Changes in Triglyceride-glucose Index Predict the Risk of Cardiovascular Diseases in the General Population: a Prospective Cohort Study

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Abstract

Background: The relationship between baseline triglyceride-glucose (TyG) index and cardiovascular disease (CVD) has been confirmed by former studies. However, the effect of longitudinal changes in TyG index on CVD remains uncertain. This study aimed to investigate the association of changes in TyG index with CVD in the general population.

Methods: The current study included 62,443 Chinese population who were free of CVD. TyG index was calculated as $\ln [\text{fasting triglyceride (mg/dL)} \times \text{fasting glucose (mg/dL)} / 2]$, changes in TyG index was defined as the difference in TyG index between 2010 and 2006. Cox proportional hazard model and restricted cubic spline was used to examine the association between changes in TyG index and CVD.

Results: During a median follow-up of 7.01 years, 2,530 (4.05%) incident CVD occurred, including 2,018 (3.23%) stroke and 545 (0.87%) MI. Risk of CVD was increased with quartiles of changes in TyG index, the adjusted hazard ratio (HR) in Q4 group versus Q1 group was 1.37 (95% confidence interval [CI], 1.21-1.54) for the overall CVD, 1.38 (95% CI, 1.19-1.60) for stroke, and 1.36 (95% CI, 1.05-1.76) for MI. Restricted cubic spline also showed cumulative increased risk of CVD with increasing changes in TyG index. Furthermore, the addition of changes in TyG index to a baseline risk model for CVD improved the C-statistics ($P=0.0097$), the integrated discrimination improvement ($P<0.0001$), and the category-free net reclassification improvement ($P<0.0001$). Similar results were observed for stroke and MI.

Conclusions: Substantial changes in TyG index can independently predict the risk of CVD in the general population. Monitoring long-term changes in TyG may be helpful in the early identification of individuals at high risk of CVD.

Background

Insulin resistance, the critical mechanism of the pathogenesis of diabetes mellitus, has been extensively demonstrated to be significantly related to be the development of cardiovascular disease (CVD).[1–3] Insulin resistance has been reported not only to be associated with CVD risk factors such as diabetes mellitus[4], hypertension[5], dyslipidemia[6], and obesity[7], but also is an independent risk factor for CVD[1–3], thus an early detection and control of insulin resistance may contribute to the prevention of CVD. Although the hyperinsulinemic-euglycemic clamp is the gold-standard test for IR assessment, it is not commonly used in clinical settings and large population studies due to the complex testing process and expensive cost.[8] In this regard, triglyceride-glucose (TyG) index, a product of triglyceride (TG) and fasting blood glucose (FBG), appears as a simple surrogate for insulin resistance with high correlation with the gold-standard test.[9–11] Cohort studies have found that TyG index was an importance risk factor for incident CVD.[12–16] However, an inherent limitation of previous studies is the TyG index was evaluated on a single time point, there has been no consideration of how the TyG index varies within individuals over time and the subsequent effect, which may yield a biased estimate of the relationship of

the TyG index and CVD risk. While the effect of longitudinal changes in TyG index over time on CVD has not been fully studied up to date.

We therefore conducted the present study to identify the potential association of changes in TyG index with CVD and its subtypes based on a large community-based prospective cohort study.

Methods

Study population

The Kailuan study is a prospective cohort study in the Kailuan community in Tangshan, China. The detailed study design and procedures have been described previously.[17-19] During June 2006 to October 2007, a total of 101,510 participants (81 110 men and 20 400 women; aged 18 to 98 years) were enrolled in the first survey (baseline) and underwent a comprehensive biennial health examination. All participants were followed up until their death or December 31, 2017. Changes in TyG index was developed from 2006 to 2010 to predict CVD risk from 2010 to 2017 (Figure S1). We excluded 3,669 and 2,042 participants with MI or stroke in or prior 2010, 30,971 participants who did not finish the survey at 2010, 1,282 and 1,103 participants with missing data on FBG or TG at baseline or the survey at 2010. Ultimately, a total of 62,443 participants were enrolled in the present study (Figure S2). The study was performed according to the guidelines of the Helsinki Declaration and was approved by the Ethics Committee of Kailuan General Hospital (approval number: 2006-05) and Beijing Tiantan Hospital (approval number: 2010-014-01). All participants were agreed to take part in the study and provided written informed consent.

