Cardiovascular Diabetology

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The association between index-year, average, and variability of the triglyceride-glucose index with health outcomes: more than a decade of follow-up in Tehran lipid and glucose study

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Abstract

Background The association between baseline triglyceride glucose index (TyG index) and incident non-communicable diseases, mainly in Asian populations, has been reported. In the current study, we aimed to evaluate the association between index-year, average, and visit-to-visit variability (VVV) of the TyG index with incident type 2 diabetes mellitus (T2DM), hypertension, cardiovascular disease (CVD), and all-cause mortality among the Iranian population.

Methods The study population included 5220 participants (2195 men) aged ≥ 30 years. TyG index was calculated as Ln (fasting triglycerides (mg/dL) × fasting plasma glucose (mg/dL)/2). Average values of the TyG index and also VVV (assessed by the standard deviation (SD) and variability independent of mean) were derived during the exposure period from 2002 to 2011 (index-year). Multivariable Cox proportional hazards regression models were used to estimate the hazard ratio (HR) and 95% confidence interval (CI) of the TyG index for incident different health outcomes.

Results During more than 6 years of follow-up after the index year, 290, 560, 361, and 280 events of T2DM, hypertension, CVD, and all-cause mortality occurred. 1-SD increase in the TyG index values at the index-year was independently associated with the incident T2DM [HR (95% CI) 2.50 (2.13–2.93)]; the corresponding values for the average of TyG index were 2.37 (2.03–2.76), 1.12 (0.99–1.26, $p_{value} = 0.05$), 1.18 (1.01–1.36), and 1.29 (1.08–1.53) for incident T2DM, hypertension, CVD, and all-cause mortality, respectively. Compared to the first tertile, tertile 3 of VVV of the TyG index was independently associated with incident hypertension [1.33 (1.07–1.64), $P_{trend} < 0.01$]. Likewise, a 1-SD increase in VVV of the TyG index was associated with an 11% excess risk of incident hypertension [1.11 (1.02–

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1.21)]. However, no association was found between the VVV of the TyG index and other outcomes. Moreover, the impact of index-year and average values of the TyG index was more prominent among women regarding incident CVD (*P* for interactions < 0.05).

Conclusion Although the higher TyG index at index-year and its VVV were only associated with the incident T2DM and hypertension, respectively, its average value was capable of capturing the risk for all of the health outcomes.

Keywords Triglyceride-glucose index, Insulin resistance, Visit-to-visit variability, Diabetes, Hypertension, Cardiovascular disease, All-cause mortality

Introduction

The pandemic of type 2 diabetes (T2DM), hypertension, and cardiovascular disease (CVD), serious non-communicable diseases (NCDs) imposes a significant burden on global health, particularly in the Middle East and North Africa (MENA) region [1–3]. According to the International Diabetes Federation (IDF), in 2019, 16.2% of all-cause mortalities that occurred in the MENA region were attributed to diabetes, which was the highest proportion of diabetes-related mortality worldwide [4]. Moreover, the Global Burden of Disease (GBD) has disclosed that from 1990 to 2019, the incidence and mortality of CVD in this region have increased by 133.45% and 78.34%, respectively [5]. During the same period, the prevalence of hypertension and hypertensive heart disease in the MENA region increased by about 7% and 8%, respectively [3, 6]. The majority of CVD's catastrophic burden is driven by five modifiable cardiometabolic risk factors, including diabetes, systolic blood pressure (SBP), body mass index (BMI), low-density lipoprotein cholesterol (LDL-C), and tobacco smoking [7].

Previously, a large number of studies have explored the association between cardiometabolic risk factors and aforementioned health outcomes by snapshot measurements or longitudinal trajectory analysis [8, 9]. Although these studies have provided valuable information, previous common methods would not consider the impact of visit-to-visit variability (VVV) on cardiometabolic risk factors. In recent years, VVV of cardiometabolic risk factors, irrespective of their mean values, has been acknowledged by researchers as a novel risk factor for T2DM, hypertension, CVD, and all-cause mortality [10, 11]. In accordance with this context, standard deviation (SD) has been reported as a reliable statistical variability index [12].

The close relationship between T2DM, hypertension, and CVD has led to the "common soil" hypothesis, which postulated shared genetic and environmental antecedents [13]. Accordingly, numerous studies have pointed to insulin resistance (IR) as one of the most critical potential antecedents [14, 15]. Moreover, some epidemiological and Mendelian randomization studies have advocated the independent association between IR and CVD [16–18]. Hyperinsulinaemic-euglycemic clamp and Homoeostasis model assessment of insulin resistance (HOMA-IR) are the most recommended validated tools of IR evaluation; however, a dramatic gap exists between clinical practice and their utilization due to complexity and costs [19]. Triglyceride-glucose index (TyG index), the logarithmized product of fasting plasma glucose (FPG) and triglycerides (TG), has emerged as an affordable and simple surrogate of IR [20].

In a prospective cohort study including 141,243 participants from 5 continents, the TyG index was significantly associated with mortality and CVD events [21]. While the association between TyG index values and CVD, hypertension, and T2DM has been studied extensively, very few studies have evaluated the association between TyG index variability and mentioned outcomes; principally were carried out on Asian populations [22, 23].

Despite the well-established role of ethnicity and the great burden of aforementioned NCDs, there is a lack of evidence regarding the TyG index in the MENA region [24]. Previously, we have found that in contrast to TG, FPG variability is significantly associated with the risk of CVD [25, 26]. In the current study, we aimed to extend the previous evidence by evaluating the predictive capacity of the TyG index at index-year, average value, and its variability for incident T2DM, hypertension, CVD, and all-cause mortality to the best of our knowledge for the first time in the MENA region.

