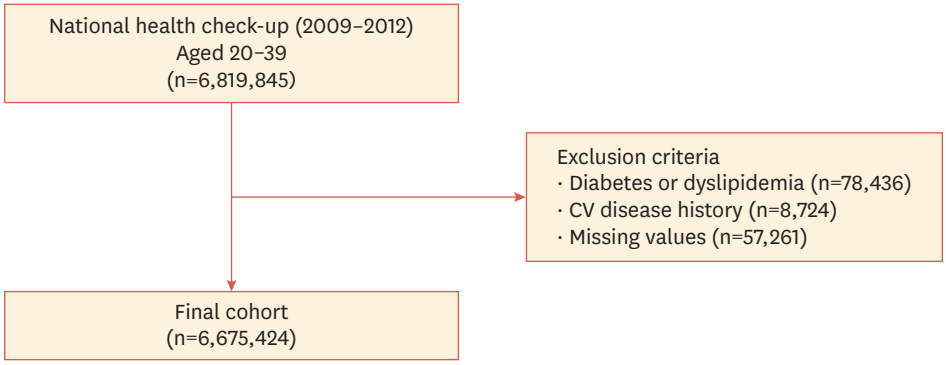

Fig. 1. Flowchart of the study cohort enrollment process.

Classification of Diseases, 10th edition (ICD-10) code I63 or I64 during hospitalization with claims for brain magnetic resonance imaging or brain computed tomography, while MI was defined as ICD-10 code I21 or I22 during hospitalization. Participants were considered to have completed the study at the date of onset of cardiovascular event or until December 31, 2018, whichever came first.

3. Covariates

Covariates from the baseline health examination included smoking habits (non-, ex-, or current smoker), drinking habits (none, moderate, or heavy drinking), and regular exercise (≥3 times per week of vigorous-intensity exercise or ≥5 times per week of moderate-intensity exercise) and total cholesterol (TC) concentrations. Moderate drinkers were defined as individuals who consumed <30 g of alcohol per day, whereas heavy drinkers were those who consumed ≥ 30 g of alcohol per day. A low socioeconomic status was defined as an income in the lowest 20% of the population. Baseline comorbidities included hypertension (ICD-10 codes I10 to I13 or I15 and treatment with antihypertensive medications, systolic blood pressure [BP] ≥140 mmHg, or diastolic BP ≥90 mmHg), T2D (ICD-10 codes E11 to E14 and treatment with antidiabetic drugs or fasting glucose level ≥126 mg/dL), hyperlipidemia (ICD-10 code E78 with consumption of lipid-lowering agents or serum TC ≥240 mg/dL), and chronic kidney disease (CKD; estimated glomerular filtration rate <60 mL/min/1.73 m^2).

4. Statistical analysis

Continuous variables are described as mean (± standard deviation [SD]) for normally distributed data and as geometric mean and 95% confidence interval (CI) for non-normally distributed data, while categorical data are expressed as percentages. Analysis of variance or the chi-square test was used to compare the baseline characteristics of the study participants based on their TyG quartiles. The incidence of stroke, MI, and mortality were estimated for each TyG quartile over the total follow-up period. Incidence curves were estimated using the Kaplan-Meier method and the log rank test. Cox proportional hazards analyses were performed to estimate the hazard ratio (HR) and 95% CI of stroke, MI, and mortality. Multivariable-adjusted models were adjusted for age, sex, body mass index (BMI), smoking, alcohol consumption, physical activities, income, presence of hypertension, and TC concentration. The group of subjects with the lowest TyG index quartile was considered the reference. Analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA) and R program version 3.4.1 (The R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org).

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RESULTS

1. Baseline characteristics of the entire cohort

Table 1 displays the baseline clinical and biochemical parameters of the study participants by TyG index quartile. An increased TyG index quartile was associated a less favorable risk profile, including higher BMI, waist circumference, systolic and diastolic BP, fasting glucose, TC, LDL cholesterol, and triglycerides (all $p<0.001$). Groups with higher TyG quartiles also included more persons who smoked, consumed alcohol, and had sedentary lifestyles (all $p<0.001$). TyG index exhibited an inverse association with HDL cholesterol level and estimated glomerular filtration rate (all $p<0.001$).