Data collection and definitions

Information on demographic characteristics, lifestyle factors (smoking status, drinking status, and physical activity), and medical history were collected via standardized questionnaire by trained staffs. Education was classified as illiteracy or primary school, middle school, and high school or above. Income was categorized into > 800 and ≤ 800 yuan/month. Smoking and drinking status were stratified into never, former or current. Physically active was classified as ≥ 4 times per week and ≥ 20 minutes at a time, < 80 minutes per week, or none. Body mass index (BMI) was calculated by dividing body weight (kg) by the square of height (m^2). Blood pressure was measured in the seated position using a mercury sphygmomanometer, the average of 3 readings were calculated as systolic blood pressure (SBP) and diastolic blood pressure (DBP). All the blood samples were analyzed using an auto-analyzer (Hitachi 747, Hitachi, Tokyo, Japan) on the day of the blood draw. The biochemical indicators tested included fasting blood glucose, serum lipids, serum creatinine, and high-sensitivity C-reactive protein (hs-CRP).

Hypertension was defined as SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg, any use of the antihypertensive drug, or self-reported history of hypertension. Diabetes was defined as FBG ≥ 7.0 mmol/L, any use of glucose-lowering drugs, or any self-reported history of diabetes. Dyslipidemia was defined as any self-reported history or use of lipid-lowering drugs, or TC ≥ 5.17 mmol/L.

Calculation of changes in TyG index

The TyG index was calculated as $\ln (\text{fasting TG [mg/dl]} \times \text{FBG [mg/dl]}/2)$ as previous done.[20, 21] Changes in TyG index was calculated as TyG index value at 2010 minus that at baseline (2006).

Assessment of outcomes

The outcome in the present study was the first occurrence of CVD events. The types of CVD included stroke and MI. We defined CVD events as described previously.[17, 22, 23] The database of CVD diagnoses was obtained from the Municipal Social Insurance Institution and Hospital Discharge Register and was updated annually during the follow-up period. An expert panel collected and reviewed annual discharge records from 11 Kailuan hospitals to identify patients who were suspected of CVD. Incident stroke was diagnosis based on neurological signs, clinical symptoms, and neuroimaging tests, including computed tomography or magnetic resonance, according to the World Health Organization criteria.[24] MI was diagnosed according to the criteria of the World Health Organization on the basis of clinical symptoms, changes in the serum concentrations of cardiac enzymes and biomarkers, and electrocardiographic results.[17, 25]

Statistical analysis

Participants were divided into four categories according to quartiles of changes in TyG index. The baseline characteristics were presented as mean $\pm$ standard deviation (SD) or frequency with percentage as appropriate. Tests of differences in characteristics across changes in TyG index categories were performed using analysis of variance or the Kruskal-Wallis test for continuous variables according to distribution and chi-square for categorical variables. The person-years were determined from the date when the message was collected at baseline to either the date of MI onset, death, or the date of participating in the last examination in this analysis, whichever came first. Kaplan-Meier methods were performed to evaluate the incidence rate of CVD and its subtypes, and differences among groups were evaluated by log-rank test.

Cox proportional hazard regression model was applied to calculated hazard ratio (HR) and 95% confidence interval (CI) for CVD and its subtypes. The proportional hazard assumption was evaluated with visualization of Schoenfeld residuals and no potential violation was observed. Two models were constructed. Model 1 was adjusted for age, sex, and TyG index at baseline. Model was additionally adjusted for education, income, smoking status, drinking status, physical activity, BMI, SBP, DBP, a history of hypertension, diabetes mellitus, and dyslipidemia, antidiabetic drugs, lipid-lowering drugs, antihypertensive drugs, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and hs-CRP at baseline. *P*-values for trend were computed using quartiles as ordinal variables. To capture the dose-response relationship between changes in TyG index and CVD, restricted cubic splines with four knots at the 5th, 35th, 65th, and 95th percentiles of TyG index change distribution with median of the Q1 group as the reference point.[26]