Method and materials

Study design and sample

This is an observational prospective study using data from the Tehran Lipid and Glucose Study (TLGS), a large-scale community-based study initially designed in 1997 with the primary aim of preventing or postponing the development of NCDs, risk factors, and outcomes. In February 1999, TLGS was started with a cross-sectional study that included 15,005 participants over 3 years of age, residents in distinct-13 of Tehran, who were chosen by the multistage cluster random sampling method (phase I). Subsequently, phase II was prospectively started in 2002, with an additional 3550 participants and 3-year intervals of data collection, which has continued until to date (phase III: 2005–2008, Phase IV: 2008–2011, phase V: 2012–2015, phase VI: 2015–2018, phase VII:

2018–2022). The rationale and methodology of TLGS have been clarified in detail elsewhere [27].

In the current study, 5220 participants aged ≥ 30 years who entered phases II and participated in consecutive phases III and IV of TLGS (exposure period) were initially selected (men = 2195); we considered phase IV as the index-year in our data analysis. After excluding those with missing data of TyG components and confounders (considering overlap features between numbers), 4496 participants remained. Then, in order to evaluate the incidence of T2DM, hypertension, and CVD, 830, 2015, and 616 participants with prevalent mentioned diseases were excluded, respectively (Fig. 1). Ethical approval of this study has been certified by the central institutional review board of the Research Institute of Endocrine Science, Shahid Beheshti University of Medical Science, Tehran, Iran. All participants have signed written consent and outlined principles in the Declaration of Helsinki and similar ethical standards have been respected in this study.

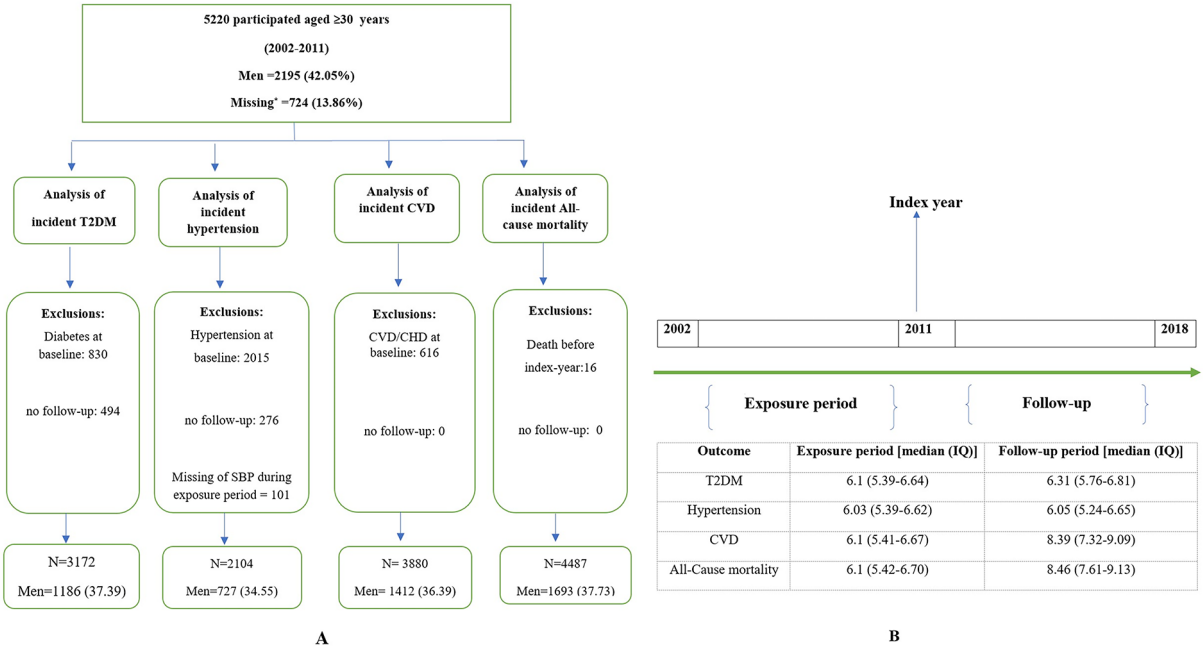
Clinical and laboratory measurements and calculations

Each participant was interviewed individually by a trained interviewer to obtain past medical history and demographic information using pretested questionnaires. Anthropometrical indices were measured as explained previously [27]. BMI was calculated as weight (kg) divided by height squared (m^2). Blood pressure was measured twice with 5-min intervals in a sitting position, after at least 15 min of rest, using a standardized mercury sphygmomanometer (calibrated by the Institute of Standards and Industrial Researches), and the mean values were documented for SBP and diastolic blood pressure (DBP).

After 12–14 h of overnight fasting, venous blood samples were collected between 7:00 A.M.–9:00 A.M. for laboratory measurements; all were analyzed in the TLGS research laboratory on the collection date. FPG and TG were assayed using the enzymatic colorimetric method with glucose oxidase, and glycerol phosphate oxidase, respectively. An oral glucose tolerance test was performed, as explained previously [28]. Estimate Glomerular Filtration Rate (eGFR) was calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [29]. Low-density lipoprotein cholesterol (LDL-C) was calculated using a modified Friedewald formula [30]. All analyses were performed using Pars Azmon kits (Pars Azmon Inc., Tehran, Iran) and Selectra 2 auto-analyzer (Vital Scientific, Spankeren, The Netherlands). Regarding FPG, both inter- and intra-assay coefficient variation (CV) were < 2.3%, and for TG, intra- and inter-assay CVs were 1.6 and 0.6%, respectively [27].

