

Triglyceride-Glucose Index Associated With the Risk of Cardiovascular Disease: the Kailuan Study

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Abstract

Purpose: Triglyceride-glucose index (TyG) index, as a marker of insulin resistance, have been associated with risk of cardiovascular disease (CVD) in older adults. Nevertheless, it is unclear to whether TyG index affects risk of CVD and the subtypes of CVD in general Chinese population.

Methods: A total of 96541 participants who met the criteria were included from the Kailuan Study. The TyG index was calculated as $\ln(\text{fasting triglyceride [mg/dL]} \times \text{fasting glucose [mg/dL]}/2)$. The study participants were divided into 4 groups (Q1, Q2, Q3 and Q4) by quartiles of the TyG index. Incident of CVD events (myocardial infarction and stroke) during 2006-2017 were confirmed by review of medical records. The Cox proportional hazard regression models were used to assess the association TyG index with the risk of CVD and the subtypes of CVD by calculating the hazard ratios (HR) and 95% confidence interval (CI).

Results: During a median 10.33 years of follow-up, we documented 6421 CVD events including 1493 myocardial infarction events and 5083 stroke events. Multivariate Cox regression analysis showed that compared with the participants in Q1 group, HR (95% CI) for CVD events were for Q2 group 1.12 (95%, 1.03-1.21), Q3 groups 1.28 (95%, 1.18-1.38), and Q4 groups 1.34 (95%, 1.23-1.45). We conducted time-dependent TyG index found compared with Q1 group, HR (95% CI) for CVD events were for Q2 group 1.09(95%, 1.02-1.18), Q3 groups 1.17(95%, 1.09-1.27), and Q4 groups 1.20 (95%, 1.11-1.30). We found similar results in myocardial infarction and stroke.

Conclusions: The TyG index is an independent risk factor for CVD. The TyG index may be useful identifying individuals at high risk of developing CVD at an early stage, it can contribution to prevent and control of CVD.

Introduction

Cardiovascular disease (CVD) is a leading cause of population death worldwide from the Global Burden of Disease Study of 2017, with 17.70 million people died from CVD, accounting for 40% of all deaths worldwide [1]. The China Cardiovascular Diseases Report 2018 shows that about 290 million patients suffer from CVD and the prevalence of CVD in China is continuously rising. And the disease burden of family and sociality is increasing [2]. The interventions and control for traditional risk factors of hypertension, smoking makes the prevention and control of CVD achieve initial results. However, the prevalence of CVD will continuously rise due to the emerging epidemic of obesity and diabetes and some uncovered factors.

Insulin resistance (IR) has been extensively demonstrated to be a significant risk factor for emergence and development of CVD because it leads to vascular damage [3]. The triglyceride-glucose (TyG) index, which was calculated as $\ln(\text{fasting triglyceride [mg/dL]} \times \text{fasting glucose [mg/dL]}/2)$, has been a reliable surrogate marker of IR [4-6]. Zhao et al. has found that the TyG index was significantly associated with arterial stiffness and microvascular damage [7,8]. Irace et al. found that that the TyG index was

associated with carotid atherosclerosis [9]. VMCUN cohort study found greater predictive value of TyG index for CVD [10]. Nevertheless, the relationship of TyG index with the risk of new-onset CVD still exist the shortage of the large cohort study in Chinese general population. Therefore, we aim to investigate the associations between TyG index and the risk of CVD in the Kailuan Study.

Methods

Study population

The Kailuan study is a large, community-based and prospective cohort study. The detailed design of the Kailuan study have been described previously [11]. Since 2006, we performed examinations in 2-year intervals up (have completed 6 times) including questionnaire assessments, physical examination and laboratory test. In this study, we included 101510 participants who participated in the survey in 2006. We excluded those with missing data of TG and FBG levels (n=1305), those with history of cancer (n=377), those with a history of CVD (n=3263), and those with BMI > 45kg/m² (n=24). Finally, 96541 participants were analyzed. This study followed the Declaration of Helsinki and was approved by the Ethics Committee of the Kailuan Medical Group. All participants signed an informed consent.