Additional analyses were performed to validate the robustness of the results. First, competing risk model was applied to assess the association between changes in TyG index and the outcomes considering non-CVD death as a competing risk event. Second, restricted analysis was conducted by excluding participants with abnormal FBG level (≥ 7.0 mmol/L) or abnormal TG level (≥ 1.7 mmol/L) at baseline. [20] Third, to explore the potential impact of reverse causality, we repeated the primary analysis using a 2-year lag period by excluding incident stroke cases from the first 2 years of follow-up. Subgroup analyses were conducted stratified participants by age (< 60 and ≥ 60 years), sex (women and men), BMI (< 25 and ≥ 25 kg/m²), and FBG (< 5.6 , 5.6 - 7.0 , and ≥ 7.0 mmol/L) to assess the possible effect modification by these variables, interactions between subgroups were tested using likelihood ratio tests comparing models with and those without multiplicative interaction terms. Additionally, we used C statistics, integrated discrimination improvement (IDI), and net reclassification index (NRI) to evaluate the incremental predictive value of change in TyG index beyond conventional risk factors.

All analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina) and R software version 3.6.1 (R Core Team, Vienna, Austria). All statistical tests were 2-sided, and $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics

A total of 62,443 eligible participants were included, the mean age was 49.07 ± 11.84 years, and 76.59% were men. Comparison of baseline characteristics between participants and non-participants due to missing the 2010 survey or incomplete data was presented in Table S1. There was a significant difference between participants and non-participants in age, sex, education, income, smoking, drinking, medical history, and laboratory indexes.

Baseline characteristics of participants according to quartiles of changes in TyG index are presented in Table 1. Compared with participants in the Q1 group, participants in other groups were more likely to be older, men, less educated, had lower income, more current smokers and drinkers, a higher prevalence of hypertension, diabetes, and dyslipidemia, more likely to take antihypertensive agents and antidiabetic agents, had a high BMI, SBP, DBP, TC, LDL-C, and hs-CRP level, and a lower HDL-C level.

Table 1

Baseline characteristics of participants according to quartiles of changes in TyG index from 2006 to 2010.

Characteristics	Overall	Quartiles of changes in TyG index				<i>P</i> value
		Q1 (<-0.31)	Q2 (-0.31-0.05)	Q3 (0.05-0.41)	Q4 (≥ 0.41)	
No. of participants	62443	15610	15611	15611	15611	
Age, years	49.07 ± 11.84	47.35 ± 11.77	48.82 ± 11.98	49.96 ± 11.95	50.15 ± 11.46	< 0.0001
Men, n (%)	47827 (76.59)	12059 (77.25)	11562 (74.06)	11806 (75.63)	12400 (79.44)	< 0.0001
High school or above, n (%)	13614 (22.56)	3755 (25.09)	3649 (24.17)	3322 (21.98)	2888 (19.02)	< 0.0001
Income > 800 RMB/month, n (%)	8878 (14.72)	2385 (15.95)	2410 (15.98)	2090 (13.84)	1993 (13.14)	< 0.0001
Body mass index, kg/m ²	25.03 ± 3.46	24.84 ± 3.44	24.86 ± 3.47	25.01 ± 3.46	25.40 ± 3.46	< 0.0001
Systolic blood pressure, mm Hg	128.36 ± 19.81	126.14 ± 19.20	126.98 ± 19.40	128.71 ± 19.95	131.60 ± 20.24	< 0.0001
Diastolic blood pressure, mm Hg	82.63 ± 11.41	81.42 ± 11.23	81.86 ± 11.16	82.78 ± 11.35	84.44 ± 11.65	< 0.0001
Current smoker, n (%)	20552 (33.81)	5082 (33.28)	4739 (31.10)	4975 (32.67)	5756 (38.25)	< 0.0001
Current alcohol use, n (%)	23413 (38.51)	5665 (37.06)	5429 (35.62)	5816 (38.19)	6503 (43.22)	< 0.0001
Active physical activity, n (%)	55080 (91.46)	13387 (89.74)	13850 (91.92)	13922 (92.31)	13921 (91.85)	< 0.0001
Hypertension, n (%)	6035 (9.66)	1416 (9.07)	1485 (9.51)	1470 (9.42)	1664 (10.66)	< 0.0001
Diabetes Mellitus, n (%)	1489 (2.38)	339 (2.17)	288 (1.85)	337 (2.16)	525 (3.36)	< 0.0001
Dyslipidemia, n (%)	3183 (5.10)	737 (4.72)	833 (5.34)	770 (4.93)	843 (5.40)	0.0166
Antihypertensive agents, n (%)	5185 (8.30)	1209 (7.75)	1273 (8.16)	1282 (8.21)	1421 (9.10)	0.0002
Antidiabetic agents, n (%)	1144 (1.83)	269 (1.72)	222 (1.42)	252 (1.61)	401 (2.57)	< 0.0001

Abbreviations: LDL, low-density lipoprotein; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; TyG, triglyceride glucose.

