Triglyceride-Glucose Index Variability and Incident Cardiovascular Disease: A Prospective Cohort Study

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Research Article

Keywords: Triglyceride-glucose index, Cardiovascular disease, Variability, Cohort study

Posted Date: April 28th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1586954/v1

Abstract

Background: Recent studies have suggested that triglyceride-glucose (TyG) index is an independent predictor of cardiovascular disease (CVD). However, the impact of long-term visit-to-visit variability in TyG index on risk of CVD is not known. We aimed to investigate the longitudinal association between baseline and mean TyG index as well as TyG variability and incident CVD in a Chinese population.

Methods: We included 52,925 participants without previous history of CVD in the Kailuan study who underwent three health examinations (2006, 2008, and 2010) and were followed-up for clinical events until 2019. TyG index was calculated as Ln [fasting triglyceride (mg/dL) × fasting glucose (mg/dL)/2]. We measured the TyG variability as the SD of the residuals obtained from a linear regression on the three TyG measurements for each individual. Multivariate-adjusted Cox models were used to estimate the adjusted hazard ratio (aHR) and 95% confidence interval (CI).

Results: During a median follow-up time of 9.0 years, 2,745 developed CVD. The highest tertile (T3) of baseline and mean TyG index were each associated with higher CVD incidence as compared with the lowest tertile (T1) group: aHR, 1.35; 95% CI, 1.20-1.51; and aHR, 1.42; 95% CI, 1.27-1.60, respectively. Tertile 3 of TyG variability was associated with increased CVD incidence compared to T1 group (aHR, 1.13; 95% CI, 1.03-1.24). Individuals in the highest tertile of baseline TyG and the highest tertile of TyG variability experienced the highest incidence of CVD (aHR, 1.30; 95% CI, 1.10-1.53).

Conclusion: Higher TyG level and greater TyG variability were each independently associated with a higher incidence of CVD.

Background

Insulin resistance has been identified as an important risk factor for the development of cardiovascular disease (CVD) [1], which a leading cause of morbidity and mortality in China and worldwide [2, 3]. A meta-analysis of cohort studies or nested case-control studies have showed that a positive prospective relationship between insulin resistance and risk of CVD in adults without diabetes [4]. Furthermore, a Mendelian randomization analysis established a causal relationship between the two conditions [5]. Therefore, early identifying insulin resistance is essential to reduce the disease burden of CVD.

In the clinical setting, measurement of insulin resistance can be challenging as there are limitations to the homeostasis model assessment for insulin resistance (HOMA-IR) and the gold standard of the euglycemic clamp is time-consuming and burdensome, hence a simpler measure of insulin resistance is needed [6]. The triglyceride-glucose (TyG) index, which is the logarithmized product of fasting triglyceride and glucose, has been shown to be a simple measure of insulin resistance [7]. Previous studies have shown that TyG index is significantly related to an increased risk of cardiovascular events [8-16]. Additionally, a recent meta-analysis of cohort studies included 5,731,294 participants without CVD at baseline showed that the highest TyG index category was associated with 1.61-fold increased risk of CVD [17]. However, most of prior studies were based on a single baseline TyG index measurement [8-12], which

may not reflect long-term exposure. Few studies have examined repeated TyG measurements to evaluate the impact of longitudinal TyG index on the risk of CVD. To our knowledge, only one study examined the association between the change TyG index at two time points and incident CVD [14]. Additionally, three studies have reported on the association between time updated average TyG index, the number of visits with a high TyG index and CVD events [8, 9]. Furthermore, although the TyG index can change over time, no study has examined the association between long-term TyG index visit-to-visit variability and CVD development.

Therefore, we conducted a large population-based study involving more than 52,000 Chinese adults who had repeated measurements in TyG index to investigate the longitudinal association between baseline TyG level, visit-to-visit variability in TyG index, and CVD incidence during a median 9.0-year follow-up in a general population. We hypothesized that higher baseline TyG as well as greater variability are both associated with increased risk of CVD.

Study population

Details of the Kailuan study cohort design, methods, and data collection have been published previously [8, 9, 14, 18]. In brief, the Kailuan study recruited 101,510 community-dwelling adults aged 18 years and over between June 2006 and October 2007 in the Kailuan community, Tangshan City, China. A standardized interview and health examinations were conducted at baseline and follow-up. This study was approved by the Ethics Committee of Kailuan General Hospital and Beijing Tiantan Hospital, Capital Medical University, and it was conducted according to the principles of the Declaration of Helsinki. All participants provided written informed consent.

In this analysis, we included participants who underwent 3 health examinations between June 2006 and December 2010 (baseline and index year). Of 56,833 participants, we excluded those who had missing data on fasting blood glucose or triglycerides (n = 1,034) and those who had a previous diagnosis of stroke or myocardial infarction during the 4-year washout period (n = 2,874). Therefore, 52,925 eligible participants were included in the current study **(Additional file 1: Figure 1)**.