Date collection and definitions

Information on demographic and clinical characteristics (age, sex, lifestyle and past medical history, etc.) were collected using a self-reported questionnaire, as detailed elsewhere [12]. Education level was classified as primary school or below, middle school, and high school or above. Smoking and drinking status were classified as never, former and current. Active physical activity was defined as “≥4 times per week and 20 min at time”. Body mass index (BMI) was calculated as the weigh (kg)/height² (m²).

Elbow venous blood samples of 5mL were collected into an anticoagulant tube containing EDTA between 7:00-9:00 am after overnight fasting for at least 8h, and centrifuged at 3000×g for 10min to collect serum. The supernatant was measured within 4 hours. All biochemical measurement including total cholesterol (TC), TG, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), high-sensitive C-reactive protein (Hs-CRP), FBG, and Uric acid (UA), and etc. was measured on the Hitachi 747 auto-analyzer (Hitachi, Tokyo, Japan).

Hypertension was defined as SBP≥140mmHg or DBP≥90mmHg, a self-reported history of hypertension, or any use of antihypertensive medication. Diabetes was defined as FBG≥7.0mmol/L, a self-reported history of diabetes, or use of antidiabetic medication. Dyslipidemia was defined as TC≥5.17mmol/L or TG≥ 1.69mmol/L or LDL-C≥ 3.62mmol/L or HDL-C≤ 1.04 mmol/L, any self-reported history of dyslipidemia, or use of lipid-lowering drugs.

Calculation of TyG index

TyG index = $\ln [TG (mg/dL) \times FBG (mg/dL) / 2]$ [13]. Since 2006, TG and FBG were measured every two years. Baseline TyG index was calculated by TG and FBG value from first health examination. Since TyG index changed over time, we entered TyG index as a time-dependent explanatory variable. The TyG index come from all using available TyG index measurement from baseline to the year before CVD occurred or to the end of follow-up. In a similar manner, antidiabetic medication and other covariates (such as BMI) that changed over time were entered into the model as time-dependent covariates.

Definition of CVD and follow-up

The study participants were followed-up from 2006 to the date of CVD events [including myocardial infarction (MI) and stroke], or death, or up to 2017 as the end of the follow-up period, whichever came first. The stroke events included ischemic stroke, hemorrhagic stroke. The definition of myocardial infarction and stroke was according to the World Health Organization criteria [14,15]. Assessment of incident of CVD events and death has been previously described in detailed [16]. For CVD events identified by a panel of 3 experienced physicians reviewed the medical records and adjudicated the cases annually. Information on death was collected from death certificates from state vital statistics offices.

Statistical Analysis

Continuous, normally distributed variables are presented as the mean \pm standard deviation (SD) and comparisons between groups were performed using one-way ANOVA. The measurement data with abnormal distribution are presented as median (Q25, Q75) and compared with Kruskal-Wallis rank sum test among groups. The count data are expressed by number and percentage (%), and the comparisons between groups were conducted by the chi-square test.

Restricted cubic splines were performed to examine the nonlinear relationship between TyG index and CVD events with 4 knots (at the 5th, 25th, 75th and 95th percentiles) [17]. The study participants were divided into 4 groups (Q1, Q2, Q3 and Q4) by TyG index quartiles and the Q1 group served as control.

The Cox proportional hazard regression model and time-dependent Cox proportional hazard regression analysis were used to assess the association TyG index with the risk of CVD and the subtypes of CVD by calculating the hazard ratios (HR) and 95% confidence interval (CI). A Cause-specific hazard function (CS) model in competing risk model was used to assess the association TyG index with the risk of CVD [18]. Model 1 was adjusted age and sex. Model 2 was adjusted as in Model 1 plus current smoking status, current drinking status, physical activity, education, BMI, hypertension, diabetes, HDL-C, LDL-C, hs-CRP, lipid-lowering medication, antidiabetic medication, and antihypertensive medication. We conducted subgroup analyses on the basis of diabetes mellitus to analyze the association between TyG index and CVD events. All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). A two-sided $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics

The population included 96541 participants in the current study. Among them, the mean age of the study participants was 51.19 ± 12.57 years, and 76858 (79.61%) were men. There is increasing trend of the indicators except for the high school or above from Q1 to Q4 groups. Baseline characteristics of participants according to the quartile are presented in Table 1.

