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Association of long-term triglyceride-glucose index patterns with the incidence of chronic kidney disease among non-diabetic population: evidence from a functional community cohort

Ning Chen¹, Lin-Lin Ma¹, Yu Zhang¹, Xi Chu², Jing Dong² and Yu-Xiang Yan^{1,3*}

Abstract

Background The triglyceride-glucose (TyG) index is a reliable surrogate marker of insulin resistance and previous studies have confirmed the association of TyG index with incident chronic kidney disease (CKD). However, the impact of longitudinal patterns of TyG index on CKD risk among non-diabetic population is still unknown. Therefore, this study aimed to investigate the association of longitudinal patterns of TyG index with incident CKD among non-diabetic population.

Methods A total of 5484 non-diabetic participants who underwent one health examination per year from 2015 to 2017 were included in this prospective study. TyG index variability and cumulative TyG index were calculated to assess the longitudinal patterns of TyG index. Cox proportional hazard models were performed to estimate the association of TyG index variability or cumulative TyG index with incident CKD.

Results During a median of 3.82 years follow-up, 879 participants developed CKD. Compared with participants in the lowest quartile, the hazard ratio (HR) and 95% confidence interval (CI) of incident CKD were 1.772 (95% CI: 1.453, 2.162) for the highest TyG index variability quartile and 2.091 (95% CI: 1.646, 2.655) for the highest cumulative TyG index quartile in the fully adjusted models. The best discrimination and reclassification improvement were observed after adding baseline TyG, TyG index variability and cumulative TyG index to the clinical risk model for CKD.

Conclusions Both TyG index variability and cumulative TyG index can independently predict incident CKD among non-diabetic population. Monitoring longitudinal patterns of TyG index may assist with prediction and prevention of incident CKD.

Keywords Triglyceride-glucose index, Chronic kidney disease, Variability, Cumulative exposure, Cohort study

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Background

Chronic kidney disease (CKD) has received increased attention as a leading public health problem in the past decades [1]. According to Global Burden of Disease (GBD), CKD was ranked as the 12th leading cause of death among 133 diseases [2]. Besides, renal failure, mortality and cardiovascular events, are all strongly affected by kidney involvement [3, 4]. Thus, it is essential to reduce the incidence of CKD and the burden caused by poor prognosis through early diagnosis and intervention.

Insulin resistance (IR) is a state in which physiologic concentrations of insulin produce a subnormal biologic response [5]. Many studies showed that IR played a critical role in the occurrence and development of CKD [6, 7]. The hyperinsulinemic-euglycemic clamp test is the golden-standard way of assessing IR but as this method is time-consuming and laborious, it is not suitable for routine large-scale clinical investigations [8]. Currently, triglyceride glucose (TyG) index, which was calculated using fasting triglyceride (TG) and fasting blood glucose (FBG), was regarded to be a simple and reliable surrogate index for IR [9, 10]. Recent studies have confirmed the positive association between TyG index and the incidence of CKD [7, 11, 12]. However, TG and FBG levels can be affected by a variety of factors such as air pollution, diet and anxiety [13–15], which in turn leads to fluctuations and changes in the TyG index over time. Therefore, compared to a single measurement, multiple repeated measurements of TyG index could provide a more accurate representation of long-term TyG index patterns over time and may be more significantly associated with adverse outcomes. Some studies have examined repeated measurements of TyG and found that longitudinal TyG index, both in terms of visit-to-visit variability and cumulative exposure, could significantly increase the risk of adverse outcomes [16, 17]. However, as for CKD, most studies focused on a single measurement and few studies have evaluated the impact of longitudinal TyG index on the risk of CKD. Besides, few studies focused on general non-diabetic population.

Considering the different effects of metabolic risk factors in different population and adverse lifestyle, environmental and psychological factors in the diabetic population could contribute to the increased vulnerability to incident CKD and thus have an impact on our results, this study assessed the association of TyG index variability or cumulative TyG index with the incidence of CKD among non-diabetic population and further determined whether these two indices have synergy on incident CKD.

Methods

Study design and participants

The present study was performed based on a prospective cohort design and the aim was to evaluate the association of TyG index variability or cumulative TyG index with the incidence of CKD among non-diabetic population. Participants who underwent annual health examination from 2015 to 2017 (baseline and index year) were included and long-term TyG index patterns from three health examination were calculated as predictors of future CKD. All the participants were annually followed under same identical conditions for the development of CKD until December 31, 2021.

The population data used in this study were obtained from the Beijing Functional Community Cohort, which was initiated in 2010 and 8671 individuals with annual examination were recruited at the Health Management Center of Xuanwu Hospital, Capital Medical University [18]. These participants were from various occupations in Xicheng District, Beijing, including medical workers, teaching staff, government workers, workers, and service industries, representing most of the occupational population in Beijing. This cohort excluded participants with a history of medication for elevated blood glucose and dyslipidaemia. Those with acute inflammatory disease, hepatic or renal failure, heart failure, autoimmune disease or cancer were also excluded. The study protocol was approved by the ethics committee of Capital Medical University and Xuanwu Hospital, and it was conducted according to the principles of the Declaration of Helsinki. All study participants were informed at enrollment.