Data collection and definitions

At baseline and follow-up surveys, demographics, lifestyles, medical histories, anthropometric measurements, and laboratory tests were collected. Information on age, sex, education (< high school or ≥ high school), income level (≤ 1000 or > 1000 RMB/month), current smoking status (yes or no), and current drinking status (yes or no), physical activity (active: > 4 times/week and > 20 min at a time or inactive: < 80 min/week or none) and history of diseases (e.g., hypertension), and medications use (e.g., antihypertensive agents) was collected via a standardized questionnaire. Trained physicians or nurses measured participants' height, weight, systolic blood pressure (SBP), and diastolic blood pressure (DBP). Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$. Fasting blood samples were collected and were measured using the Hitachi 747 auto-analyzer (Hitachi, Tokyo, Japan). Serum total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol

(LDL-C), fasting blood glucose (FBG), creatinine, and high-sensitivity C-reactive protein (hs-CRP) were measured via a standardized protocol. Hypertension was defined as a self-reported history of hypertension, use of antihypertensive medications, SBP ≥140 mm Hg, or DBP ≥ 90 mm Hg. Diabetes was defined as self-reported history of diabetes, use of glucose-lowering drugs, or FBG ≥ 7.0 mmol/l. Hypercholesterolemia was defined as self-reported history of dyslipidemia, use of lipid-lowering medications or TC ≥ 5.17 mmol/l. Estimated glomerular filtration rate (eGFR) was calculated by the Chronic Kidney Disease Epidemiology Collaboration creatinine equation [19]. Chronic kidney disease was defined as an eGFR < 60 mL/min/1.73 m². High hs-CRP was defined as a hs-CRP > 3 mg/dL [20].

Definition of Baseline, Mean and Variability of TyG index

According to previous studies [8, 14], the TyG index was calculated as Ln[TG (mg/dL) × FBG (mg/dL)/2]. The baseline TyG index was calculated by using serum TG and FBG measured in 2010. Mean TyG index was defined as the average of TyG index measured in 2006, 2008, and 2010. The TyG index variability was defined as intraindividual variability in TyG levels measured on these three health examinations. As previously described [21, 22], we used residual SD, defined as visit-to-visit TyG index variability calculated as the root-mean-square error (RMSE) of the residuals (i.e., differences between observed TyG and predicted TyG) obtained from a simple linear regression analysis of the three TyG measurements of each participant.

Study outcome and follow-up

The study outcome was newly diagnosed CVD, which was defined as a composite of myocardial infarction and stroke. As previously described [14, 23], all participants were linked to the Municipal Social Insurance Institution and the Hospital Discharge Register for incidence of CVD, which cover all the Kailuan study participants. To further identify potential CVD cases, we reviewed the discharge lists from the 11 hospitals during 2006 to 2019 and asked for a history of CVD via a questionnaire during the biennial interview. For all suspected CVD events, three experienced physician adjudicators who were blinded to the study design reviewed the medical records. Myocardial infarction was defined as the recording of ICD-10 codes I21. Stroke was defined as the recording of ICD-10 codes I63, or I60 to I61. The vital status was obtained from Hebei Provincial Vital Statistics Offices or directly contacting the participants' family members.

Statistical Analysis

Baseline characteristics of Kailuan study participants were described across TyG variability tertiles. Continuous variables were summarized as mean ± SD or median (interquartile range) depending on variable distribution, and categorical variables as count (proportion). Continuous variables were compared using one-way ANOVA or the Kruskal-Wallis test, and categorical variables were compared using the χ^2 test across tertiles of TyG variability.

We analyzed risk of CVD according to the tertiles of baseline, mean, and variability of TyG index, and the combination of baseline TyG tertiles and TyG variability tertiles. Person-years of follow-up for each participant were calculated as the amount of time from the index date to the first of the following events: incident CVD, death, or December 31st, 2019. Incidence rate of CVD per 1000 person-years was calculated. Time to first CVD event was first examined using Kaplan-Meier survival curves and compared using log-rank test. Then, multivariable-adjusted Cox proportional hazards regression models were used to estimate the hazard ratios (HR) and 95% confidence intervals (CI). The proportional hazards assumption was verified by inspecting negative log-log survival plots and no violation was observed. Model 1 was adjusted for age and sex. Model 2 was adjusted for age, sex, education, income, current smoking status, current drinking status, physical activity, BMI, diabetes, hypertension, chronic kidney disease, and hs-CRP. Model 3 was additionally adjusted for use of lipid-lowering agents, TC, LDL-C, and LDL-C. Model 4 was additionally adjusted for baseline TyG index. In the trend test, the categorical variable (i.e., TyG variability tertile) was statistically examined as an ordinal variable (continuous variable) in Cox regression model.