Characteristics	Overall	Quartiles of changes in TyG index				<i>P</i> value
		Q1 (<-0.31)	Q2 (-0.31-0.05)	Q3 (0.05-0.41)	Q4 (≥ 0.41)	
Lipid-lowering agents, n (%)	465 (0.74)	102 (0.65)	134 (0.86)	108 (0.69)	121 (0.77)	0.1526
Total cholesterol, mmol/L	4.91 ± 1.13	4.90 ± 1.04	4.94 ± 1.02	4.97 ± 1.02	4.84 ± 1.40	< 0.0001
HDL cholesterol, mmol/L	1.56 ± 0.39	1.58 ± 0.40	1.56 ± 0.39	1.55 ± 0.39	1.53 ± 0.40	< 0.0001
LDL cholesterol, mmol/L	2.29 ± 0.89	2.25 ± 0.94	2.28 ± 0.86	2.31 ± 0.87	2.32 ± 0.89	< 0.0001
Hs-CRP,mg/dL	2.29 ± 6.37	2.14 ± 4.96	2.21 ± 5.37	2.23 ± 6.94	2.60 ± 7.79	< 0.0001
Abbreviations: LDL, low-density lipoprotein; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; TyG, triglyceride glucose.						

Association of changes in TyG index with CVD and its subtypes

During a median follow-up of 7.01 years (interquartile range: 6.64–7.31 years), 2,530 (4.05%) incident CVD were identified, of which 2,018 (3.23%) were incident stroke and 545 (0.87%) were incident MI. The incidence of CVD increased substantially with increasing changes in TyG index quartiles, reaching an incidence of 6.73 (95% CI, 6.25–7.24) per 1,000 person-years. The cumulative risk of CVD increased over time by changes in TyG index quartile (Fig. 1A) and remained significant even after adjustment for potential confounding factors (*P* for trend < 0.001), the fully adjusted HR (model 2) was 1.18 (95% CI, 1.06–1.32), 1.26 (95% CI, 1.12–1.42), and 1.42 (95% CI, 1.26–1.60) for Q2, Q3, and Q4 groups versus Q1 group of changes in TyG index (Table 2). Moreover, there was a linear association between changes in TyG index and risk of CVD, per 1 SD increase in changes in TyG was associated with 16% higher risk of CVD (HR, 1.16; 95% CI, 1.11–1.21; Fig. 2A). In the subtype analyses of CVD, similar results were yield for stroke and MI, with HR increased across increasing changes in TyG quartiles (Table 2, Fig. 1B-C, and Fig. 2B-C).

Table 2
HR and 95% CI for the association between changes in TyG index from 2006 to 2010 and cardiovascular diseases and its subtypes

Quartiles of changes in TyG index					
	Q1 (<-0.31)	Q2 (-0.31-0.05)	Q3 (0.05-0.41)	Q4 ($\geq$ 0.41)	<i>P</i> for trend
CVD					
Case, n (%)	585(3.75)	594(3.81)	646(4.14)	705(4.52)	
Incidence rate, per 1000 person-y	5.54(5.11-6.01)	5.65(5.21-6.12)	6.17(5.71-6.66)	6.73(6.25-7.24)	
Model 1	Reference	1.18(1.06-1.32)	1.26(1.12-1.42)	1.42(1.26-1.60)	< 0.0001
Model 2	Reference	1.17(1.04-1.30)	1.24(1.11-1.40)	1.37(1.21-1.54)	< 0.0001
Stroke					
Case, n (%)	465(2.98)	473(3.03)	528(3.38)	552(3.54)	
Incidence rate, per 1000 person-y	4.39(4.01-4.80)	4.48(4.10-4.91)	5.03(4.62-5.47)	5.24(4.82-5.70)	
Model 1	Reference	1.24(1.08-1.41)	1.27(1.11-1.47)	1.44(1.24-1.66)	< 0.0001
Model 2	Reference	1.22(1.07-1.40)	1.26(1.09-1.45)	1.38(1.19-1.60)	< 0.0001
MI					
Case, n (%)	126(0.81)	126(0.81)	128(0.82)	165(1.06)	
Incidence rate, per 1000 person-y	1.18(0.99-1.40)	1.19(1.00-1.41)	1.21(1.02-1.44)	1.55(1.33-1.81)	
Model 1	Reference	1.05(0.82-1.34)	1.22(0.95-1.57)	1.41(1.09-1.82)	0.0050
Model 2	Reference	1.02(0.80-1.30)	1.19(0.93-1.53)	1.36(1.05-1.76)	0.0115
Abbreviations: CI, confidence interval; CVD, cardiovascular disease; MI, myocardial infarction; HR, hazard ratio; TyG index, triglyceride-glucose index.					
Model 1: adjusted for age, sex, and TyG index at baseline.					
Model 2: further adjusted for education, income, smoking status, drinking status, physical activity, body mass index, systolic blood pressure, diastolic blood pressure, a history of hypertension, diabetes mellitus, and dyslipidemia, antidiabetic agents, lipid-lowering agents, antihypertensive agents, high-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and high-sensitivity C-reactive protein at baseline.					