In this analysis, as the collection of information on the cohort population was more limited prior to 2015, we included participants who underwent one health examination per year between January 2015 and December 2017. Of 6759 participants, we excluded those with missing data on FBG or lipid in 2015, 2016 or 2017 wave ($n=286$) and those who were treated with antidiabetic or lipid-lowering agents ($n=371$). We further excluded those with a history of type 2 diabetes (T2D) or CKD in 2017. Finally, 5484 participants were included in our analysis and were annually followed under same identical conditions for the development of CKD until December 31, 2021. Fig. S1 in Additional file 1 showed the flow chart of this prospective cohort study and Table S1 in Additional file 1 presented the baseline characteristics of participants included and excluded from this study.

Clinical measurements

Venous blood samples were collected between 7:30 and 8:30 am after an overnight fast. In a calm state, all samples were immediately centrifuged for laboratory measurements. Low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), TG,

alanine aminotransferase (ALT), aspartate aminotransferase (AST), Urea, creatinine (Cr) and uric acid (UA) were measured using standard laboratory methods (Hitachi Autoanalyzer 7060; Hitachi, Tokyo, Japan). FBG was determined by the glucose oxidase method. Hemoglobin A1c (HbA1c) levels were measured by Ion-exchange chromatography. T2D was defined as FBG ≥ 126 mg/dL or HbA1c $\geq 6.5\%$ or self-reported history of T2D.

Calculation of TyG index, TyG index variability and cumulative TyG index

The TyG index was measured $\ln(\text{fasting TG [mg/dL]} \times \text{FPG [mg/dL]}/2)$. TyG index variability was defined as intraindividual variability recorded in the health examinations from 2015 to 2017 and coefficient of variation (CV) was first used to determine the variability of TyG [17, 19]. Standard deviation (SD), average real variability (ARV) and variability independent of the mean (VIM) were also used to determine the variability of TyG in sensitivity analysis and detailed information was presented in Supplementary Materials.

As previous studies described [20, 21], cumulative TyG index was defined as the summation of the average TyG index for each pair of consecutive examinations multiplied by the time between these two consecutive visits, in years: $([\text{TyG index}_{\text{visit } 1} + \text{TyG index}_{\text{visit } 2}]/2 \times \text{time}_{1-2}) + ([\text{TyG index}_{\text{visit } 2} + \text{TyG index}_{\text{visit } 3}]/2 \times \text{time}_{2-3})$.

TyG index_{visit 1}, TyG index_{visit 2}, TyG index_{visit 3} indicate the TyG index at the first, second and third examinations, respectively, and time₁₋₂, time₂₋₃ indicate the participant-specific time intervals between consecutive visits in years.

Definition of outcome

In this study, CKD was defined as estimate glomerular filtration rate (eGFR) < 60 ml/min/1.73 m² or onset of macroalbuminuria (UACR > 300 mg/g) according to Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [22]. Besides, self-reported diagnosis of CKD was also included in the diagnostic criteria for CKD in this study.

eGFR was calculated based on Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [23]. The sex specific formula is as follows:

Women: if Cr ≤ 0.7 mg/dL, $eGFR = 144 * (\text{Cr}/0.7)^{-0.329} * (0.993)^{\text{Age}}$.

if Cr > 0.7 mg/dL, $eGFR = 144 * (\text{Cr}/0.7)^{-1.209} * (0.993)^{\text{Age}}$.

Men: if Cr ≤ 0.9 mg/dL, $eGFR = 141 * (\text{Cr}/0.9)^{-0.411} * (0.993)^{\text{Age}}$.

if Cr > 0.9 mg/dL, $eGFR = 141 * (\text{Cr}/0.9)^{-1.209} * (0.993)^{\text{Age}}$.

Covariates definition

Factors associated with outcomes were considered as covariates. Based on previous studies, covariates in this

study included age, sex, current smoking, current drinking, educational level, physical activity, hypertension, BMI, LDL-C, HDL-C, ALT, AST, Cr, UA, Urea, eGFR and baseline TyG index.

Structured standard questionnaires were used to collect basic information about the study participants, including sex, age, current smoking, current drinking, education level, and physical activity. Current smoking was defined as those who smoked ≥ 1 cigarette per day. Current drinking was defined as the intake of wine/beer/cider/spirits ≥ 1 time per week. Physical activity was defined as walking or cycling ≥ 15 min per day, exercising or physical activity > 2 h per week or lifting or carrying heavy loads at work per day.

Height and weight were measured while the participants wearing light clothing without shoes, and body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m²). Blood pressure (BP) was averaged after three consecutive measurements using a standard mercury sphygmomanometer on the right arm of the study subject after 5 min of sitting still. Hypertension was defined as systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg or self-reported history of hypertension.

Statistical analysis

Categorical variables were presented as number (proportions), continuous variables were presented as mean \pm SD or median (quartiles). Difference between groups were compared using Chi-square test for categorical variables and t test, One-way ANOVA or Kruskal-Wallis rank sum test for continuous variables, as appropriate.