Net reclassification improvement (NRI) for survival data were used to estimate the improvement in discrimination and reclassification after adding baseline and variability of TyG levels to the conventional clinical risk model [24]. A risk threshold of 5% for 9-year CVD risk (median follow-up time) was used to calculate categorical NRI. 95% CI for continuous and categorical NRI were estimated with 500 bootstrap replications.

To estimate the population impact of TyG measures on CVD risk, we estimated the absolute risk difference for between baseline, mean, and variability of TyG index and incident CVD. Predicted cumulative incidence and absolute risk differences were presented as per 1000 population over 10 years and were estimated by use of flexible parametric survival models on the cumulative hazard scale [25], similar to what has been done previously [26]. We also plotted the adjusted cumulative incidence curves for CVD by extrapolating to 10 years using *stpm2* and *standsurv* command in Stata, which were standardized to the baseline covariates.

Several sensitivity analyses were conducted as follows: (1) excluding lipid-lowering agent users; (2) excluding antidiabetic agent users; (3) excluding FBG ≥ 7.0 mmol/L or TG ≥ 1.7 mmol/L at baseline; (4) using Fine-Gray competing risk regression treating deaths as competing risk events [27] ; (5) excluding CVD events that occurred within 2 years of follow-up (2-y lag analysis); (6) other variability, including SD, coefficient of variation (CV), and independent of the mean (VIM) were calculated [18]; (7) to assess the influence of unmeasured confounding, E-value, which is defined as the minimum strength of association, was calculated based on the estimated HR and 95% CI for CVD [28].

Statistical analyses were conducted using STATA MP, version 16.0 (StataCorp) and R software, version 4.1.3. All *P*-values were 2-sided and a $P < 0.05$ was considered statistically significant, unless otherwise stated.

Results

Among the 52,925 participants **(Additional file 1: Figure 1)**, the mean age was 53.0 ± 11.8 years at baseline, and 40,396 (76.3%) were male. The mean baseline TyG level of the total study population was 8.7 ± 0.7, and the median TyG variability was 0.2 (interquartile range, 0.1-0.4). **Table 1** shows the baseline characteristics of the study participants according to tertiles of TyG variability. Participants in the highest tertile of TyG variability were slightly younger, more frequently male, current smokers and alcohol drinker, and had lower rates of regular exercise, and lower education and income. They also had higher prevalence of hypertension, diabetes, and hypercholesterolemia, and had higher mean BMI, SBP, DBP, FBG, and TG.

Association Between Baseline and Mean TyG index and the Incidence of CVD Risk

During a median 9.0 years of follow-up (452,732 person-years) after the TyG variability assessment period, 2,745 (5.2%) participants developed CVD. The overall incidence rate of CVD was 6.1 per 1000 person-years.

Table 2 presents the association between baseline and mean TyG level and CVD risk. In Model 3, which was adjusted for all covariates, the baseline and mean TyG index was positively correlated with the risk of CVD incidence. The HR of CVD in the highest baseline TyG tertile was 1.35 (95% CI: 1.20-1.51) compared to that in the lowest tertile of baseline TyG index (*P* for trend <0.001). The CVD risk of highest tertile of mean TyG level was higher (HR, 1.42; 95% CI: 1.27-1.60) than that of lowest tertile of mean TyG level (*P* for trend <0.001). The Kaplan-Meier survival curves show that the incidence of CVD risk increased with higher levels of baseline **(Figure 1A)** and mean TyG level **(Figure 1B)**.

Association Between TyG Variability and Incident CVD

After adjusting for all covariates, including baseline TyG index (Model 4), participants in the highest tertile of TyG variability showed an increased risk of CVD (HR, 1.13; 95% CI, 1.03-1.24) compared to those in lowest tertile (*P* for trend = 0.01; **Table 2**). **Figure 1C** shows Kaplan-Meier survival curves for the development of CVD according to the tertiles of TyG variability during follow-up period. The log-rank tests showed that participants in the highest tertile of TyG variability had higher cumulative risk of CVD than in the other tertiles (log-rank *P* = 0.003).

Associations Between Combination of the Baseline TyG Level, TyG Variability, and CVD

Figure 2 shows the risk of CVD incidence according to the combined groups of the baseline TyG index and TyG variability after adjusting for multiple covariates. Specifically, the group with the highest risk of CVD was in the highest tertile of both baseline TyG and TyG variability (HR, 1.30; 95% CI: 1.10-1.53), compared with the group with the tertile 1 of baseline TyG and the tertile 1 of TyG variability.