2. Risk of incident stroke, MI, and mortality according to TyG index quartile

During a mean 7.4 years of follow-up, 8,506 cases of stroke (overall incidence of 0.13% or 0.17 cases/1,000 person-years), 12,312 cases of MI (overall incidence of 0.18% or 0.25 cases/1,000 person-years), and 22,667 deaths (overall incidence of 0.34% or 0.46 cases/1,000 person-years) were recorded. **Fig. 2** shows the Kaplan-Meier curves for cumulative incidences of stroke, MI, and death for TyG index quartiles. The highest TyG index quartile was associated with the highest probability of developing incident stroke, MI, and death; these probabilities decreased sequentially for lower quartiles (all log rank, $p<0.001$; **Fig. 2**).

Age- and sex-adjusted HRs for stroke increased across TyG index quartiles: 1.115 (95% CI, 1.038–1.197), 1.324 (95% CI, 1.237–1.417), and 1.751 (95% CI, 1.642–1.868) for the 2nd, 3rd, and 4th quartiles, respectively, compared with that for the 1st quartile (p for trend <0.001; **Supplementary Table 2**). After full adjustment for age, sex, smoking, alcohol consumption, regular physical activity, low socioeconomic status, BMI, hypertension, and TC level, there

Table 1. Characteristics of study participants by TyG quartiles

Variables	TyG quartiles				*p*-value
	Q1 (n=1,668,760)	Q2 (n=1,668,910)	Q3 (n=1,668,231)	Q4 (n=1,669,523)	
Age (yr)	29.3±4.96	30.39±4.97	31.17±4.93	32.15±4.76	<0.0001
Male (%)	995,646 (59.66)	994,365 (59.58)	995,498 (59.67)	995,104 (59.6)	0.2399
BMI (kg/m^2)	21.67±2.83	22.36±3.17	23.19±3.5	24.66±3.85	<0.0001
WC (cm)	74.09±8.3	75.97±9.17	78.03±9.88	81.53±10.37	<0.0001
SBP (mmHg)	114.93±12.03	116.43±12.47	118.07±12.95	120.99±13.81	<0.0001
DBP (mmHg)	71.7±8.62	72.86±8.92	74.07±9.26	76.16±9.89	<0.0001
Smoking					<0.0001
Non	1,003,366 (60.13)	945,312 (56.64)	896,541 (53.74)	821,971 (49.23)	
Ex	159,955 (9.59)	171,567 (10.28)	178,489 (10.7)	178,188 (10.67)	
Current	505,439 (30.29)	552,031 (33.08)	593,201 (35.56)	669,364 (40.09)	
Drinking					<0.0001
Non	660,456 (39.86)	636,014 (38.39)	617,059 (37.25)	592,048 (35.71)	
Mild	893,763 (53.94)	896,582 (54.11)	890,921 (53.78)	864,837 (52.16)	
Heavy	102,791 (6.2)	124,241 (7.5)	148,544 (8.97)	201,167 (12.13)	
Regular exercise	265,222 (15.89)	227,175 (13.61)	210,559 (12.62)	196,531 (11.77)	<0.0001
Low income	498,666 (29.88)	453,687 (27.18)	438,607 (26.29)	451,983 (27.07)	<0.0001
HTN (%)	55,850 (3.35)	83,140 (4.98)	119,657 (7.17)	200,810 (12.03)	<0.0001
CKD (%)	32,261 (1.93)	30,680 (1.84)	31,280 (1.88)	33,710 (2.02)	<0.0001
FPG (mg/dL)	84.98±9.37	88.49±9.99	90.98±11.09	97.16±21.03	<0.0001
TC (mg/dL)	169.35±27.67	179.24±29.4	187.51±31.49	200.97±35.94	<0.0001
HDL-C (mg/dL)	61.31±13.88	58.65±14.23	56.03±14.87	52.13±18.15	<0.0001
LDL-C (mg/dL)	97.15±25.5	104.2±27.92	108.39±29.97	107.42±33.51	<0.0001
TG (mg/dL)	52.16 (52.14–52.18)	79.47 (79.43–79.5)	111.19 (111.14–111.25)	194.13 (193.99–194.27)	<0.0001

TyG, triglyceride-glucose; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HTN, hypertension; CKD, chronic kidney disease; FPG, fasting plasma glucose; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride.