Intraclass correlation coefficient (ICC) was first calculated to assess the stability and consistency of repeated TyG index measurements and if the ICC is greater than 0.75, it indicates a high stability of the repeated measurements. Multivariable-adjusted Cox proportional hazards regression models were used to estimate the association of quartiles of baseline TyG index, TyG index variability or cumulative TyG index with incident CKD and hazard ratios (HR) and 95% confidence intervals (CI) were listed. Model 1 was adjusted for age and sex. Model 2 was further adjusted for current smoking, current drinking, educational level, physical activity, hypertension, BMI, LDL-C, HDL-C, ALT, AST, Cr, UA, Urea and eGFR based on Model (1) Model 3 was further adjusted for baseline TyG index based on Model (2) Time to first CKD event was examined using Kaplan-Meier survival curves and compared using Log-rank test. Restricted cubic spline (RCS) was conducted to exploit the dose-response relationship between TyG index variability or cumulative TyG index and the incidence of CKD. We further divided participants into four groups according to median of

TyG index variability and median of cumulative TyG index and compared the risks of CKD among different groups. The relative excess risk due to interaction (RERI) and the attributable proportion due to interaction (AP) were also calculated to assess the synergy. If 0 is outside the 95% CIs of RERI and AP, there are additive interactions of TyG index variability and cumulative TyG index on the incidence of CKD. C statistics, net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were used to estimate the improvement in discrimination and reclassification after adding baseline TyG index, TyG index variability and cumulative TyG index to the clinical risk model for CKD prediction [24].

Multiple sensitivity analyses were performed to validate the robustness and reliability of our results. First, participants experiencing CKD within one year were excluded to minimize potential reverse causality. Second, to account for the possible changes in TyG index levels before index year, the mean values of TyG from 2015 to 2017 instead of baseline values was adjusted in Model 3

of the Cox proportional-hazards model. Third, considering the possible influence of abnormal TG concentrations on TyG index levels or outcomes, restricted analysis was performed by excluding participants with baseline TG concentrations ≥ 1.7 mmol/L. Besides, SD, VIM and ARV were further used to determine the variability of TyG index and the primary analysis was repeated. The potential effect modification by age, sex, BMI and hypertension categories was also evaluated using stratified analysis and interaction testing using a likelihood ratio test.

Statistical analyses were performed using R software (version: 4.2.1; R Foundation for Statistical Computing) and MedCalc® Statistical Software (version 20.100; MedCalc Software Ltd, Ostend, Belgium; <https://www.medcalc.org>; 2022). The difference was considered statistically significant at two-side significance level of $P < 0.05$.

Results

Finally, 5484 participants were included in this study and Table 1 showed the baseline characteristics of these participants. Among them, the mean age at the baseline

Table 1 Baseline characteristics of study participants

	Total N = 5484	CKD N = 879	Non-CKD N = 4605	P
Age, y	52.49 ± 14.67	55.51 ± 14.75	51.91 ± 14.59	< 0.001
Men, n (%)	2486 (45.33)	434 (49.37)	2052 (44.56)	0.009
Smoking, n (%)	343 (6.25)	57 (6.48)	286 (6.21)	0.759
Drinking, n (%)	673 (12.27)	109 (12.40)	564 (12.25)	0.899
Physical activity, n (%)	3982 (72.61)	642 (73.04)	3340 (72.53)	0.757
Education, n (%)				0.206
Primary school and below	155 (2.83)	17 (1.93)	138 (3.00)	
Junior high school	1442 (26.29)	229 (26.05)	1213 (26.34)	
High school and above	3887 (70.88)	633 (72.01)	3254 (70.66)	
Hypertension, n (%)	1306 (23.81)	266 (30.26)	1040 (22.58)	< 0.001
SBP, mmHg	123 [112, 136]	127 [116, 139]	122 [111, 135]	< 0.001
DBP, mmHg	75 [68, 82]	77 [70, 84]	75 [68, 82]	< 0.001
BMI, kg/m ²	24.22 [22.03, 26.56]	24.83 [22.63, 27.08]	24.11 [21.90, 26.42]	< 0.001
AST, U/L	19 [14, 26]	19 [15, 27]	19 [14, 26]	0.002
ALT, U/L	21 [18, 25]	22 [19, 25]	21 [18, 25]	0.002
TG, mg/dL	114.29 [80.63, 163.25]	128.47 [91.26, 182.07]	111.64 [78.85, 159.48]	< 0.001
LDL-C, mg/dL	112.89 [93.17, 134.25]	115.98 [95.88, 139.18]	112.11 [92.78, 132.99]	0.002
HDL-C, mg/dL	54.90 [46.01, 64.95]	53.35 [44.07, 63.02]	54.90 [46.39, 64.95]	< 0.001
Glu, mg/dL	93.78 [88.38, 100.08]	95.58 [90.00, 102.87]	93.42 [88.02, 99.72]	< 0.001
HbA1c, %	5.3 [5.0, 5.6]	5.4 [5.1, 5.7]	5.3 [5.0, 5.6]	< 0.001
Urea, mmol/L	4.91 [4.15, 5.85]	5.20 [4.31, 6.09]	4.87 [4.13, 5.79]	< 0.001
UA, μmol/L	314 [263, 374]	324 [274, 380]	312 [262, 372]	0.001
Cr, mg/dL	0.72 [0.63, 0.85]	0.75 [0.64, 0.87]	0.72 [0.62, 0.85]	< 0.001
eGFR, ml/min/1.73 m ²	102.23 [93.16, 111.15]	99.22 [90.88, 107.95]	102.88 [93.80, 111.58]	< 0.001
Baseline TyG	8.60 [8.23, 8.97]	8.72 [8.37, 9.11]	8.57 [8.20, 8.93]	< 0.001
Cumulative TyG index	17.05 [16.21, 17.88]	17.41 [16.68, 18.20]	16.97 [16.13, 17.82]	< 0.001
TyG index variability	0.026 [0.016, 0.037]	0.029 [0.019, 0.040]	0.025 [0.016, 0.037]	< 0.001