Definition of terms

In our primary analysis for different independent variables of the TyG index, we defined T2DM as FPG ≥ 7 mmol/L (126 mg/dL) or a history of glucose-lowering medication. Specifically for incident T2DM, we also defined T2DM using 2-h post-challenge glucose (2hPG) criteria, with the cut-off point of ≥ 11 mmol/L (200 mg/dL) [31]. Individuals



Outcome	Exposure period [median (IQ)]	Follow-up period [median (IQ)]
T2DM	6.1 (5.39-6.64)	6.31 (5.76-6.81)
Hypertension	6.03 (5.39-6.62)	6.05 (5.24-6.65)
CVD	6.1 (5.41-6.67)	8.39 (7.32-9.09)
All-Cause mortality	6.1 (5.42-6.70)	8.46 (7.61-9.13)

Fig. 1 Flowchart and timeline of the study. **A** Flowchart of study population, **B** timeline of the study. T2DM, type 2 diabetes mellitus; CVD, cardiovascular disease. *Either missing data regarding triglyceride/fasting plasma glucose during the exposure period or covariates at the index-year

with missing data on 2hPG who simultaneously had fasting glucose < 5 mmol/L (90 mg/dL) were considered T2DM-free [32].

Following the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7), hypertension was defined as SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, or any history of anti-hypertensive medication. Prevalent CVD was defined as any history of percutaneous coronary intervention, coronary artery bypass graft, acute coronary syndrome leading to coronary care unit admission, angiographic-proven coronary artery disease, or stroke events. History of MI, stroke, or SCD in male and female first-degree relatives aged < 55 and < 65 years, respectively, were considered as a family history of premature CVD (FH-CVD). Diagnosed DM in first-degree relatives was defined as a family history of DM (FH-DM). Obesity was defined as BMI ≥ 30 kg/m^2. The habit of smoking any tobacco product at the time of examination, either daily or occasionally, was considered a current smoker. Educational level was categorized into three levels: < 6 years of education, 6–12 years of education, and > 12 years of education. Marital status was categorized as married and single.

Main exposures

TyG index is calculated as Ln (fasting TG (mg/dL) × FPG (mg/dL)/2) [20, 33]. Besides the TyG index at the index-year as one of the exposures, we also calculated the average of the TyG index using the mean of three consecutive assessments of the TyG index during the exposure period. Moreover, the VVV of the TyG index was evaluated by the SD method [12]. We also assessed VVV, applying variability independent of mean (VIM) as another independent variable for incident health outcomes. Accordingly, it was calculated as $100 \times SD/mean^{\beta}$ (β is the regression coefficient of the natural logarithm of the SD on the mean (Ln SD/Ln mean) [34].

CVD outcome and mortality events

Collecting data and the manner of determining outcomes in TLGS have been explained in detail previously [27]. In summary, annual telephone follow-ups were performed by trained nurses to record any new medical event. Afterward, additional information about events of interest was provided by trained physicians through home visits, reviewing medical records, and hospital documents. Ultimately, Outcomes were determined at the discretion of the outcome committee (incorporating an endocrinologist, cardiologist, epidemiologist, internist, pathologist, and any other experts if needed), based on the collected information and a particular code was assigned to each event using ICD-10 criteria and American Heart Association classification for cardiovascular events. Notably, the outcome committee was blinded to the baseline risk factors.

Based on the electrocardiogram, biomarkers, and medical records, coronary heart disease (CHD) was defined as cases of either definite or probable myocardial infarction (MI), unstable angina, angiographic-proven CHD, and CHD-related deaths. Stroke and transient ischemic attack (TIA) were defined based on the World Health Organization (WHO) criteria [35]. CVD was defined as a composite of CHD, stroke, and cerebrovascular death.

Statistical analysis

Summary statistics for the study population are expressed as mean (± SD) values and frequencies (%) for continuous and categorical variables, respectively. Comparison of the index-year characteristics of the participants stratified by the tertile of TyG index variability was performed using the ANOVA and Chi-squared test, as appropriate.

Person-years of follow-up were calculated for each participant from the index-year to the first event. Crude incidence rates of the outcomes per 1000 person-years were also calculated, and the exposure and follow-up durations were reported as medians (interquartile range). Kaplan–Meier survival curves were plotted, and cumulative incidence rates of each health outcome across the tertiles of the index-year, average, and variability of the TyG index were compared using the log-rank test (see additional file 1). Multivariable-adjusted restricted cubic spline analysis was conducted to assess the shape of the association between index-year, average, and variability of the TyG index and each health outcome (considering model 2, see below); generally, linear associations were observed (see additional file 2).

Multivariable Cox proportional hazards regression models were used to assess the association of the TyG index with different outcomes. These associations were evaluated in age- and sex-adjusted model (Model 1) and multivariable analysis (model 2), further adjusted for BMI, LDL-C, high-density lipoprotein cholesterol, eGFR, lipid-lowering medication, anti-hypertensive medication, smoking, education, marital status, SBP (except for incident hypertension which was adjusted for average of SBP), prevalent T2DM (except incident T2DM), prevalent CVD (except for incident CVD), FH-CVD, FH-DM (only for the outcome of T2DM). Model 3 was additionally adjusted for the average of the TyG index. To minimize the possible effects of change in the confounders during the exposure period, we considered their last values (measured at the index-year) in our data analysis; a similar approach was applied in other studies [36, 37].

We also examined the association between tertiles of VVV of the TyG index with different outcomes as a categorical variable using the SD method, considering the first tertile as a reference. The trend test was performed

Table 1 Baseline characteristics of the eligible participants for all-cause mortality analysis; Tehran lipid and glucose study