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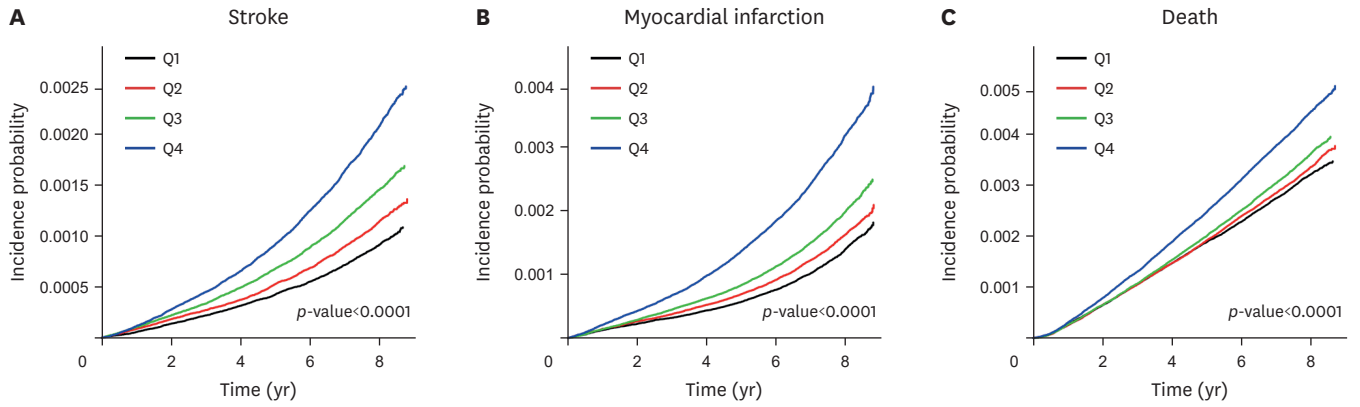

Fig. 2. Kaplan-Meier curves of (A) stroke, (B) myocardial infarction, and (C) stroke by TyG index quartile.
TyG, triglyceride-glucose.

was a significant increase in the risk of stroke in the 3rd (HR, 1.120; 95% CI, 1.044–1.201) and 4th (HR, 1.253; 95% CI, 1.167–1.346) TyG index quartiles compared to the 1st quartile. The age- and sex-adjusted HR for MI was also increased for the 2nd (HR, 1.093; 95% CI, 1.030–1.159), 3rd (HR, 1.274; 95% CI, 1.204–1.349), and 4th (HR, 1.933; 95% CI, 1.834–2.038) TyG index quartiles compared to the 1st quartile (*p* for trend < 0.001; **Supplementary Table 2**). After full adjustment, the risk of MI was still significantly increased in the 4th quartile (HR, 1.258; 95% CI, 1.187–1.334). The multivariable-adjusted HR for mortality was also increased for the 4th (HR, 1.151; 95% CI, 1.104–1.200) TyG index quartile compared to the 1st quartile (**Fig. 3**). In addition, the HRs for all three outcomes in the highest quartiles were higher when the TyG index was applied than when triglyceride or fasting glucose alone was applied (**Fig. 3**).