CKD: chronic kidney disease, SBP: systolic blood pressure, DBP: diastolic blood pressure, BMI: body mass index, TG: triglyceride; AST: aspartate aminotransferase; ALT: alanine aminotransferase; Cr: creatinine; UA: uric acid; Glu: plasma glucose, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, TyG index: triglyceride glucose index

was 52.49 ± 14.67 years and 2486 (45.33%) were men. The median TyG index variability was 0.026 (interquartile range: 0.016–0.037), the median cumulative TyG index was 17.05 (interquartile range: 16.21–17.88). The ICC value was 0.768 (95% CI: 0.759, 0.777) (Table S2 in Additional file 1), which showed the stability of repeated TyG measurements in this study and the importance of utilizing repeated measurements instead of relying solely on single measurement in our study. Table S3 and S4 in Additional file 1 presented baseline characteristics of these participants according to quartiles of TyG index variability and cumulative TyG index. During a median of 3.82 years follow-up, 879 participants developed CKD. Participants who developed CKD were slightly older, current smokers and alcohol drinkers. They also had higher prevalence of hypertension and had higher median BMI, SBP, UA, Glu, TG, baseline TyG index, TyG index variability and cumulative TyG index. Fig. S2 in Additional file 1 showed the incidence of CKD according to quartiles of TyG index variability or cumulative TyG index and participants in higher quartiles of TyG index variability or cumulative TyG index showed significantly higher incidence of CKD ($P < 0.001$).

Table 2 presented the association of baseline TyG index, TyG index variability and cumulative TyG index with incident CKD. In Model 2, the baseline TyG index, TyG index variability and cumulative TyG index were all significantly associated with the incidence of CKD.

Compared with participants in the lowest quartile (Q1), the HRs of incident CKD in the highest baseline TyG quartile, TyG index variability quartile and cumulative TyG index quartile were 1.572 (95% CI: 1.227, 2.015), 1.772 (95% CI: 1.453, 2.162) and 2.091 (95% CI: 1.646, 2.655), respectively. After further adjusted for baseline TyG index, risks of incident CKD of participants in higher quartiles of TyG index variability and cumulative TyG index also significantly increased compared to those in the lowest quartile (P for trend < 0.001). Kaplan-Meier curve showed similar results and participants in higher quartiles of TyG index variability and cumulative TyG index had higher risks of developing CKD ($P < 0.001$) (Fig. 1).

The dose-response impacts on CKD of TyG index variability and cumulative TyG index were showed in Fig. S3 in Additional file 1. Both TyG index variability and cumulative TyG index reported significant dose-response relationships on incident CKD ($P < 0.001$) and nonlinear test were significant (TyG index variability: $P = 0.003$, cumulative TyG index: $P = 0.048$). The estimated HRs of incident CKD increased with higher TyG index variability and cumulative TyG index from the linear spline model ($P < 0.001$).

As Table 3 presented, we further divided participants into four groups according to median of TyG index variability and cumulative TyG index. We found compared to the group with both low TyG index variability and

Table 2 Association of baseline, variability, cumulative of TyG index with the incidence of CKD

	Model 1		Model 2		Model 3	
	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
Baseline TyG index						
Q1	-		-		-	
Q2	1.246 (1.009, 1.538)	0.041	1.172 (0.937, 1.465)	0.164	-	
Q3	1.384 (1.125, 1.702)	0.002	1.303 (1.034, 1.642)	0.025	-	
Q4	1.811 (1.486, 2.206)	< 0.001	1.572 (1.227, 2.015)	< 0.001	-	
<i>P</i> for trend		< 0.001		< 0.001		
TyG index variability						
Q1	-		-		-	
Q2	1.199 (0.976, 1.474)	0.084	1.177 (0.951, 1.456)	0.134	1.179 (0.953, 1.459)	0.129
Q3	1.537 (1.264, 1.869)	< 0.001	1.491 (1.219, 1.822)	< 0.001	1.488 (1.217, 1.819)	< 0.001
Q4	1.757 (1.447, 2.135)	< 0.001	1.772 (1.453, 2.162)	< 0.001	1.714 (1.403, 2.094)	< 0.001
<i>P</i> for trend		< 0.001		< 0.001		< 0.001
Cumulative TyG index						
Q1	-		-		-	
Q2	1.195 (0.953, 1.498)	0.122	1.144 (0.906, 1.445)	0.258	1.138 (0.899, 1.442)	0.282
Q3	1.732 (1.400, 2.142)	< 0.001	1.634 (1.299, 2.056)	< 0.001	1.617 (1.268, 2.061)	< 0.001
Q4	2.206 (1.795, 2.711)	< 0.001	2.091 (1.646, 2.655)	< 0.001	2.049 (1.549, 2.711)	< 0.001
<i>P</i> for trend		< 0.001		< 0.001		< 0.001