Variables	Total ($n=4487$)	Tertile 1 ($n=1496$)	Tertile 2 ($n=1496$)	Tertile 3 ($n=1495$)	P_{value}
Age (years)	54.4 (±12.3)	54.9 (±12.5)	54.2 (±12.2)	54.1 (±12.1)	0.18
Sex (men)	1693 (37.7)	561 (37.5)	569 (38.0)	563 (37.7)	0.95
SBP (mmHg)	122.4 (±20.1)	122.5 (±20.5)	121.5 (±19.0)	123.1 (±20.6)	0.08
BMI (kg/m^2)	29.1 (±9.6)	28.9 (±4.7)	29.5 (±15.2)	29.0 (±4.6)	0.22
LDL-C (mg/dL)	119.2 (±32.3)	119.6 (±30.6)	120.3 (±32.1)	117.8 (±34.1)	0.09
HDL-C (mg/dL)	47.7 (±11.1)	48.4 (±11.4)	48.2 (±11.0)	46.4 (±10.8)	**<0.01**
eGFR, ml/min/1.73 m^2	73.3 (±13.8)	73.3 (±13.6)	73.6 (±13.1)	73.2 (±14.6)	0.76
Education, years					
<6	1704 (38.0)	559 (37.4)	592 (39.6)	553 (37.0)	0.49
6–12	2117 (47.2)	722 (48.3)	679 (45.4)	716 (47.9)	
≥12	666 (14.8)	215 (14.4)	225 (15.0)	226 (15.1)	
Marital status (married)	3794 (84.6)	1242 (83.0)	1269 (84.8)	1283 (85.8)	0.10
Current smoker (yes)	550 (12.3)	160 (10.7)	207 (13.8)	183 (12.2)	**0.03**
Prevalent DM (yes)	808 (18.0)	172 (11.5)	209 (14.0)	427 (28.6)	**<0.01**
FH-DM (yes)	1515 (33.8)	457 (30.5)	477 (31.9)	581 (38.9)	**<0.01**
Prevalent CVD (yes)	568 (12.7)	172 (11.5)	178 (11.9)	218 (14.6)	**0.02**
FH-CVD (yes)	870 (19.4)	266 (17.8)	305 (20.4)	299 (20.0)	0.15
Lipid lowering medication (yes)	790 (17.6)	219 (14.6)	219 (14.6)	352 (23.5)	**<0.01**
Anti-hypertensive medication (yes)	1023 (22.8)	319 (21.3)	332 (22.2)	372 (24.9)	**0.05**
TyG index index-year*	8.9 (±0.6)	8.8 (±0.5)	8.8 (±0.5)	9.0 (±0.7)	**<0.01**
TyG index average**	8.9 (±0.6)	8.8 (±0.5)	8.8 (±0.5)	9.0 (±0.6)	**<0.01**

Data are presented according to the tertiles of the TyG index variability, assessed by the SD method: Tertile 1: SD≤0.1783; tertile 2: 0.1784≤SD≤0.3005; tertile 3: SD≥0.3006

Continuous variables are shown as mean (±SD), and all have a normal distribution. Categorical variables are presented as number (%)

TyG index, triglyceride-glucose index; SD, standard deviation; SBP, systolic blood pressure; BMI, body mass index; LDL-A, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; DM, diabetes mellitus; CVD, cardiovascular disease; prevalent DM, history of diagnosed DM; FH-DM, family history of DM; FH-CVD, family history of CVD; prevalent CVD, history of diagnosed CVD

*TyG index in phase IV (2008–2011); **Average of TyG index during the exposure period

P_{values} less than 0.05 considered significant and bolded

by treating the TyG index variability tertile as an ordinal variable in the Cox regression models. The Cox regression models were also applied to assess the relation between 1-SD increase in index-year TyG index, average TyG index, and TyG index variability with different outcomes in the same models, as mentioned above. The proportionality assumption in the Cox regression models was examined using the Schoenfeld residuals test, and generally, no significant departure was found from proportionality in hazards over time. For the CVD and All-cause mortality outcomes, the event date was defined with the exact date of the incidence of the event. Regarding T2DM and hypertension, the event date was defined as the time at the follow-up visit when the diagnosis was made for the first time. We defined censoring as being lost to follow-up, death, and reaching the end of the study. Follow-up time was calculated as the difference between the time of study entrance and either event date or censoring, whichever happened first. We assessed the presence of multicollinearity by calculating the variation inflation factor (VIF) statistic in the regression models. Considering the VIF of less than 5, no multicollinearity was found between variables in different models.

In order to assess the robustness of the observed results, we conducted three additional analyses. First, we re-evaluated the association between independent variables of the TyG index and incident T2DM, considering 2hPG as another diagnostic criteria. Second, we re-evaluated the association between TyG variability and incident health outcomes, using VIM instead of SD as the method of variability assessment [34]. Third, we separately assessed the effect of 1-SD increment in independent variables of the TyG index for different health outcomes among men and women and examined the effect modification of sex in the multivariate analysis.

The statistical analyses were conducted using STATA version 17 SE (Stata Corp LP, TX, USA) and R version 4.2.1, with a two-tailed *p*-value of less than 0.05 considered statistically significant.

Results

Baseline characteristics

Table 1 presents the baseline characteristics of eligible participants according to the tertiles of the TyG index variability at the index-year, for all-cause mortality outcome, which comprised the highest number of participants compared to other outcomes. In total, 4487 participants (37.7% men) with a mean (±SD) age and BMI of 54.4 (±12.3) years and 29.1 (±9.6) kg/m^2 were included, respectively. Equal to the index-year, the average of the TyG index during the exposure period was 8.9 (±0.6). In addition, participants were divided according to the tertile of TyG index variability. Generally, compared to the lowest tertile, higher percentages of smoking

and consuming anti-hypertensive or lipid-lowering medications were observed in the highest tertile. Moreover, DM, FH-DM, and CVD were more prevalent in the highest tertile. TyG index, either in index-year or average values was higher in the highest tertile; however, in the case of high-density lipoprotein cholesterol (HDL-C), it was vice versa. The pattern of index-year characteristics according to tertiles of the TyG index remained essentially unchanged, considering hypertension as the outcome (see additional file 3).

The association between the TyG index at index-year and average values with incident health outcomes

During more than 6 years of follow-up after the exposure period, 290, 560, 361, and 280 cases of T2DM, hypertension, CVD, and all-cause mortality, with annual incidence rates of 14.87, 48.43, 11.8, and 7.68 per 1000 person-year were observed, respectively.