3. Sensitivity analysis: effects of clinical variables on associations of TyG index with stroke, MI, and mortality

Associations of TyG index with stroke, MI, and both were generally consistent across subgroups according to clinical variables after multivariable adjustment (**Supplementary Table 3**). We also classified the population according to baseline characteristics (age and sex) or cardiovascular

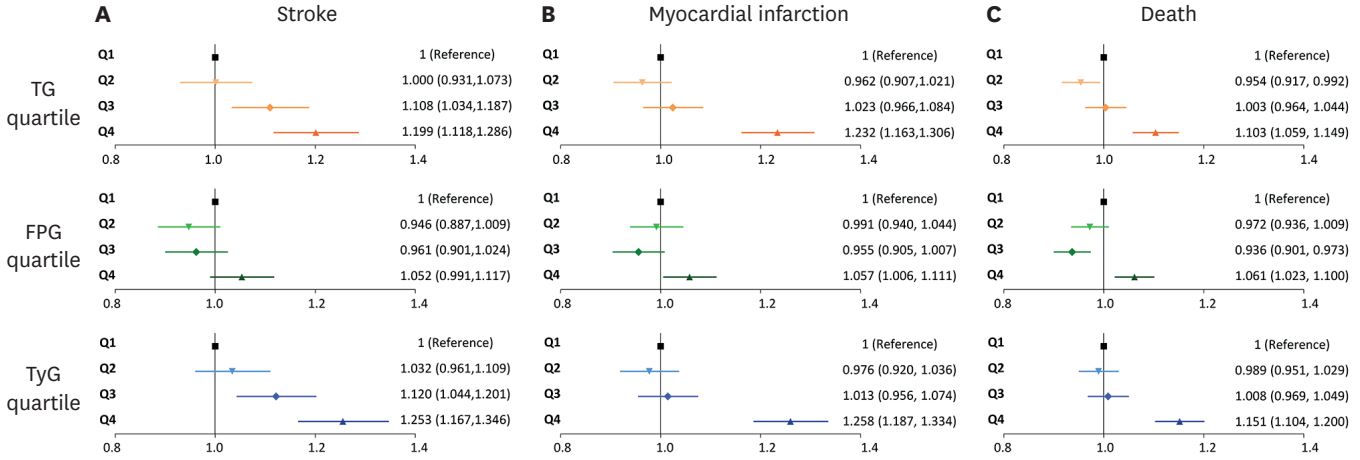

Fig. 3. Multivariable-adjusted hazard ratios (95% confidence intervals) for (A) stroke, (B) myocardial infarction, and (C) stroke by quartiles of triglyceride, fasting plasma glucose, and TyG index.
TG, triglyceride; FPG, fasting plasma glucose; TyG, triglyceride-glucose.

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risk factors (current smoking, drinking, hypertension, diabetes, dyslipidemia, general obesity by BMI, central obesity by WC, and CKD). Regardless of the presence of cardiovascular risk factors, associations of TyG index with stroke, MI, and both were generally consistent. Those aged ≥30 years and non-smokers had a more increased risk of MI by the 4th quartile of the TyG index compared to those aged <30 years (p for interaction <0.001) and smokers (p for interaction=0.0179), respectively. The risks of MI (p for interaction <0.001) and death (p for interaction=0.0006) for the 4th quartile of the TyG index in women were significantly higher than those of men.

DISCUSSION

Using a large-scaled nationwide cohort dataset, the current study evaluated the relationship between TyG index and cardiovascular risk in a young Korean population. A high TyG index was related with a substantially higher risk of future MI, stroke, and mortality, even after the adjustment for conventional cardiovascular risk factors in young people. In our subgroup analysis, this association was particularly observed among women. Our results suggest that TyG index, as a surrogate marker of IR, may be an independent predictor of cardiovascular risk and mortality in young people.

The TyG index, a product of TG and FPG, demonstrated high sensitivity and specificity for detecting IR.[4,13,14] The hyperinsulinemic-euglycemic clamp (HEC) technique, first described by De-Fronzo, is widely considered the gold standard for measuring IR.[14] However, its application in practice is impractical due to economic burden and ethical issues.[14] According to Guerrero-Romero et al.,[13] the TyG index has high sensitivity and specificity, indicating that it could be beneficial for the identification of individuals with impaired insulin sensitivity. A study that validated the hyperglycemic clamp reported that TyG index was significantly correlated to IR assessed by a hyperglycemic clamp with better performance than the HOMA-IR index.[15] Furthermore, several studies reported a link between TyG index and CVD risk.[9,16,17] In the Vascular Metabolic CUN cohort including 5,014 subjects, a higher level of TyG index was substantially associated with an increased risk of developing CVD independent of confounding factors; furthermore, adding this index to the Framingham risk score improved the predictive power for future CVD.[17] Recently, Hong et al.[9] demonstrated that higher TyG index was significantly associated with increased risk of future MI and stroke in the Korean population. However, to date, the implication of the TyG index on cardiovascular risk in a young population has not been studied.