Associations between the quartiles of TyG index with the risk of CVD

After a mean follow-up of 10.33 years, we observed 6421 CVD events (MI events: 1493, Stroke:5083). The incidence for CVD events per 1000 person-years was an increasing trend from Q1 to Q4 groups and highest in the Q4 group (8.66/1000 person-years) (Table 2). After adjustment for confounding factors in the model 2, the HRs (95%CI) for CVD events were 1.12(1.03-1.21) for Q2 group, 1.28(1.18-1.38) for Q3 group, 1.34(1.23-1.45) for Q4 group (Table 2). We found similar results in MI, stroke and ischemic stroke incidence and a non-significantly increased risk of hemorrhagic stroke (Table 2). 7414 competing events (non-CVD deaths) occurred among the study participants during the follow-up. The result of the Cox model is similar with the competing risk model (Table 2). Multivariable adjusted spline regression model showed a nonlinear relationship between TyG index and the risk of CVD (Figure 1).

Associations between the quartiles of TyG index and the risk of CVD with time-dependent variables

Since many individuals having Q1/Q2 groups at baseline might have moved to Q3/Q4 groups during follow-up, we entered the quartiles of TyG index as a time-dependent Cox regression analysis, in which at each point in time, the last available TyG index was considered (Table 3). In a similar way, lipid-lowering medication and other covariates changed over time were entered into model as a time-dependent covariate. In the time-dependent Cox regression analysis, the HRs (95%CI) for CVD events were 1.09(1.02-1.18) for Q2 group, 1.18(1.09-1.27) for Q3 group, 1.20 (1.11-1.30) for Q4 group (Table 3). We found similar results in MI, stroke and ischemic stroke and a non-significantly increased risk of hemorrhagic stroke (Table 3).

Subgroup analysis

In the subgroup analysis, Cox regression models were recalculated in participants with and without diabetes mellitus (Supplement Table 1). Higher quartiles of TyG index were associated with an increased risk of CVD, MI, stroke, ischemic stroke in participants without diabetes mellitus. The highest quartile of TyG index were associated with an increased risk of CVD and ischemic stroke in participants with diabetes mellitus. There was no interaction between TyG index and diabetes mellitus status for the risk of outcomes (P for interaction > 0.05).

Cox regression models were recalculated in participants who were younger than 60 years and 60 years or older (Supplement Table 2). Highest quartiles of TyG index were associated with an increased risk of CVD in participants younger than 60 years and older than 60 years. We found similar results in MI and

ischemic stroke. There was no interaction between TyG index and age for the risk of outcomes (P for interaction > 0.05).

Discussion

We found that TyG index were associated with an increased risk of CVD (MI, stroke, and ischemic stroke). Similar results were found for the association of the time-dependent TyG index with CVD. To our knowledge, this is the first large, prospective cohort study to show a high long-term TyG index and short-term TyG index were associated with the increase risk of CVD in general Chinese population.

In a 10.33-year follow-up, we indicated that the TyG index was an independent risk factor of CVD. The risk of incident CVD was increased with increasing TyG index. Traditional Cox regression was identified as the sole events for outcomes and not designed to account for the competing risk of death, they can lead to biased results [19]. The present study, during about 10.33-year follow-up, showed the participants who died could not know whether CVD would occur. CVD events correlated not independently with death, suggesting that competing risk existed. Therefore, competing risk model was used to assess the association TyG index with the risk of CVD. Our results found that the difference between conventional Cox models and competing risk models was small. In other words, the death may not play a role in the association of TyG index with CVD events.