The sensitivity analyses with competing risk model (Fig. 3A), excluding participants with abnormal FBG or TG level at baseline (n = 21,901, Fig. 3B), and excluding the outcome events occurred within the first 2 years of the follow-up period (n = 1,162, Fig. 3C), all generated similar findings with the primary analysis.

Subgroup analyses

Results of subgroup analyses are presented in Table S2. The association of changes in TyG index with the risk of CVD and its subtypes were consistent across difference subgroups, including age (< 60 and ≥ 60 years), sex (women and men), BMI (< 25 and ≥ 25 kg/m²), and FBG (< 5.6, 5.6-7.0, and ≥ 7.0 mmol/L). We did not observe significant interactions between changes in TyG index and stratified variables (*P* for interaction > 0.05 for all).

Incremental predictive value of changes in TyG index

We evaluated whether changes in TyG index would further increase the predictive value of conventional risk (Table 3). The C statistics by the conventional model significantly improve with the addition of change in TyG index (from 0.739 to 0.742, *P* = 0.0097), the discriminatory power and risk reclassification also appeared to be substantially better, with the IDI of 0.09% (95%CI, 0.05–0.13; *P* < 0.0001), and the NRI of 12.58% (95% CI, 8.61–16.56; *P* < 0.0001). Similar results were observed when stroke and MI was the outcome of interest.

Table 3
Reclassification and discrimination statistics for baseline and changes in TyG index

C statistics			IDI		Category-free NRI	
	Estimate (95% CI)	<i>P</i>	Estimate (95% CI), %	<i>P</i>	Estimate (95% CI), %	<i>P</i>
CVD						
Conventional model*	0.739(0.731–0.748)		Reference		Reference	
Conventional model +changes in TyG index	0.742(0.733–0.751)	0.0097	0.09(0.05–0.13)	< 0.0001	12.58(8.61–16.56)	< 0.0001
Stroke						
Conventional model*	0.740(0.730–0.750)		Reference		Reference	
Conventional model +changes in TyG index	0.742(0.732–0.752)	0.0435	0.06(0.02–0.09)	0.0010	10.83(6.40-15.26)	< 0.0001
MI						
Conventional model*	0.749(0.731–0.766)		Reference		Reference	
Conventional model +changes in TyG index	0.752(0.735–0.770)	0.0412	0.03(0.01–0.05)	0.0365	16.69(8.26–25.12)	0.0001
Abbreviations: CVD, cardiovascular disease; IDI, integrated discrimination improvement; MI, myocardial infarction; NRI, net reclassification index; TyG index, triglyceride-glucose index.						
*Conventional model was adjusted for age, sex, TyG index, education, income, smoking status, drinking status, physical activity, body mass index, systolic blood pressure, diastolic blood pressure, a history of hypertension, diabetes mellitus, and dyslipidemia, antidiabetic agents, lipid-lowering agents, antihypertensive agents, high-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and high-sensitivity C-reactive protein at baseline.						

Discussion

In this prospective cohort study, we found that substantial changes in TyG index was significant associated with the risk of CVD. Notably, the risk of CVD increased with elevated TyG index over time.