Absolute Risk Difference for CVD by TyG Levels and Variability

In terms of absolute risk difference, participants in the highest tertile of baseline TyG, mean TyG, and TyG variability were associated with 31.4 (95% CI: 17.5-45.2), 36.7 (95% CI: 22.3-51.1), and 7.5 (95% CI: 1.6-

13.4) more cases of CVD per 1000 population over 10 years, respectively, compared with participants in Tertile 1 **(Table 3)**. The standardized cumulative incidence curves for CVD by tertiles of baseline TyG, mean TyG and TyG variability were displayed in the **Additional file 1: Figure 2**.

CVD Risk Reclassification by Baseline TyG Level and TyG Variability

Adding the baseline TyG level and TyG variability to the clinical risk model, there was a significant reclassification improvement in a two-category risk assessment (< 5%; ≥ 5%) (NRI 0.85%, 95% CI: 0.002% to 1.71%; continuous NRI = 13.93%, 95% CI: 9.85% to 18.06%) **(Table 4)**.

Sensitivity Analyses

In a sensitivity analysis limited to adults without use of lipid-lowering agents or antidiabetic agents, the association between TyG variability and incident CVD persisted (**Additional file 1: Table 1**). Results remained qualitatively similar after excluding individuals with FBG ≥ 7.0 mmol/L or TG ≥ 1.7 mmol/L at baseline (HR, 1.13, 95% CI: 1.02-1.25). Also, results did not change substantially after excluding events that occurred during the first 2 years of follow-up (HR, 1.14, 95% CI: 1.03-1.27). When competing risk models were applied, the association between TyG variability and incident CVD did not appreciably change (HR, 1.13, 95% CI: 1.03-1.32). No significant associations were found between TyG variability measured by SD, CV, or VIM in relation to incident CVD (**Additional file 1: Figure 3**). E-values were 1.76, 1.87, and 1.40 for the baseline TyG, mean TyG, and TyG variability, respectively (**Additional file 1: Figure 4**), which suggested the associations did not influence by the potential unmeasured confounding in our study.

Discussion

Among 52,925 Chinese adults followed up for a median of 9 years, higher baseline TyG, mean TyG, and TyG variability were each significantly associated with a higher risk of incident CVD, and these associations persisted even after adjustment for other established cardiovascular risk factors. Furthermore, in the analysis of the combination of baseline TyG and TyG variability, the group with the highest baseline TyG and highest TyG variability was at the greatest risk of developing CVD. Overall, our data suggest that TyG variability is a marker of increased CVD risk among Chinese adults.

Several prior studies have evaluated the association between baseline TyG index and cardiovascular events in the general population [8-12, 15, 16]. The Tehran Lipid and Glucose Study, with 16 years of follow-up, showed that elevated baseline TyG index was associated with a 61% and 84% increased risk of CVD and coronary heart disease, respectively [11]. In the 10-year follow-up VMCUN (Vascular Metabolic CUN) cohort, higher TyG index was associated with an increased risk of ischemic heart disease, cerebrovascular disease, and peripheral arterial disease, and TyG index could provide additional predictive value to the Framingham risk score for new-onset CVD [15], which was in accordance with our results. Another recent study with 5,593,134 persons ≥ 40 years from the Korea National Health Information Database showed that TyG index is an independent predictor of myocardial infarction and

stroke during 8.2 years of mean follow-up [16]. Similar results were observed in our previous studies from the Kailuan cohort investigating the association between baseline TyG index and CVD [8, 9]. Consistent with previous studies, we confirmed that a higher TyG index at baseline was significantly associated with a 35% increased risk of future CVD.

To our knowledge, the present study is the first to investigate longitudinal associations between TyG variability and risk of CVD in a prospective fashion. The associations we observed were independent of traditional cardiovascular risk factors as well as the baseline TyG index and thus had incremental value on CVD risk prediction. Our results indicate that participants with both high baseline and high variability in TyG index had the highest risk of CVD. This suggests the important effects of both the absolute value and the variability of TyG index in terms of the risk of CVD in the general population.

The present study demonstrated that fluctuation of TyG level was also associated with incident CVD. Recently, the association between visit-to-visit variability in various biological measures (e.g., blood pressure, cholesterol, and glucose) and incident CVD have been examined [18, 29, 30]. Several measures have been proposed to calculate visit-to-visit variability (eg, SD, CV, and VIM) [18, 29, 30]. However, to date, there has been no consensus on a gold-standard approach to measure visit-to-visit variability [31]. Generally, SD is widely applied and is influenced by extreme values. It is known that the VIM and CV are weakly correlated with the mean value compared to SD. Based upon the relevant literature to date, residual SD and VIM may be an ideal approach [31]. Recently, residual SD has been used to define visit-to-visit variability in previous studies [21, 22]. We compared residual SD, SD, CV, and VIM as indices of TyG variability, but only TyG variability measured by residual SD was associated with risk of CVD, after adjusting for baseline TyG level. These results led us to conclude that the TyG variability measured by residual SD tended to be superior to other indices in predicting the incidence of CVD. Further large prospective studies are needed to validate our findings.