In categorical analysis, compared to the first tertile, the highest tertile of the TyG index at the index-year was associated with a more than six-fold increased risk of incident T2DM [HR, 95% CI 6.23 (3.96–9.79)] (see additional file 4). Furthermore, the highest tertile of the average of the TyG index showed a significant risk of incident T2DM [6.29 (4.18–10.51)]; CVD [1.47 (1.03–2.09)]; and all-cause mortality [1.55 (1.03–2.35)], compared to the first tertile (see additional file 5). The association between index-year and its average values of the TyG index and incident T2DM did not change, using 2hPG as another diagnostic criteria ($n=2705$) (see additional files 6–8).

Considering the TyG index as a continuous variable showed that a 1-SD increase in the index-year values was associated with a 150% excess risk of incident T2DM [2.50 (2.13–2.93)]. Furthermore, 1-SD increase in the average value of the TyG index during the exposure period was accompanied by 137, 12, 18, and 29% elevated risk of incident T2DM, hypertension, CVD, and all-cause mortality, respectively (all $p_{values} \leq 0.05$) (Fig. 2B and C).

Variability of TyG index and health outcomes

Table 2 shows the hazard ratio (HR, 95% CI) of incident health outcomes in three models, according to the tertile of the TyG index variability. In model 1, which was adjusted for age and sex, the highest tertile of variability was accompanied by a 35% increased risk of CVD events (P_{trend} =0.01); however, this association reached null after further adjustments for conventional risk factors. In the case of hypertension, tertile 2 and 3 of the variability of the TyG index showed 27% and 33% increased incidence risk in the full model, with a significant trend (P_{trend} < 0.01). Considering the TyG index variability as a continuous variable, we observed that 1-SD increment was associated with the risk of incident hypertension [1.11 (1.02–1.21)]; no such relationship was found for other outcomes (Fig. 2A).

Furthermore, we re-evaluated the association between TyG variability and incident health outcomes, considering VIM to assess the variability, instead of SD. Then, in line with SD, the only significant relationship was found between VIM and incident hypertension (see additional file 9).

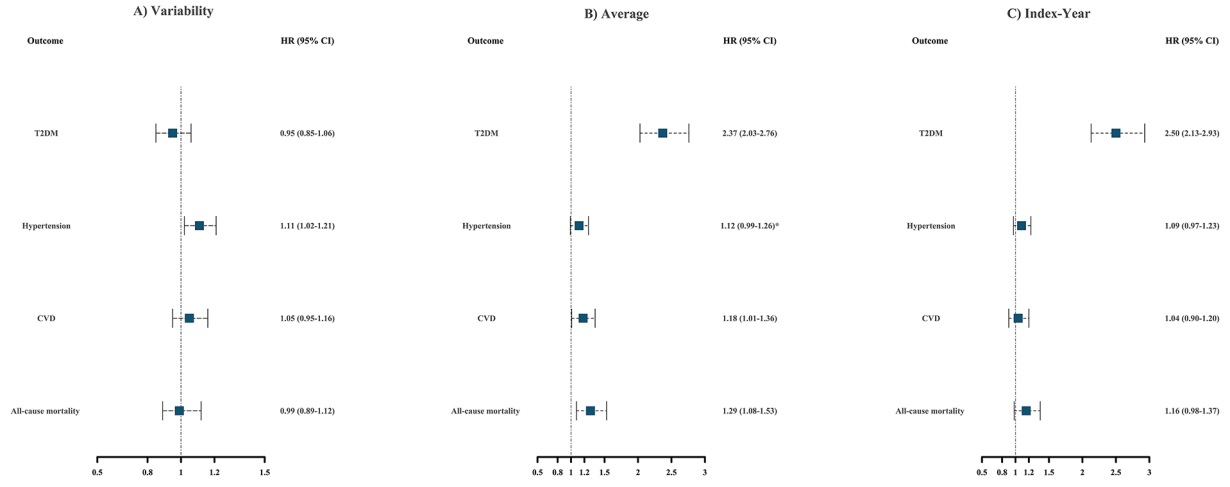


Fig. 2 Multivariable-adjusted HRs (95% CI) for incident health outcomes per 1-SD increase in TyG index. TyG index: triglyceride-glucose index; SD, standard deviation; CVD, cardiovascular disease; T2DM, type 2 diabetes mellitus. Values are adjusted for age, sex, body mass index, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, estimated glomerular filtration rate, lipid-lowering medication, anti-hypertensive medication, smoking, education, marital status, systolic blood pressure (SBP) (except for incident hypertension which was adjusted for average of SBP), prevalent T2DM (except incident T2DM), prevalent CVD (except for incident CVD), FH-CVD, FH-DM (only for the outcome of T2DM), average values of the TyG index (for variability analysis). *p_{value}= 0.05. **A** 1-SD increase in the variability of the TyG index; **B** 1-SD increase in the average values of the TyG index; **C** 1-SD increase of the TyG index at index-year

Table 2 Association between tertiles of the TyG variability* and incident health outcomes; Tehran lipid and glucose study