Guerrero-Romero et al.,[10] who proposed the TyG index as a novel index for the early recognition of IR,[13] further validated the TyG index as a diagnostic test for IR in healthy young adults. The study population included healthy college students aged 18–23 years; the researchers performed the HEC technique and additionally calculated HOMA-IR and TyG index. They showed that the TyG index has a high negative predictive value and low negative likelihood ratio by HEC as well as high diagnostic concordance with HOMA-IR, which strongly suggests that it could be used as an alternative test for screening for IR in young adults.[10] Furthermore, Koo et al.[18] recently reported that, in the Korean population aged 30–49 years, high TG levels independently increased future CVD risk in both men and women. However, the prognostic value of the TyG index in CVD was not previously evaluated; to our knowledge, our study is the first to reveal the prognostic value of the TyG index for CVD and mortality in young adults.

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Our results showed that the HRs for stroke, MI, and mortality in the highest index quartiles were even higher when the TyG index was applied than when triglyceride or fasting glucose was applied alone (**Supplementary Table 2**, **Fig. 3**). In patients typifying the IR, at a normal plasma insulin level, target tissues are unable to mount a normal coordinated glucose-lowering response involving suppression of endogenous glucose production, suppression of lipolysis, cellular uptake of available plasma glucose, and net glycogen synthesis.[19-24] This IR necessitates increased insulin secretion to compensate; thus, fasting plasma insulin levels increase later.[19,25,26] However, in the early stage of IR, increased lipolysis of stored triglycerides in adipose tissue produces more fatty acids before the rise in plasma glucose level.[9] Furthermore, IR leads to subclinical TG elevation, even in nonobese people with normal TG levels[27]; therefore, a combination of fasting blood glucose and TG could be an early surrogate marker of IR, especially in healthy young people who have not developed clinically detectable dyslipidemia or diabetes. Clinically, the major advantage of the TyG index is that measurement of insulin level is not needed. Insulin measurement is not available in primary medical care and nationwide-level health check-ups, while fasting glucose level and TG level are routinely and simply measured. Therefore, the TyG index could be a convenient marker for screening for IR and estimating future cardiovascular risk in young adults in a real-world setting.

This study, however, has some limitations. First, our analyses included only Korean participants; therefore, the results might not be generalizable to people of other ethnicities. Second, because the NHID does not include insulin levels, we were unable to provide evidence supporting the advantages of the TyG index over HOMA-IR or HEC, the gold standard measurement of insulin sensitivity. Third, our definition of cardiovascular events based on the claims data might not be totally reliable. However, we defined the outcomes by combining diagnosis and prescription history to improve accuracy. Finally, although the TyG index seemed to have more powerful predictive value in women in our subgroup analyses, we did not measure sex hormones or adiposity distribution despite both issues being related with the development of IR. However, considering the aim of this study, this limitation exerts minimal influence on our conclusions. We assessed the predictive efficacy of the TyG index for CVD risk and mortality using a large nationwide health screening cohort, which enabled us to identify the efficacy of TyG index in healthy and young population.

In conclusion, herein, we demonstrated that a higher TyG index is associated with a higher risk of CVD and mortality in the young population. Given its ease of calculation and that TG and glucose levels are routinely measured in the clinical setting, the TyG index could be a promising tool for CVD risk predictions in young adults.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

The mean value and the range of TyG index in each quartile groups

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Supplementary Table 2

Hazard ratios (95% confidence intervals) for (A) stroke, (B) myocardial infarction, and (C) death according to the quartiles of triglyceride, fasting plasma glucose, and the TyG index

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Supplementary Table 3

Risk of myocardial infarction, stroke, and death according to a prespecified subgroup comparing the highest triglyceride-glucose index quartile with all others

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