The potential underlying mechanisms by which high TyG variability may be associated with higher risk of CVD are still not known. First, since TyG is a composite index of fasting TG and FBG, high TyG variability may be directly linked to greater serum TG and FBG variability, which were demonstrated to be associated with adverse CVD events in many previous studies [29, 32, 33]. Second, greater TyG variability leads to greater chronic inflammation [34] and [35] as well as progression of the vulnerable plaque [36]. Third, TyG variability may be linked to body weight variability, which was demonstrated to be associated with cardiovascular events [37].

Our study has several key strengths. First, the present study is the first to demonstrate an association between TyG variability and risk of CVD. This study provides the first evidence showing that high TyG and TyG fluctuation was independent of traditional cardiovascular risk factors. Second, this study used longitudinally and repeatedly collected TyG data at the individual level before the incidence of CVD, which allowed us to directly evaluate the long-term effect of TyG variability on CVD risk. Third, we adjusted all available confounding factors and conducted several sensitivity analyses.

This study also has some limitations. First, owing to the observational nature of the study, we could not establish a causal association between the TyG index and the risk of MI. Therefore, our findings need to be confirmed in future studies. Furthermore, although potential cardiac risk factors were adjusted for, we still cannot exclude the possibility of residual or unmeasured confounding given the observational study design of the present analysis. Second, selection of study population based on the number of health examinations could be subject to selection bias. Third, the study population consisted of Chinese men and women living in the Kailuan community, located in Tangshan, Hebei, China; hence, it is uncertain whether these findings can be generalized to other population. Finally, variability in TyG index may be affected by time-varying factors such as diet during follow-up, information our data did not collect.

Conclusions

In a prospective cohort of Chinese adults, we found that higher baseline TyG, mean TyG, as well as greater TyG variability, were each associated with higher risk of CVD. In addition, there was a greater risk of developing CVD in the group with the highest baseline TyG level and highest TyG variability. Future research is required to validate our findings and elucidate the exact mechanisms underlying the association between TyG variability and CVD.

Abbreviations

BMI: Body mass index; CVD: Cardiovascular disease; eGFR: Estimated glomerular filtration rate; TyG: Triglyceride-glucose; FBG: fasting blood glucose; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; TC: Total cholesterol; TG: Triglycerides; Hs-CRP: High-sensitivity C-reactive protein; SBP: Systolic blood pressure; DBP: diastolic blood pressure; HR: Hazard ratio; CI: Confidence interval.

Declarations

Acknowledgments

We thank all study participants, their relatives, the members of the survey teams at the 11 regional hospitals of the Kailuan Medical Group, and the project development and management teams at the Beijing Tiantan Hospital and the Kailuan Group.

Authors' contributions

HBL and SHC contributed to the study concept and design, analysis and interpretation of data, drafting of the manuscript, and served as the equally contributing first authors of the manuscript. FQ, XT, YTZ, XL, and XHG contributed to the interpretation of data and revision of the drafting of the manuscript. SLW and AXW contributed to the study concept and design, study supervision or coordination, revision of the drafting of the manuscript, and served as the corresponding authors of the manuscript. All authors read and approved the final manuscript.

Sources of Funding

This study was supported by the National Key R&D Program of China (2018YFC1312400, 2018YFC1312402), Beijing Excellent Talents Training Program (20180000021469G234), National Natural Science Foundation of China (8210120410), and Golden Seed Program of Beijing Chaoyang Hospital (CYJZ202101).

Availability of data and materials

The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Kailuan General Hospital and Beijing Tiantan Hospital. All of the participants provided written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1. Baseline Characteristics of Study Participants According to the Tertiles of Variability of TyG index