In addition, we indicated that the short-term TyG index changes were an independent predictor of CVD. Since many participants having low quartiles at baseline might have moved to high quartiles during follow-up, we entered TyG index as a time-dependent explanatory variable in the time-dependent Cox regression analysis. And the antidiabetic medication and other covariates (such as BMI) that changed over time were entered into the model as time-dependent covariates. Compared with the lowest level of TyG index (Q1), then Q2, Q3, Q4 of TyG index were found to be associated with 1.09-, 1.08-, and 1.20-fold risks of CVD, respectively. Traditional Cox proportional hazard regression model focused on the long-term effects on outcomes, and based on the exposure information of baseline. However, time-dependent Cox regression analysis focused the short-term effects of time-varying exposures to outcomes, and explored the association between exposure and outcomes using exposure information changes [20]. Therefore, the TyG index represents an independent risk factor for CVD either long or short-term effects.

Compared to previous similar studies, we obtained similar results. In the cohort study including 6078 Chinese older adults (age 60 years or older), Li et al found that Q3, Q4 of TyG index were found to be associated with 1.33- and 1.72-fold risks of CVD compared with the lowest level of TyG index [21]. The study population comprised older adults aged 60 or over with a higher CVD risk, could exist the risk of selection bias. Hence, we need to cover different ages (youth, middle age and old age) to demonstrated. We found that TyG index was associated with the increased risk of CVD in individuals younger than 60 years and 60 years or older. And the risk of CVD was higher in individuals younger than 60 years than those 60 years or older. The prevalence of CVD for youth and middle age was increasing year on year from China Cardiovascular Diseases Report 2018. A study found that the association between type 2

diabetes and the relative risks of CVD were more evident in younger-onset type 2 diabetes [22]. Therefore, TyG index will be measured as a significant measure of CVD risk assessments. And the young could identify individuals at high risk of developing CVD by TyG index, intervention comprising lifestyle and medication may contribute to prevent CVD.

The finding from the present study showed that the TyG index is an independent risk factor for CVD, we found that the association between TyG index and MI or stroke is different. This study found that the influence of TyG index on the MI was higher than that on stroke. We found that increasing risk of stroke was association with ischemic but not hemorrhagic stroke. This is because insulin resistance is stronger associated with endothelial dysfunction [23,24]. The endothelial dysfunction contributes to the onset of disease such as atherosclerosis and ischemic stroke through insulin resistance [25]. Insulin resistance in the heart may effect energy balance and metabolism during vessel endothelial damage that can lead to lipotoxicity [26].

As living standards improve and lifestyle, the prevalence of diabetes and dyslipidemia is gradually increased. The prevalence of dyslipidemia has increased from 18.6% in 2002 year to 40.4% in 2012 year, and the prevalence of diabetes has increased from 4.5% in 2002 year to 10.4% in 2012 year. The status which glucose and lipid metabolism is abnormal and prevalence increase is significant. The control rate in dysglycemia and dyslipidemia in China is lower than in western developed countries. The prevention and treatment of dyslipidemia is more backward, the prevention and control of CVD is not optimistic.

The shortcomings of this study may have the following points. Firstly, we attempted to introduce as many potential confounders as possible into the analysis, but factors such as environmental varying and genetic factors were not collected due to the study design. Secondly, the lifestyle and medications data were collected based on self-reported, which might lead to recall biases. Finally, due to unable to assess insulin resistance (HOMA), we could not compare the role of the TyG index and HOMA-IR in onset of CVD. The predictive effect of the TyG index and HOMA index on CVD need to be further compared in future.

The findings from the present show that the TyG index is an independent risk factor for CVD in the study with up to 10.33 years follow-up. When compared to different parameters including insulin resistance, the clinical application of the TyG index is suitable for real-life work due to be easy to measure and calculate. Hence, the TyG index may be useful identifying individuals at high risk of developing CVD at an early stage, intervention comprising lifestyle and medication in early life may contribute to prevent and control of CVD.

Declarations

Funding: None

Conflicts of interest/Competing interests: None

Availability of data and material: De-identified data are available to researchers upon request by contacting with the corresponding author.

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Ethics approval: This study followed the Declaration of Helsinki and was approved by the Ethics Committee of the Kailuan Medical Group.

Consent of participate: All participants signed an informed consent.

Data Availability

De-identified data are available to researchers upon request by contacting with the corresponding author.