CKD: chronic kidney disease, TyG index: triglyceride glucose index

Model 1 was adjusted for age and sex

Model 2 was additionally adjusted for current smoking, current drinking, educational level, physical activity, hypertension, BMI, LDL-C, HDL-C, ALT, AST, Cr, UA, Urea and baseline eGFR

Model 3 was additionally adjusted for baseline TyG index

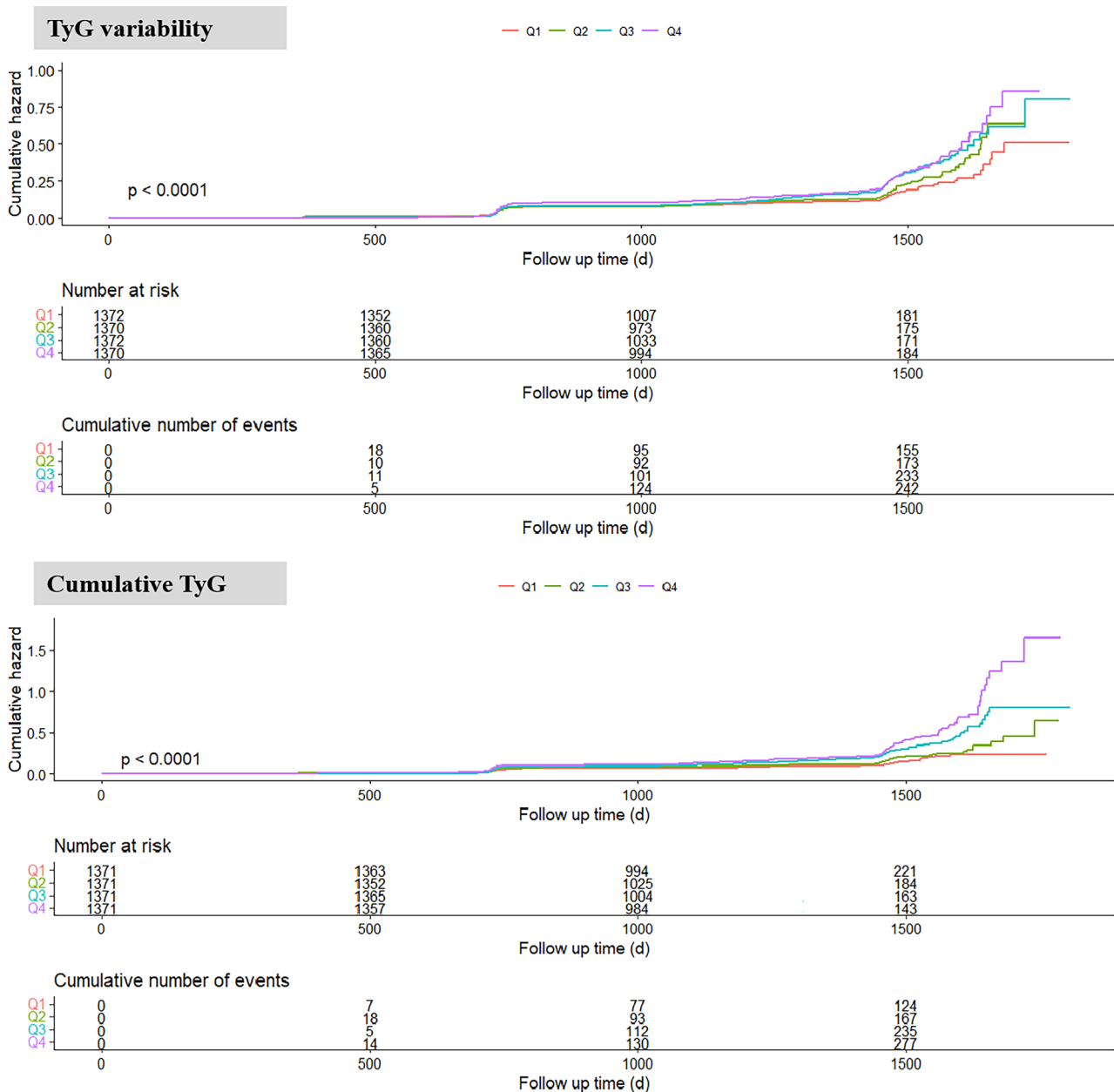


Fig. 1 Kaplan-Meier curves of incidence of chronic kidney disease according to different quartiles of TyG index variability or cumulative TyG index

Table 3 Combined association of TyG index variability and cumulative TyG index with the incidence of CKD

	Low cumulative TyG index HR (95% CI)	High cumulative TyG index HR (95% CI)	RERI (95% CI)	AP (95% CI)
Low TyG index variability	-	1.574 (1.233, 2.010)	0.42 (0.23, 0.60)	0.20 (0.11, 0.29)
High TyG index variability	1.463 (1.162, 1.843)	2.298 (1.820, 2.903)		

CKD: chronic kidney disease, TyG index: triglyceride glucose index, RERI: relative excess risk due to interaction; AP: the attributable proportion due to interaction

cumulative TyG index, those with both high TyG index variability and cumulative TyG index showed highest risk of incident CKD, with HR of 2.298 (95% CI: 1.820, 2.903). Besides, significant additive interactions of TyG index variability and cumulative TyG index on the incidence

of CKD were found (RERI: 0.42, 95% CI: 0.23, 0.60; AP: 0.20, 95% CI: 0.11, 0.29).