Outcome	E/*N*	Model 1	P_{value}	Model 2	P_{value}	Model 3	P_{value}
T2DM							
Tertile 1 (0.1703 ≥ SD)	92/1058	Reference		Reference		Reference	
Tertile 2	98/1057	1.07 (0.80–1.42)	0.63	1.08 (0.81–1.44)	0.59	0.99 (0.74–1.32)	0.95
Tertile 3 (0.2830 ≤ SD)	100/1057	1.14 (0.86–1.52)	0.36	1.06 (0.80–1.41)	0.68	0.99 (0.74–1.31)	0.93
P_{trend}			0.36		0.70		0.93
Hypertension							
Tertile 1 (0.1773 ≥ SD)	169/702	Reference		Reference		Reference	
Tertile 2	190/701	1.21 (0.99–1.49)	0.06	1.26 (1.02–1.56)	**0.03**	1.27 (1.02–1.56)	**0.03**
Tertile 3 (0.2968 ≤ SD)	201/701	1.32 (1.08–1.63)	**< 0.01**	1.33 (1.08–1.65)	**< 0.01**	1.33 (1.07–1.64)	**< 0.01**
P_{trend}			**< 0.01**		**< 0.01**		**< 0.01**
CVD							
Tertile 1 (0.1768 ≥ SD)	97/1496	Reference		Reference		Reference	
Tertile 2	79/1416	0.88 (0.68–1.15)	0.36	0.84 (0.65–1.10)	0.20	0.84 (0.64–1.10)	0.20
Tertile 3 (0.2977 ≤ SD)	104/1495	1.35 (1.05–1.72)	**0.01**	1.06 (0.82–1.37)	0.63	1.04 (0.80–1.33)	0.78
P_{trend}			**0.01**		0.63		0.78
All-cause mortality							
Tertile 1 (0.1783 ≥ SD)	92/1058	Reference		Reference		Reference	
Tertile 2	98/1057	0.88 (0.65–1.18)	0.39	0.87 (0.64–1.17)	0.35	0.85 (0.63–1.15)	0.30
Tertile 3 (0.3006 ≤ SD)	100/1057	1.29 (0.98–1.71)	0.07	1.10 (0.83–1.47)	0.50	1.04 (0.77–1.40)	0.80
P_{trend}			0.07		0.52		0.83

Data are presented as hazard ratio (95% confidence interval)

For each outcome, included participants were categorized into three tertiles according to the SD of their TyG index

TyG index, triglyceride-glucose index; SD, standard deviation; CVD, cardiovascular disease; T2DM, type 2 diabetes mellitus; E, events; N, numbers

Model 1: adjusted for age and sex; model 2: adjusted for model 1 + body mass index, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, estimated glomerular filtration rate, lipid-lowering medication, anti-hypertensive medication, smoking, education, marital status, systolic blood pressure (SBP) (except for incident hypertension which was adjusted for average of SBP), prevalent T2DM (except incident T2DM), prevalent CVD (except for incident CVD), FH-CVD, FH-DM (only for the outcome of T2DM); model 3: model 2 + average values of the TyG index

*Assessed by SD

P_{values} less than 0.05 considered significant and bolded

Subgroup analysis

We found no significant interaction between sex and independent variables of the TyG index for incident health outcomes in terms of hypertension, T2DM, and all-cause mortality. In contrast, the association between the index-year and average values of the TyG index with CVD events was more prominent among women compared to men (*P* for interaction = 0.037 and 0.049, respectively) (Fig. 3).

Discussion

In a population-based study conducted in the metropolitan city of Tehran, we examined the association between variability and average values of the TyG index during about 6 years of the exposure period, as well as its values at the index-year, with different health outcomes. Accordingly, we found that variability of the TyG index, as assessed by SD, was significantly associated with the incidence of hypertension, independent of a large set of confounders, including its average values, whereas this relationship was not found for other outcomes. Furthermore, the average value of the TyG index, independent of its variability, was a significant predictor for all of the outcomes; the corresponding risk per 1-SD increase was about 10, 20, 30, and 100% for hypertension, CVD, all-cause mortality, and T2DM, respectively. Moreover, the value of TyG at the index-year was an independent predictor only for the incidence of T2DM. Additionally, the association between index-year and average values of the TyG index was more prominent among women, compared to men, in terms of incident CVD.

Previously, numerous studies, principally in the Asian region, have individually evaluated the association between the TyG index and some NCDs, such as CVD and hypertension, by snapshot measurements [21, 38]. In the current study, the TyG index at the index-year emerged as a significant independent predictor of T2DM, aligning with a systematic review and meta-analysis encompassing 14 studies with over 270,000 participants, which has calculated the relative risk of incident T2DM for high TyG index as 3.21 (95% CI 2.75–4.54) [39]. Furthermore, a prospective cohort study involving 141,243 participants aged 35–70 from 22 countries, including Iran, has demonstrated an association between elevated TyG index and the incidence of CVD and T2DM, particularly in low- and middle-income countries [21]. Although snapshot measurements represent valuable information, they are incapable of capturing the impact of prolonged exposure and

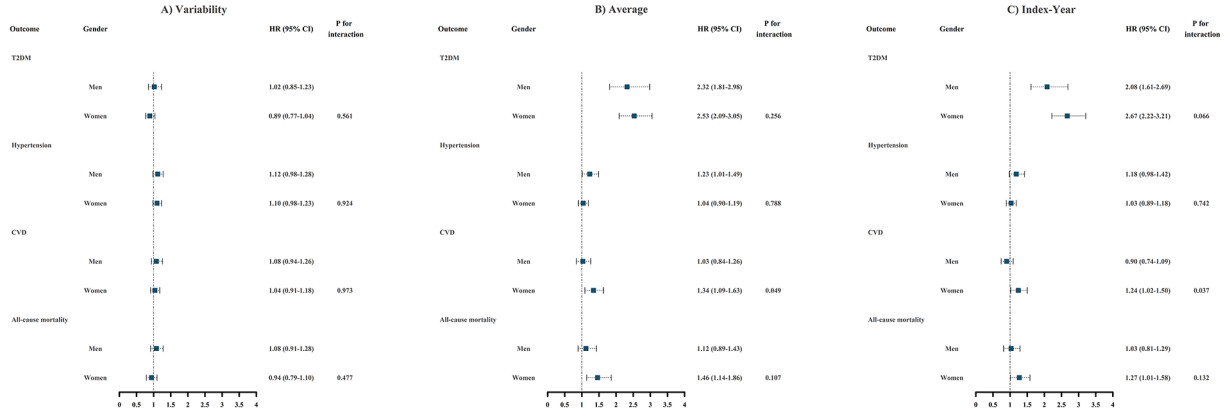


Fig. 3 Sex-specific multivariable-adjusted HRs (95% CI) for incident health outcomes per 1-SD increase in TyG index. TyG index: triglyceride-glucose index; SD, standard deviation; CVD, cardiovascular disease; T2DM, type 2 diabetes mellitus. Values are adjusted for age, sex, body mass index, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, estimated glomerular filtration rate, lipid-lowering medication, anti-hypertensive medication, smoking, education, marital status, systolic blood pressure (SBP) (except for incident hypertension which was adjusted for average of SBP), prevalent T2DM (except incident T2DM), prevalent CVD (except for incident CVD), family history of CVD, family history of DM (only for the outcome of T2DM), average values of the TyG index (for variability analysis). **A** 1-SD increase in the variability of the TyG index; **B** 1-SD increase in the average values of the TyG index; **C** 1-SD increase of the TyG index at the index-year