		TyG index variability			
	Total	**Tertile 1**	**Tertile 2**	**Tertile 3**	***P* value**
	(n = 52,925)	(n = 17,642)	(n = 17,642)	(n = 17,641)	
Age, y	53.0 ± 11.8	53.7 ± 12.1	53.1 ± 11.8	52.2 ± 11.5	<0.001
Age ≥ 60 y	13677 (25.8)	4978 (28.2)	4664 (26.4)	4035 (22.9)	<0.001
Male sex	40396 (76.3)	13219 (74.9)	13384 (75.9)	13793 (78.2)	<0.001
Education (≥ high school)	14562 (27.6)	4913 (28.0)	4938 (28.1)	4711 (26.9)	0.016
Income (≤ 1000 RMB/month)	23778 (46.0)	7749 (44.9)	7930 (46.0)	8099 (47.2)	<0.001
Current smoker	17841 (33.8)	5696 (32.4)	5856 (33.3)	6289 (35.8)	<0.001
Alcohol drinker	18833 (35.7)	6024 (34.3)	6145 (35.0)	6664 (37.9)	<0.001
Physical activity	34995 (66.4)	11777 (67.0)	11696 (66.5)	11522 (65.6)	0.020
Hypertension	24497 (46.4)	8090 (45.9)	8058 (45.7)	8349 (47.4)	0.002
Diabetes	5595 (10.6)	1596 (9.0)	1675 (9.5)	2324 (13.2)	<0.001
Hypercholesterolaemia	21281 (40.2)	7056 (40.0)	6979 (39.6)	7246 (41.1)	0.011
Chronic kidney disease	3364 (6.4)	1192 (6.8)	1142 (6.5)	1030 (5.8)	0.001
Antihypertensive agents	5633 (10.8)	1891 (10.8)	1857 (10.6)	1885 (10.8)	0.800
Antidiabetic agents	1716 (3.3)	450 (2.6)	517 (3.0)	749 (4.3)	<0.001
Lipid-lowering agents	489 (0.9)	141 (0.8)	157 (0.9)	191 (1.1)	0.018
Body mass index, kg/m^2	25.1 ± 3.4	25.0 ± 3.4	25.1 ± 3.4	25.2 ± 3.3	<0.001
Body mass index ≥ 25 kg/m^2	27114 (51.2)	8965 (50.8)	8964 (50.8)	9185 (52.1)	0.025
Systolic blood pressure, mm Hg	130.6 ± 19.2	130.5 ± 19.4	130.4 ± 19.1	131.0 ± 19.0	0.016

Diastolic blood pressure, mm Hg	84.2 ± 10.8	84.0 ± 10.8	84.1 ± 10.8	84.6 ± 10.7	<0.001
Fasting glucose, mmol/L	5.6 ± 1.8	5.6 ± 1.5	5.6 ± 1.4	5.8 ± 2.2	<0.001
Estimated glomerular filtration rate	90.4 ± 19.9	89.8 ± 19.8	90.5 ± 20.1	90.9 ± 19.9	<0.001
Total cholesterol, mmol/L	5.0 ± 1.3	5.0 ± 1.2	5.0 ± 1.1	5.0 ± 1.5	0.030
LDL-C, mmol/L	2.6 ± 0.9	2.6 ± 0.9	2.6 ± 0.8	2.6 ± 1.1	0.012
HDL-C, mmol/L	1.6 ± 0.5	1.6 ± 0.5	1.6 ± 0.5	1.5 ± 0.5	<0.001
Triglycerides, mmol/L	1.3 (0.9-1.9)	1.3 (0.9-1.8)	1.2 (0.9-1.8)	1.4 (0.9-2.2)	<0.001
Hs-CRP, mg/dL	1.0 (0.5-2.5)	1.0 (0.5-2.5)	1.0 (0.5-2.4)	1.0 (0.5-2.5)	0.380
Hs-CRP > 3 mg/dL	10452 (20.0)	3475 (19.9)	3423 (19.6)	3554 (20.5)	0.110
Baseline TyG index	8.7 ± 0.7	8.6 ± 0.6	8.6 ± 0.6	8.8 ± 0.8	<0.001
Mean TyG index	8.7 ± 0.6	8.6 ± 0.6	8.6 ± 0.6	8.8 ± 0.6	<0.001
Variability of TyG index	0.2 (0.1-0.4)	0.1 (0.0-0.1)	0.2 (0.2-0.3)	0.5 (0.4-0.7)	<0.001

Abbreviations: TyG index = triglyceride-glucose index; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; Hs-CRP = high-sensitivity C-reactive protein.

Values are presented as number (%), mean ± SD, or median (interquartile range).

Table 2. Association Between Tertiles of Baseline, Mean, and Variability of TyG Index and the Incidence of Cardiovascular Disease

	Hazard ratio (95% CI) [a]			
	Tertile 1	**Tertile 2**	**Tertile 3**	***P* for trend [b]**
Baseline TyG index				
No. of cases/Population	659/17642	913/17642	1173/17641	
Incidence rate per 1000 person-years	4.35	6.03	7.82	
Model 1 [c]	1 [Reference]	1.40 (1.27-1.55)	1.93 (1.75-2.12)	<0.001
Model 2 [d]	1 [Reference]	1.27 (1.14-1.41)	1.44 (1.29-1.60)	<0.001
Model 3 [e]	1 [Reference]	1.22 (1.10-1.36)	1.35 (1.20-1.51)	<0.001
Mean TyG index				
No. of cases/Population	616/17642	911/17642	1218/17641	
Incidence rate per 1000 person-years	4.05	6.02	8.14	
Model 1 [c]	1 [Reference]	1.47 (1.33-1.63)	2.05 (1.86-2.26)	<0.001
Model 2 [d]	1 [Reference]	1.31 (1.17-1.45)	1.51 (1.35-1.69)	<0.001
Model 3 [e]	1 [Reference]	1.25 (1.12-1.40)	1.42 (1.27-1.60)	<0.001
TyG Variability				
No. of cases/Population	866/17642	890/17642	989/17641	
Incidence rate per 1000 person-years	5.74	5.90	6.55	
Model 1 [c]	1 [Reference]	1.06 (0.96-1.16)	1.23 (1.12-1.35)	<0.001
Model 2 [d]	1 [Reference]	1.02 (0.93-1.13)	1.15 (1.04-1.26)	0.004
Model 3 [e]	1 [Reference]	1.03 (0.93-1.13)	1.14 (1.04-1.25)	0.007
Model 4 [f]	1 [Reference]	1.03 (0.93-1.13)	1.13 (1.03-1.24)	0.013