Similar patterns were observed for stroke and MI. The trend remained robust among multiple sensitivity analyses and the stratified analyses. Furthermore, the addition of changes in TyG index to the baseline risk model including traditional risk factors significantly promoted the ability of risk stratification.

The present analyses showed that participants with elevated TyG index over time had a higher risk of developing CVD relative to their counterparts with decreased TyG index over time. Previous studies, which were generally based on a single TyG index assessment, generated the consistent results regarding the association between baseline TyG index and CVD risk. The Vascular Metabolic CUN cohort with 5,014 subjects found that a higher level of TyG index was significantly associated with an increased risk of developing CVD in Caucasian population, participants in the highest quintile group had 2.32-fold higher risk of CVD than the lowest quintile group.[12] Another retrospective cohort analysis of 6,078 participants aged over 60 years showed the fourth quarter of TyG index was associated with 72% higher risk of CVD events.[13] The Tehran Lipid and Glucose Study with 7,521 Iranians revealed that the significant relationship between the TyG index and risk of CVD/coronary heart disease was more prominent among the younger population.[14] Similarly, data from the National Health Information Database showed that participants in the highest TyG index quartile were at higher risk for stroke and MI, independently of other traditional cardiovascular risk factors.[15]

Of note, the TyG index is calculated based on TG and FBG, both of which vary over time, thus evaluating the TyG index only at baseline was unable to examine the longitudinal association between the dynamic changes in TyG index and CVD risk. Moreover, one single measurement of the TyG index was also subject to potential regression dilution bias and reverse causation issue.[27] To address these knowledge gaps and methodological limitations, the concept of assessing the effect of change in TyG index on clinical outcomes has been proposed. In a rural Chinese cohort study, the author used the difference in TyG index between follow-up and baseline to predict the risk of type 2 diabetes, the results showed that risk of incident diabetes was increased with quartiles of TyG difference in normal-weight people.[28] While the relationship between changes in TyG index and CVD has not been established by previous studies. In line with above-mentioned study, our study found that risk of CVD was increased with quartiles of changes in TyG index, suggesting that participants with a huge increase in TyG index may warrant particular vigilance and should be followed up closely in case of the development of CVD .

Another important finding of our study was that the addition of changes in TyG to the conventional risk model had an incremental effect on the predictive value for CVD. The predictive role of baseline TyG index for CVD has been confirmed by previous studies. Data from the Kaohsiung Medical University Hospital showed that the TyG index was a useful parameter and a stronger predictive factor than hemoglobin A_{1c} for events and may offer an additional prognostic benefit in patients with type 2 diabetes.[16] The Vascular Metabolic CUN cohort showed that the areas under the curve of receiver-operating characteristics curve increased from 0.708 to 0.719 by adding TyG index to the Framingham model.[12] Our findings showed that a longitudinal changes in TyG index predicts a high risk of CVD that is beyond the models including baseline TyG index, highlighting the importance of monitoring longitudinal patterns of changes in TyG index in clinical practice.

The potential mechanism underlying the association of changes in TyG index with development and progression of CVD remains uncertain, several theories have been proposed. First, study have shown that FBG mainly reflects IR from liver, whereas fasting TGs mainly reflects IR from adipose cell.[29] Therefore, it can be concluded that elevated TyG index over time may reflect a severe insulin resistance from two aspects. Insulin resistance can play a critical role in the formation of atherosclerotic plaques by leading to chronic inflammation, oxidative stress, endothelium dysfunction, and the facilitated the formation of foam cells, and by changing the gene expression pattern associated with estrogen receptor, as reported in animal models.[30–33] Second, in our study, participants with substantial changes in TyG index tended to combine with more severe and complex clinical conditions in terms of BMI, blood pressure, lipid profiles, hypertension, diabetes, and dyslipidemia, which were a cluster of risk factors of CVD.[34, 35] Changes in TyG index could modify and influence the role of cardiovascular risk factors and contribute to the progression of CVD. Third, it has been demonstrated that the TyG index was related to artery stiffness evaluated by pulse wave velocity, ankle–brachial index, and carotid intima–media thickness through affecting platelet adhesion, activation and aggregation[36, 37], elevating TyG index over time may accelerate the development of artery stiffness thus may lead to the development of CVD.