variability of the TyG index. Additionally, according to the theory of "metabolic memory" evaluating the TyG index as an IR surrogate over a long-term period provides deeper insights regarding the history of IR and possible consequences [40, 41]. In this context, we attempted to extend the previous findings by evaluating the predictive capacity of the long-term average and variability of the TyG index for the incidence of different health outcomes.

A limited number of studies have evaluated the average values of the TyG index, primarily for incident CVD and stroke [42, 43]. A prospective study with approximately 6 years of follow-up and 44,000 participants from China has claimed that participants in the fourth quartile of the cumulative TyG index have a 39% excess risk of CVD events compared to the first quartile [43]. Moreover, a retrospective study with 12 years of follow-up and about 15,000 participants from China has found a similar association between the TyG index and incident hypertension [44]. Of note; the impact of variability was not considered in the mentioned studies. Our results indicated that the long-term average of the TyG index, irrespective of its variability, has a superior predictive capacity for incidence of health outcomes rather than a single measurement at the index-year.

According to the time-varying nature of FPG and TG, two main components of the TyG index, single measurement of this index may cause potential regression dilution bias [45]. Although some studies have evaluated the impact of change in the TyG index on the incidence of different NCDs, very limited number of studies have assessed the impact of its VVV (Table 3). The vast majority of previous studies were conducted in the Asian population, which limited the generalizability of prior findings due to the influence of ethnicity and culture [23, 46]. In the present study, we found VVV of the TyG index (assessed by SD and VIM methods) as an independent predictor only for the incidence of hypertension, irrespective of conventional risk factors and average values; however, this association was not significant regarding other health outcomes. The association between the TyG index and hypertension is declared by several studies; a systematic review and meta-analysis including eight observational studies and about 200,000 participants have claimed that the highest category of TyG index is associated with the incidence of hypertension [adjusted risk ratio: 1.53 (1.26–1.85); I^2=54%]; however, the impact of VVV was not considered [47]. Furthermore, a cohort study from China, including approximately 18,000 participants with a mean age of 60.5 years, has noted that TyG change (assessed by subtracting baseline value from the end of the follow-up) was not associated with the incidence of hypertension, whereas VVV was not evaluated in this study [48]. On the other hand, two other studies from China have advocated the independent association between VVV (assessed by SD, coefficient of variation, and average real variability) of the TyG index and the incidence of T2DM and CVD, which contradicts our results [46, 49]. Finally, it is worth noting that the observed difference between our and previous results could be interpreted by some essential issues, such as ethical differences, the method of evaluating the VVV, and the manner of dealing with the confounders. To the best of our knowledge, this is the first report on the association between VVV of the TyG index and hypertension.

Our epidemiological findings regarding the association between the TyG index and hypertension could be interpreted by IR, which is accompanied by compensatory hypersecretion of insulin in the early stages. Following

Table 3 Literature review of studies evaluated the association between TyG variability and incident health outcomes

First author (year of publication)	Country	Exposure	Variability assessment	Confounders in full model	Outcome	Main results	References
Li et al. (2022)	China	TyG variability	SD	Age, sex, education, income, smoking status, alcohol consumption, physical activity, BMI, diabetes, hypertension, CKD, hs-CRP, hypercholesteremia, HDL-C, LDL-C, TyG index (for variability analysis)	CVD	After about 9 years of follow-up, the highest tertile of TyG variability was associated with a 12% excess risk of CVD incident: 1.12 (1.01–1.24)	[22]
Wang et al. (2022)	China	TyG variability	SD	Age, sex, TyG index, HDL-C, LDL-C, hs-CRP, BMI, smoking status, alcohol consumption, physical exercise, educational level, hypertension, lipid-lowering medication	Diabetes	During the study period of about 8 years, the highest quartile of variability was associated with a 1.18 (1.08–1.29) risk of incident diabetes.	[46]
Chen et al. (2022)	China	TyG variability	SD, CV, ARV	Age, sex, BMI, SBP, HDL-C, LDL-C, hypertension, diabetes, and mean TyG	CVD	During about a median follow-up of 6 years, a higher quartile of TyG variability was associated with the increased risk of CVD event [1.18 (1.05–1.34)]	[49]
Xu et al. (2023)	China	Long-term level and change of TyG index	SD, CV	Age, sex, educational level, smoking status, alcohol consumption, salt status, BMI, physical activity, HDL-C, LDL-C, hs-CRP, eGFR, anti-hypertensive and lipid-lowering medication	Cardiometabolic disease	During about 8 years of follow-up, the highest quartile of long-term TyG and TyG-SD was associated with a 3.15 (2.84–3.9) and 1.13 (1.04–1.22) risk of cardiometabolic disease incident.	[23]
Chen et al. (2024)	China	TyG variability and cumulative TyG	SD, CV, VIM, ARV	Age, sex, educational level, smoking status, alcohol consumption, physical activity, hypertension, BMI, LDL-C, HDL-C, ALT, AST, Cr, UA, urea, eGFR, baseline TyG index	CKD	After a median of 3.8 years of follow-up, the hazard ratio (95% CI) of incident CKD for the highest quartiles of variability and cumulative TyG index was 1.772 (1.453–2.162) and 2.091 (1.646–2.655), respectively	[56]
Current study (2024)	Iran	Index-year, average values, and variability of the TyG index	SD and VIM	Age, sex, BMI, LDL-C, high-density lipoprotein cholesterol, eGFR, lipid-lowering medication, anti-hypertensive medication, smoking, education, marital status, SBP, prevalent T2DM, prevalent CVD, FH-CVD, FH-DM, TyG average	T2DM, hypertension, CVD, all-cause mortality	During about 6 years of follow-up, we found that although the higher TyG index at index-year and its VVV increased the risk of incident T2DM and hypertension, respectively, however; its average value was capable of capturing the risk for all of the health outcomes.	–