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Tables

Due to technical limitations, table 1-3 is only available as a download in the Supplemental Files section.

Figures

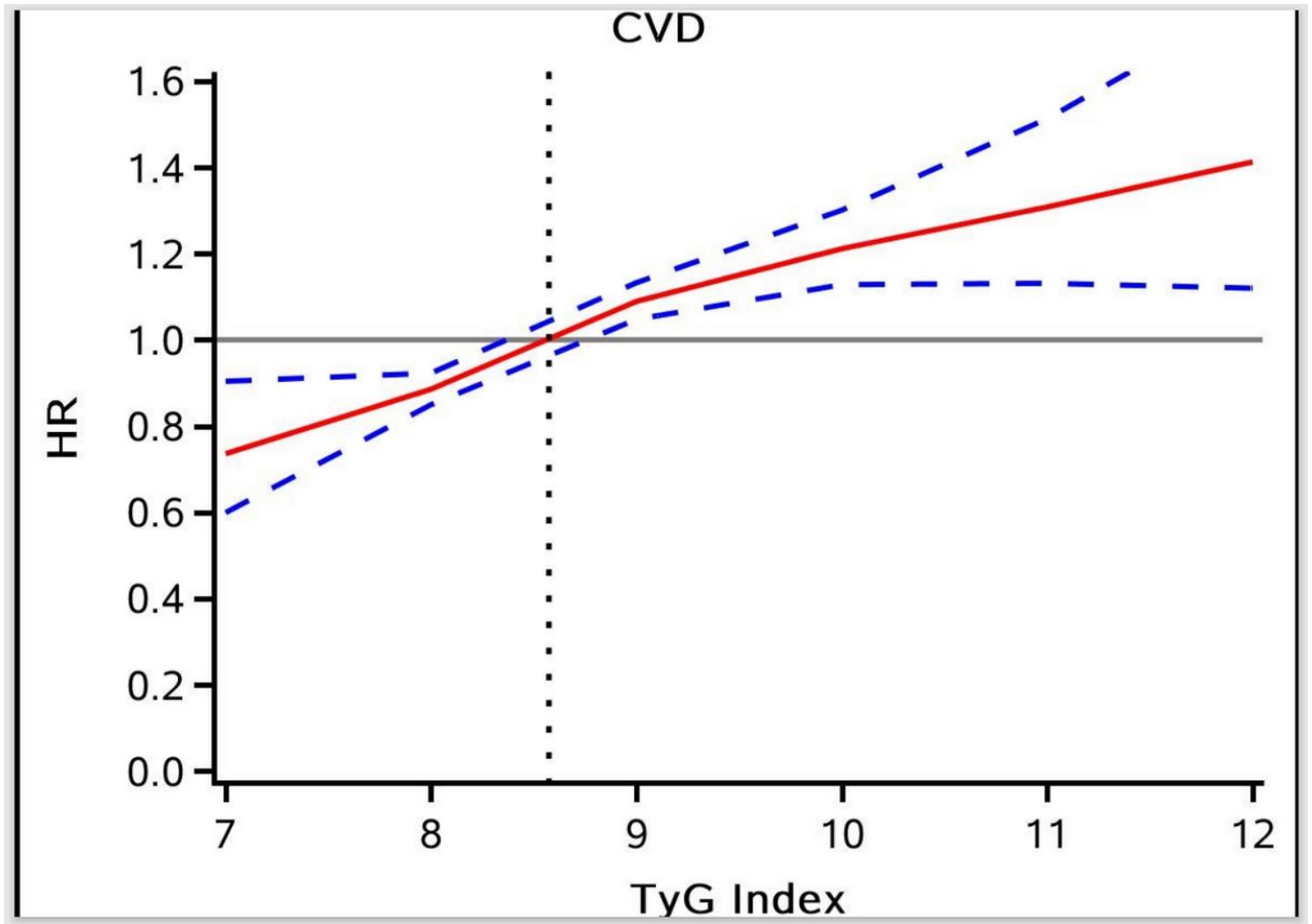


Figure 1

Restricted cubic splines curve

Supplementary Files

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