As was shown in Table 4, the addition of baseline TyG index to clinical models could increase the C-statistic for CKD prediction although it was not statistical significant.

Table 4 Reclassification and discrimination statistics for predicting CKD by adding baseline TyG index, TyG index variability and cumulative TyG index

	C-statistic	P	NRI	P	IDI	P
Men						
Clinical risk model ^a	0.610 (0.590, 0.629)					
+baseline TyG index	0.610 (0.590, 0.630)	0.690 ^b	-0.130 (-0.236, -0.025)	0.015 ^b	-0.17% (-0.36%, 0.01%)	0.060 ^b
+baseline TyG index and TyG index variability	0.633 (0.614, 0.653)	0.008 ^c	0.240 (0.135, 0.345)	<0.001 ^c	0.85% (0.36%, 1.35%)	<0.001 ^c
+baseline TyG index and cumulative TyG index	0.629 (0.609, 0.648)	0.006 ^c	0.097 (-0.009, 0.202)	0.072 ^c	0.42% (0.02%, 0.81%)	0.039 ^c
+baseline TyG index, TyG index variability and cumulative TyG index	0.649 (0.629, 0.668)	<0.001 ^c	0.309 (0.204, 0.414)	<0.001 ^c	1.50% (0.88%, 2.12%)	<0.001 ^c
		0.007 ^d	0.088 (-0.017, 0.194)	0.101 ^d	0.42% (0.00%, 0.83%)	0.048 ^d
		0.010 ^e	0.243 (0.138, 0.348)	<0.001 ^e	0.95% (0.45%, 1.45%)	<0.001 ^e
Women						
Clinical risk model ^a	0.612 (0.593, 0.630)					
+baseline TyG index	0.615 (0.597, 0.633)	0.318 ^b	0.143 (0.039, 0.246)	0.007 ^b	0.17% (0.02%, 0.32%)	0.027 ^b
+baseline TyG index and TyG index variability	0.629 (0.611, 0.647)	0.019 ^c	0.189 (0.084, 0.294)	<0.001 ^c	0.38% (0.12%, 0.64%)	0.004 ^c
+baseline TyG index and cumulative TyG index	0.623 (0.605, 0.641)	0.107 ^c	0.156 (0.051, 0.261)	0.004 ^c	0.22% (0.02%, 0.42%)	0.035 ^c
+baseline TyG index, TyG index variability and cumulative TyG index	0.636 (0.617, 0.653)	0.004 ^c	0.233 (0.129, 0.338)	<0.001 ^c	0.64% (0.29%, 0.99%)	<0.001 ^c
		0.152 ^d	0.178 (0.073, 0.283)	<0.001 ^d	0.26% (0.04%, 0.48%)	0.023 ^d
		0.026 ^e	0.192 (0.087, 0.297)	<0.001 ^e	0.42% (0.14%, 0.70%)	0.003 ^e

CKD: chronic kidney disease, TyG: triglyceride-glucose, NRI: net reclassification improvement, IDI: integrated discrimination improvement

^a The clinical risk model for incident CKD include age, SBP, DBP, WC, FBG, serum gamma-glutamyl transferase, ALT, AST, TC, HDL-C, LDL-C (only for men), TG, HbA1c, eGFR, BMI, alcohol intake, smoking status, physical activity, past medical history (heart disease, stroke, hypertension, diabetes mellitus (only for women), and hyperlipidemia), and family history (heart disease, stroke, and hypertension). When no information of predictors was available in this cohort, a fixed value for the "missing variables" (i.e., "0" for categorical variables and a fixed number for continuous variables) was used for analysis

^b Compared to clinical risk model

^c Compared to clinical model with baseline TyG index added

^d Compared to clinical model with baseline TyG index and TyG index variability added

^e Compared to clinical model with baseline TyG index and cumulative TyG index added

Further addition of TyG index variability or cumulative TyG index to the clinical model to which baseline TyG index has been added can significantly improve the C-statistics. Significant reclassification improvement were also observed. After adding baseline TyG, TyG index variability and cumulative TyG index to the clinical models for CKD prediction, the best discrimination and reclassification improvement were observed.

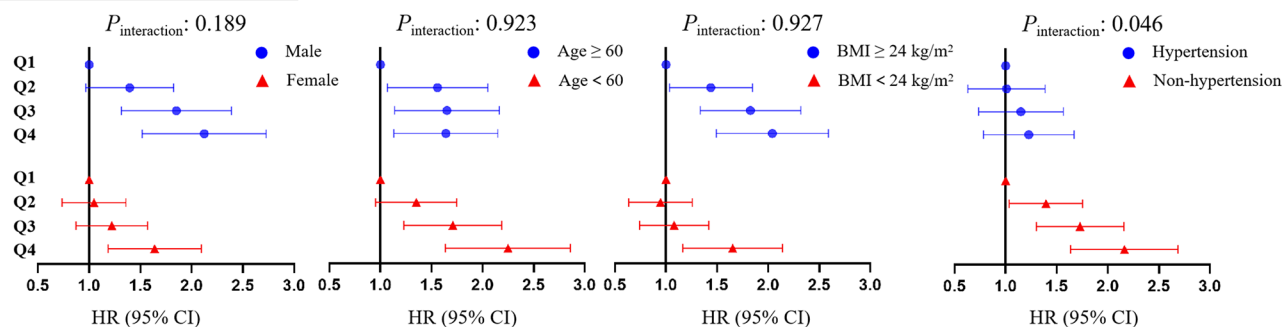
In sensitivity analyses (Table S5 and S6 in Additional file 1), our results all remained consist and participants in higher quartiles of TyG index variability or cumulative TyG index had a higher risk of developing CKD (P for trend<0.001). As Fig. 2 showed, subgroup analyses stratified by sex, age, BMI and hypertension were performed and we did not find significant interaction between quartiles of TyG index variability or cumulative TyG index and age (<60, ≥60), sex (men, women) or BMI (<24, ≥24 kg/m²). Significant interaction was observed