TyG index, triglyceride glucose index; VVV, variability independent of mean; SD, standard deviation; CV, coefficient of variation; VIM, variability independent of mean; ARV, average real variability; CKD, chronic kidney disease; CVD, cardiovascular disease; BMI, body mass index; SBP, systolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ALT, alanine transaminase; AST, aspartate aminotransferase; Cr, creatinine; UA, uric acid; eGFR, estimated glomerular filtration rate; hs-CRP, high sensitivity C-reactive protein; FH-CVD, family history of cardiovascular disease; FH-DM, family history of diabetes mellitus

hyperinsulinemia, sympathetic nerves would be hyper-excited, which induces renin secretion, increased sodium reabsorption, and subsequent increase of vascular resistance and cardiac output [50]. Additionally, hyper-excited sympathetic nerves promote catecholamine release, and prolonged high plasma concentration of catecholamines is a major risk factor for vascular damage through several mechanisms [51]. In later stages of IR, endothelial cells' production and response to the vasodilators are suppressed, rooted in persistent exposure to hyperglycemia and oxidative stress [52, 53]. Interestingly, these biologically plausible explanations are also supported by epidemiological findings of two systematic reviews and meta-analyses, which have claimed that the highest category of TyG index is associated with approximately 83% and 96% augmented risk of arterial stiffness [54, 55].

The current study has some strengths that should be noted; this is the first long-term population-based prospective study that has assessed variability and average values of the TyG index in the MENA region, which has a high burden of NCDs. This study has provided a holistic overview regarding the clinical implication of three independent variables of the TyG index for predicting the incidence of major health outcomes. However, our results should be interpreted with caution due to several limitations: First, this study was conducted among residents of the metropolitan city of Tehran, limiting our results' generalizability. Second, although we tried to adjust a wide spectrum of conventional confounders for each health outcome specifically, we cannot refuse the possibility of some residual confounders, which is the inherent feature of observational studies. Third, hemoglobin A1C was not assessed among TLGS participants. Finally, nutritional habits and energy intake, which might affect the TyG index values, were not recorded; however, related confounders such as lipid indices and BMI were adjusted in the analysis.

Conclusion

In a population-based study, TyG values at the index year were only associated with the incidence of T2DM. Regarding the TyG average values that were assessed during about 6 years, besides hypertension, strong association was also demonstrated for incident T2DM, CVD, and all-cause mortality events. Last but not least, the VVV of the TyG index was a significant predictor of hypertension, even after considering a large set of confounders including its average values. So, we hypothesize that the average values of the TyG index, rather than its single measurement, could be implemented in clinical practice to estimate the risk of different health outcomes. Moreover, keeping the TyG index in a narrow range is recommended to prevent hypertension.

Abbreviations

TLGS	Tehran lipid and glucose study
MENA	Middle East and North Africa
IR	Insulin resistance
FPG	Fasting plasma glucose
TG	Triglyceride
TyG index	Triglyceride glucose index, calculated as Ln (fasting triglycerides (mg/dL) × fasting plasma glucose (mg/dL)/2)
NCD	Non-communicable disease
T2DM	Type 2 diabetes mellitus
2hPG	2-Hour post-challenge glucose
CHD	Coronary heart disease
CVD	Cardiovascular disease
VVV	Visit-to-visit variability
SD	Standard deviation
VIM	Variability independent of mean
HR	Hazard ratio
CI	Confidence interval
BMI	Body mass index
SBP	Systolic blood pressure
LDL-C	Low-density lipoprotein cholesterol
HDL-C	High-density lipoprotein cholesterol
eGFR	Estimated glomerular filtration rate
FH-DM	Family history of DM
prevalent CVD	History of diagnosed CVD
FH-CVD	Family history of CVD
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration equation

Supplementary Information

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Additional file 1: Kaplan-Meier survival curves according to the tertiles of the independent variables of the TyG index for incident type 2 diabetes, hypertension, cardiovascular disease, and all-cause mortality.

Additional file 2: Multivariable-adjusted restricted cubic spline for the relationship between independent variables of the TyG index and incident type 2 diabetes, hypertension, cardiovascular disease, and all-cause mortality. Adjusted for: age, sex, body mass index, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, estimated glomerular filtration rate, lipid-lowering medication, anti-hypertensive medication, smoking, education, marital status, systolic blood pressure (SBP) (except for incident hypertension which was adjusted for average of SBP), prevalent T2DM (except incident T2DM), prevalent CVD (except for incident CVD), family history of CVD, and family history of DM (only for the outcome of T2DM).

Additional file 3.

Additional file 4.

Additional file 5.

Additional file 6.

Additional file 7.

Additional file 8.

Additional file 9.

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Author contributions

DM, FH, MT, and NC conceived and planned the study. DM performed literature research. NC conducted the analyses. FH, DM, MT, and NC contributed to the interpretation of the data. FH and MT conducted a critical revision of the manuscript. DM developed the first draft of the manuscript. All authors have read and approved the final manuscript.

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Availability of data and materials

The used datasets for analysis of the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

Ethical approval of this study has been certified by the central institutional review board of the Research Institute of Endocrine Science, Shahid Beheshti University of Medical Science, Tehran, Iran. The outlined principles in the Declaration of Helsinki have been respected in this study. All participants have signed written consent.

Consent for publication

All authors have declared their consent for publication.

Competing interests
The authors declare no competing interests.

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