Abbreviations: TyG = triglyceride-glucose; CI = confidence interval.

[a] The tertile cutoff were < 8.4, 8.4 to 8.9, ≥ 8.9 for baseline and mean TyG, and < 0.2, 0.2 to 0.4, ≥ 0.4 for TyG variability.

[b] *P* value from linear trend test when tertiles were treated as an ordinal variable in the Cox model.

[c] Adjusted for age and sex.

[d] Adjusted for age, sex, education, income, current smoking, current drinking, physical activity, body mass index, diabetes, hypertension, chronic kidney disease, and high-sensitivity C-reactive protein.

[e] Adjusted for covariates in model 2 plus use of lipid-lowering agents, total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol.

[f] Adjusted for covariates in model 3 plus baseline TyG index.

Table 3. Absolute Risk Difference (per 1000 Population over 10 Years) of Cardiovascular Disease by the Baseline, Mean, and Variability of TyG Index

	Predicted incidence per 1000 population over 10 years†	Absolute risk difference per 1000 population over 10 years‡
Baseline TyG index		
Tertile 1	53.6 (49.4 to 58.3)	Reference
Tertile 2	64.6 (60.5 to 69.0)	11.0 (4.9 to 17.0)
Tertile 3	85.0 (75.2 to 96.1)	31.4 (17.5 to 45.2)
Mean TyG index		
Tertile 1	51.9 (47.7 to 56.5)	Reference
Tertile 2	64.0 (59.9 to 68.4)	12.1 (6.1 to 18.1)
Tertile 3	88.7 (78.4 to 100.3)	36.7 (22.3 to 51.1)
TyG Variability		
Tertile 1	60.8 (56.8 to 65.0)	Reference
Tertile 2	62.3 (58.3 to 66.7)	1.6 (−4.2 to 7.4)
Tertile 3	68.2 (64.1 to 72.7)	7.5 (1.6 to 13.4)

Abbreviations: TyG = triglyceride-glucose.

†Calculated as $CIF_{t=10} \times 1000$, where the predicted 10-year CIF (cumulative incidence function) of CVD was estimated from the flexible parametric survival models, which was standardized to the baseline variable.

†Calculated as the difference between the predicted incidence per 1000 population over 10 years across the baseline, mean, and variability of TyG Index tertiles.

Table 4. Net Reclassification Improvement after Adding Baseline and Variability of TyG Index to Clinical Risk Model

Clinical risk model [a]	Clinical model + baseline and variability of TyG index		
	< 5% [b]	≥ 5%	Total
CVD			
< 5%	597	71	668
≥ 5%	50	1784	1834
Total	647	1855	2502
Non-CVD			
< 5%	16204	544	16748
≥ 5%	498	7912	8410
Total	16702	8456	25158
Net reclassification improvement (NRI)			
NRI for CVD (95% CI), %			0.85 (0.002 to 1.71)
NRI for Non-CVD (95% CI), %			0.01 (-0.17 to 0.21)
NRI (95% CI), %			0.86 (0.001 to 1.82)
Continuous NRI for CVD (95% CI), %			13.68 (9.70 to 17.47)
Continuous NRI for Non-CVD (95% CI), %			0.25 (-0.75 to 1.29)
Continuous NRI, %			13.93 (9.85 to 18.06)

Abbreviations: TyG = triglyceride-glucose; NRI = net reclassification improvement; CVD = cardiovascular disease; CI = confidence interval.

[a] Clinical risk model was included age, sex, education, income, current smoking, current drinking, physical activity, body mass index, diabetes, hypertension, chronic kidney disease, high-sensitivity C-reactive protein, use of lipid-lowering agents, total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol, which was based on complete data analysis (N = 48505).

[b] The cutoff of 5% was the median of predicted CVD risk at the median of follow-up time for the total population.