The strengths of the study include its prospective design, large community-based sample, long follow-up period, and consider the effect of changes in TyG index on CVD and its subtypes in the general population. The results should be interpreted in the context of some limitations. First, due to the shortage of records insulin, we could not compare the predictive value of TyG index with homeostasis model assessment insulin resistance (HOMA-IR) and the hyperinsulinaemic euglycaemic clamp test for occurrence of CVD. Second, the distribution of gender is unbalanced due to a large proportion of participants were coal miners, however, the association of changes in TyG index and CVD and subtypes were statistically robust, as the results did not show significant interaction when stratified by gender. Third, owing to the observational nature of the study, we could not establish a causal association between TyG index and the risk of CVD and our findings need to be confirmed in future studies. Finally, although potential cardiac risk factor were adjusted for, we still cannot exclude the possibility of residual or unmeasured confounding given the observational study design of the present analysis.

Conclusions

In conclusion, we found that changes in TyG index was an independent predictor of CVD and its subtypes. Elevated TyG index over time was associated with higher risk of CVD, stroke and MI. Our findings emphasize the importance of monitoring the longitudinal changes in TyG index for identifying individuals at high risk of development CVD.

Abbreviations

BMI=body mass index; CI=confidence interval; CVD=cardiovascular disease; DBP=diastolic blood pressure; FBG=fasting blood glucose; HDL-C=high-density lipoprotein cholesterol; HOMA-IR=homeostasis model assessment insulin resistance; HR=hazard ratio; hs-CRP=high-sensitivity C-reactive protein;

IDI=integrated discrimination improvement; LDL-C=low-density lipoprotein cholesterol; NRI=net reclassification index; SBP=systolic blood pressure; SD=standard deviation; TG=triglyceride; TyG=triglyceride-glucose

Declarations

Ethics approval and consent to participate

The study was performed according to the guidelines of the Helsinki Declaration and was approved by the Ethics Committee of Kailuan General Hospital (approval number: 2006-05) and Beijing Tiantan Hospital (approval number: 2010-014-01). All participants were agreed to take part in the study and provided informed written consent.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request

Competing interests

These authors declare that they have no conflicts of interests.

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Author Contributions

S.W. and Y.W. contributed to the conception and design of the study; A.W. and X.T. contributed to manuscript drafting; A.W., X.T., Y.Z. and S.C. contributed to the statistics analysis; S.C. and X.M. contributed to the acquisition of data; S.W., Y.W. and A.W. contributed to critical revisions of the manuscript. All authors read and approved the final manuscript.

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Figures

Figure 1

Kaplan-Meier estimation of (A) cardiovascular diseases (B) stroke (C) myocardial infarction by quartiles of changes in TyG index. Abbreviation: TyG, triglyceride-glucose

Figure 2

Multivariable-adjusted hazard ratios for (A) cardiovascular diseases (B) stroke (C) myocardial infarction based on restricted cubic splines with 5 knots at 5th, 25th, 50th, 75th, and 95th percentiles of changes in TyG index. Abbreviation: HR, hazard ratio; SD, standard deviation; TyG, triglyceride-glucose Red line represent references for hazard ratios, and red area represent 95% confidence interval. Model was adjusted for age, sex, TyG index, education, income, smoking status, drinking status, physical activity, body mass index, systolic blood pressure, diastolic blood pressure, a history of hypertension, diabetes mellitus, and dyslipidemia, antidiabetic agents, lipid-lowering agents, antihypertensive agents, high-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and high-sensitivity C-reactive protein at baseline.

Figure 3

Sensitivity analyses for the association of changes in TyG index from 2006 to 2010 with cardiovascular disease and its subtypes Abbreviation: CVD, cardiovascular disease; MI, myocardial infarction; TyG index, triglyceride-glucose index. Model was adjusted for age, sex, TyG index, education, income, smoking status, drinking status, physical activity, body mass index, systolic blood pressure, diastolic blood pressure, a history of hypertension, diabetes mellitus, and dyslipidemia, antidiabetic agents, lipid-lowering agents, antihypertensive agents, high-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and high-sensitivity C-reactive protein at baseline. A. Taking non-CVD related death as competing risk event rather than censoring. B. Restricted analysis was excluded those with abnormal FBG (≥ 7.0 mmol/L) or abnormal TG level (≥ 1.7 mmol/L) at baseline (n=21,901). C. Excluded person time and stroke events from the first 2 years of follow-up (n=1162).

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