in hypertension and non-hypertension participants (TyG index variability: $P_{\text{interaction}}=0.046$, cumulative TyG index: $P_{\text{interaction}}=0.012$). The significant association of TyG index variability or cumulative TyG index with the incidence of CKD were mainly found in non-hypertension participants.

Discussion

In this study, we selected non-diabetic participants who had one health examination per year from 2015 to 2017 and during a median of 3.82 years follow-up, 16.03% participants developed CKD. We found longitudinal TyG index, both in terms of visit-to-visit variability and cumulative exposure, could significantly increase the risk of incident CKD. Risks of incident CKD of participants in higher quartiles of TyG index variability or cumulative TyG index significantly increased compared to those in the lowest quartile (P for trend<0.001) and sensitivity

TyG index variability



Cumulative TyG index

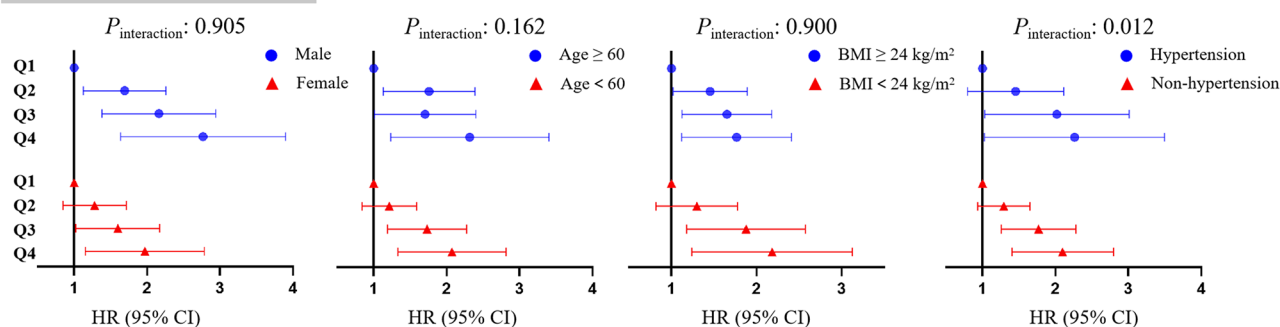


Fig. 2 Subgroup analyses: association of TyG index variability or cumulative TyG index with incident chronic kidney disease

analyses validated the robustness of our results. We further divided participants into four groups according to median of TyG index variability and median of cumulative TyG index and found the group with both high TyG index variability and cumulative TyG index had the highest risk of developing CKD. After adding baseline TyG, TyG index variability and cumulative TyG index to the clinical models for incident CKD prediction, the best discrimination and reclassification improvement were observed.

Several studies have confirmed the association of TyG index with the incidence of CKD, but subgroup analysis according to the status of diabetes showed different results. Among diabetic population, such association remained significant in most relevant studies. However, among non-diabetic population, Li et al. and Shi et al. still found significant association of TyG index and incident CKD [11, 25], while Gao et al., Liu et al. and Zhu et al. did not find that TyG index can increase the risk of CKD among non-diabetic population [12, 26, 27]. The use of hypoglycaemic drugs in diabetic populations can have an effect on FBG levels and further affect TyG index [28]. Besides, adverse lifestyle, environmental and psychological factors in the diabetic population could contribute to the increased vulnerability to incident CKD. Considering the above factors and the inconsistency of the association of TyG index and incident CKD in non-diabetic

populations, this study aimed to assess whether TyG index was the risk factor of incident CKD among non-diabetic population and significant association were found between baseline TyG index and incident CKD.

As researches processed, growing evidence have showed the importance of long-term monitoring of TyG index and the association of long-term TyG index with adverse outcomes has been generally confirmed. A study conducted in China found that high change of TyG index change could significantly increase SBP and DBP ($P < 0.05$) [29]. Another Chinese study showed that the HR for the highest quartile cumulative TyG index group versus the lowest quartile group were 1.59 (95% CI, 1.17–2.16), 1.97 (95% CI, 1.19–3.26), and 1.66 (95% CI, 1.02–2.70) for overall major adverse cardiovascular events, CVD death, and non-fatal myocardial infarctions, respectively [16]. As for incident CKD, no evidence existed. To our knowledge, this is the first study to assess the association of long-term TyG index with incidence of CKD and our study confirmed that both TyG index variability and cumulative TyG index could significantly increase the risk of incident CKD among non-diabetic population and independently of baseline TyG index.