Figures

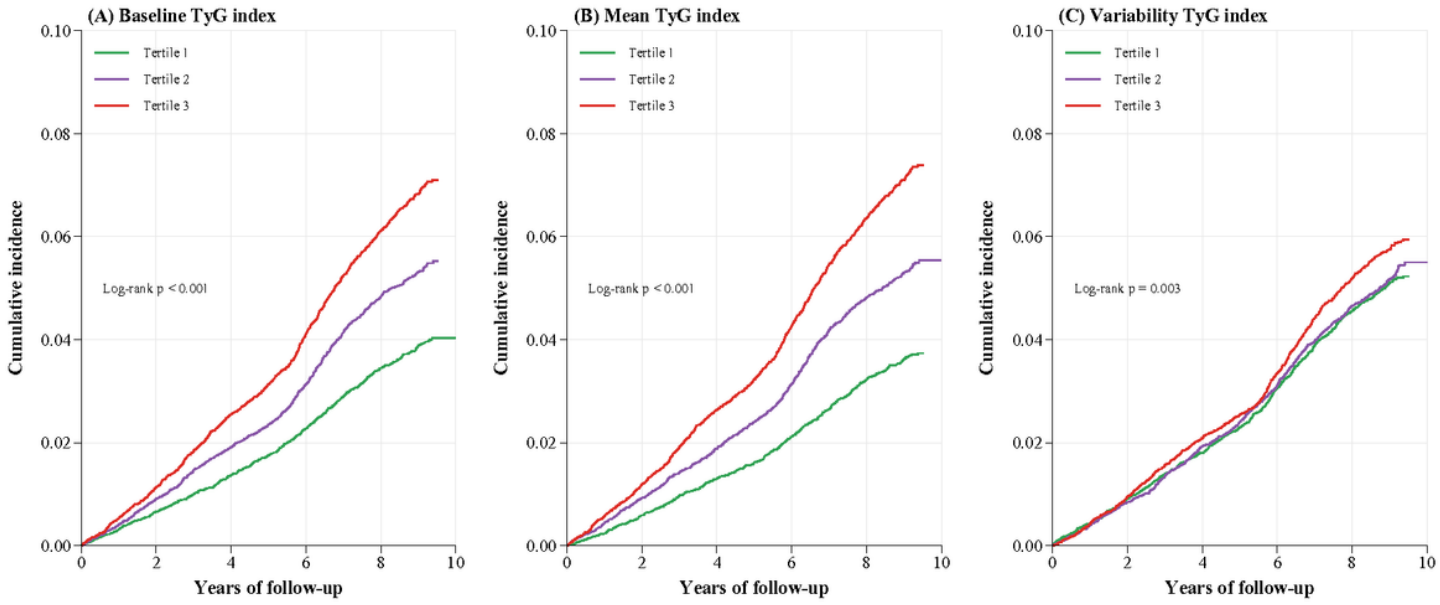

Figure 1

Kaplan-Meier Survival Curves for Cardiovascular Disease Development by Tertiles of Baseline, Mean, and Variability of Triglyceride-Glucose (TyG) Index

Baseline	Variability	Population (n)	Events (n)	IR	Adjusted HR (95% CI)
T1	T1	6136	262	5.00	1 [Reference]
	T2	6212	201	3.75	0.76 (0.63-0.92)
	T3	5294	196	4.30	0.95 (0.78-1.15)
T2	T1	6253	293	5.46	0.99 (0.83-1.18)
	T2	5994	322	6.27	1.12 (0.94-1.33)
	T3	5395	298	6.44	1.21 (1.01-1.43)
T3	T1	5253	311	6.96	1.08 (0.90-1.29)
	T2	5436	367	7.98	1.25 (1.05-1.49)
	T3	6952	495	8.36	1.30 (1.10-1.53)

IR = incidence rate per 1,000 person-years; T1 = the lowest tertile; T3 = the highest tertile.

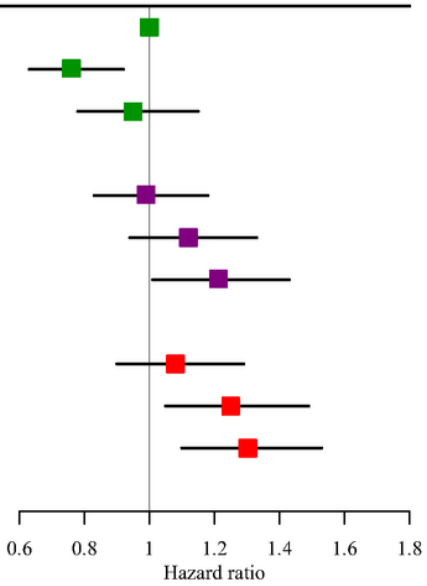

Figure 2

Hazard Ratios and 95% Confidence Intervals of Developing Cardiovascular Disease According to the Combination Group of Baseline Triglyceride-Glucose (TyG) Index and TyG Variability

Supplementary Files

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