CKD progresses very quickly and can lead to fatal diseases such as kidney failure [30]. However, as the progression process of CKD is not easily detectable, early prediction of this disease is particularly important [31].

Currently, studies have developed different risk predictive models for incident CKD and all showed good performance on CKD prediction [32, 33]. A latest sex-specific predictive model for the development of CKD showed good performance and Harrell's C of the developed prediction models were 0.82 for men and 0.79 for women [24]. Our study extended TyG index variability or cumulative TyG index to this sex-specific model and the highest incremental effect was observed after extending both TyG index variability and cumulative TyG index to the prediction model, which highlighted the importance of long-term monitoring of TyG index. Today, handheld and mobile technologies essentially put continuous monitoring devices in people's pockets, and many health systems record all information electronically [34]. Participants' electronic medical records provide great convenience and feasibility for rapidly integrating data across multiple time points and calculating their long-term variability and cumulative exposure, so as to provide a compelling rationale for using routinely collected electronic health information to assess the long-term impact of risk factors [16].

The mechanisms underlying the relationship between cumulative TyG index and incident CKD remained unclear, but some explanations could be suggested. First, IR was positively associated with elevated levels of inflammatory markers [35] and many studies have confirmed inflammation as an independent risk factor of incident CKD [36]. Besides, releases of proinflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor (TNF)- α could induce endothelial dysfunction, which was also associated with incident CKD [37, 38]. Second is oxidative stress. IR can activate the mitochondrial electron transport chain, induce excessive production of reactive oxidative stress (ROS), and further lead to kidney tissue fibrosis [7]. Third, hyperinsulinemia has been reported to affect renal function by inducing glomerular hyperfiltration, endothelial dysfunction and increased vascular permeability [39]. Thus, a higher cumulative TyG index means a longer period of exposing to high TyG and further more severe damage to kidney function. As for TyG index variability, a study found that changes in IR may have effects on inflammation and endothelial function, which might be risk factors of incident CKD [40]. Changes in TyG index have also been found to be associated with increased BP, which might play an important role in this association [29]. Besides, we hypothesized that the underlying metabolic dysfunction leads to changes in biomarker levels, altered lipid exchange and catabolism may all have impacts on the development of CKD [41]. It is noted that further studies are still needed to elucidate the mechanisms underlying the association of TyG index variability with increased risk of CKD.

The strength of this study included that it was the first prospective study to investigate the association of longitudinal pattern of TyG index and incident CKD among non-diabetic population. Using longitudinally and repeatedly collected TyG data at the individual level before the incidence of CKD, visit-to-visit variability and cumulative exposure were both assessed. Besides, all available confounders were adjusted and different sensitivity analyses were performed. However, our study also has some limitations. First, as this was an observational study, the causal relationship of TyG index variability or cumulative TyG index with incident CKD could not be fully demonstrated. Second, selection of study population based on the number of health examinations could be subject to selection bias. Finally, participants in this study were limited to adults in northern China living in Beijing. Despite these limitations, our study provided some confirmation of the association of long-term TyG index patterns with incident CKD among non-diabetic population and further studies with different ages, regions and ethnic groups are still needed to validate our results.

Conclusions

Overall, during a median of 3.82 years follow-up, we found that TyG index variability and cumulative TyG index can both increase the risk of incident CKD among non-diabetic population. Besides, extending baseline TyG index, TyG index variability and cumulative TyG index to the latest sex-specific risk predictive models for incident CKD showed the highest incremental effect. The current increasing ease and accuracy of collecting electronic health information by health systems provides a feasible and theoretical basis for assessing the long-term impact of TyG index, and we therefore believe that this study has substantial clinical implications and can provide basis for reducing the incidence and subsequent progression of CKD among non-diabetic population.

Abbreviations

CKD	chronic kidney disease
GBD	Global Burden of Disease
IR	insulin resistance
TyG	triglyceride glucose index
TG	triglyceride
FBG	fasting plasma glucose
T2D	type 2 diabetes
LDL-C	low-density lipoprotein cholesterol
HDL-C	high-density lipoprotein cholesterol
AST	aspartate aminotransferase
ALT	alanine aminotransferase
Cr	creatinine
UA	uric acid
HbA1c	Hemoglobin A1c
CV	coefficient of variation
SD	standard deviation
ARV	average real variability
VIM	variability independent of the mean
eGFR	estimate glomerular filtration rate
KDIGO	Kidney Disease:Improving Global Outcomes

CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
BMI	body mass index
BP	blood pressure
SBP	systolic blood pressure
DBP	diastolic blood pressure
ICC	intraclass correlation coefficient
HR	hazard ratio
CI	confidence intervals
RCS	restricted cubic spline
RERI	relative excess risk due to interaction
AP	attributable proportion due to interaction
NRI	net reclassification improvement
IDI	integrated discrimination improvement
IL	interleukin
TNF	tumor necrosis factor
ROS	reactive oxidative stress

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12933-023-02098-7>.

Supplementary Material 1

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Author contributions

NC: Conceptualization, Formal analysis, Writing - original draft. LLM: Formal analysis. YZ: Formal analysis. XC: Data curation. JD: Data curation. YXY: Conceptualization, Supervision, Writing - review & editing. All authors reviewed the manuscript.

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Data availability

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

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committees of Capital Medical University and Xuanwu Hospital. All participants gave informed consent to participate before taking part.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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