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Association of the triglyceride glucose index with all-cause and cardiovascular mortality in a general population of Iranian adults

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Abstract

Background The triglyceride glucose (TyG) index is a new and low-cost marker to determine insulin resistant which may be a predictor of cardiovascular disease (CVD). Although available evidence showed that its association with CVD mortality (CVM) and all-cause mortality (ACM) may differ in different populations, scarce data are available in this regard specially in low and middle-income countries.

Purpose To examine the association between TyG index and risk of CVM and ACM in Iranians.

Methods This prospective cohort study included 5432 adults (age ≥ 35 years) with no history of CVD events. Fasting glucose and triglyceride were measured at baseline in all participants and TyG index was calculated. Cox frailty model was used to calculate hazard ratios (HRs) for CVM and ACM across the tertiles of TyG index.

Results After a median follow-up of 11.25 years, a total number of 191 cardiovascular deaths, and 487 all-cause mortality was recorded. The risk of both CVM and ACM increased across the tertiles of TyG index. In the adjusted model for lifestyle and metabolic variables, the risks of ACM and CVM increased by 41% (95% CI 1.11, 1.81; P for trend = 0.005) and 64% (95% CI 1.07, 2.50; P for trend = 0.024), respectively. However, adjustment for diabetes mellitus disappeared the significance for both ACM and CVM. These associations may vary by sex. TyG was not related to the risk of non-CVD mortality.

Conclusion The predicting value of TyG index for ACM and CVM might be mediated by diabetes status. Further studies are required to confirm these findings.

Keywords Insulin resistance, Triglyceride-glucose index, All-cause mortality, Cardiovascular mortality

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Page 2 of 11

Introduction

Coronary artery disease (CAD), peripheral artery disease (PAD), and stroke are all regarded to be forms of cardiovascular disease (CVD). CVD and its ensuing complications make up for a significant economic burden and the leading cause of mortality in developed countries and increasingly so in low and middle-income countries [1]. In the following decades, cardiovascular mortality is expected to escalate by 137% and 120% in males and females, respectively [2]. Identifying those who are more susceptible to CVD in its early stages and improving their lifestyles has been proposed to surmount these problems.

Insulin resistance (IR) is identified as the leading culprit of metabolic abnormalities connected to CVD [3]. IR is characterized by impaired responsiveness of peripheral tissue to insulin and is linked to increased mortality and morbidity [3, 4]. A previous meta-analysis reported that IR is independently associated with a higher risk of CVD and all-cause mortality in the non-diabetic individuals [5]. Traditionally, hyper insulinemic-euglycemic (HIEC) clamp test and the homoeostasis model assessment of insulin resistance (HOMA-IR) have been used to measure IR. However, in recent years, triglyceride glucose index (TyG) has been presented as a more convenient and reliable IR surrogate than HIEC and HOMA-IR [6].

A series of recent studies have indicated that elevated TyG index is linked to a higher risk of CVD [7], CAD [8], PAD [9], and stroke [10]. Nevertheless, the relationship between TyG index and CVD mortality (CVM) and all-cause mortality (ACM) is still obscure. In old hypertensive individuals (>60 y), a nine-linear association was observed between TyG and ACM while the lowest risk was found at the level of 9.45 and values lower and higher than 9.45 were associated with increased incidence risk of ACM [11]. This study failed to find any significant association between TyG and CVM. A recent systematic review and meta-analysis of twelve cohort studies demonstrated an association between TyG index and CAD, CVD, and myocardial infarction (MI); but no statistically significant relationship was found between TyG index and CVM and ACM [6].

Low- and middle- income countries (LMIC) has experienced a remarkable rise in the frequency of CVD and CVM in recent decades [12]. Eighty percent of CVM cases in recent years have been reported in LMIC, particularly in Middle Eastern countries [7, 8]. Furthermore, studies have demonstrated that Iranians exhibit a greater prevalence of risk factors for CVD, central obesity [13], metabolic syndrome [14], and diabetes mellitus (DM) [15] when compared to the general population of other countries[16, 17] that indicate impaired metabolism and hyperinsulinemia [18, 19].

Despite the importance of identifying individuals from the general population with increased risk of CVD incidence and accompanying mortality, the literature on predictive value of the TyG index regarding CVM and CAM is inconsistent. Therefore, we aimed to investigate whether a higher TyG index in the general Iranian population can predict the risk of cardiovascular and all-cause death.

Methods

Study population

The ICS is a population-based study that included 6504 people with ages equal to or greater than 35 years old (3168 men and 3336 women). Participants had no prior CVD at baseline and were chosen from 3 cities in Iran (Isfahan, Arak, Najaf-Abad).

The study design has already been described in further details [20]. Initially, the researchers collected information on lifestyle factors, such as diet, through in-person interviews and followed up with participants every two years to monitor specific outcomes. If no cardiovascular events occurred during these follow-ups, all variables, including lifestyle factors, were reassessed in a subsequent survey after six years (in 2007 and 2013). In the present analysis, we enrolled participants who had complete information on their medical status, triglyceride, glucose and relevant confounding factors. Each individual involved in the study gave their written consent after being informed about the details of the study. The research adhered to the guidelines laid out in the Declaration of Helsinki. The Ethic Committee of the Research Council of the Isfahan Cardiovascular Research Center, a World Health Organization partner facility in Isfahan, Iran (#1402114), gave its approval to this study. Figure 1 illustrates the flowchart of our study selection process, outlining the inclusion of patients and providing reasons for the exclusion of other participants.

Data collection

A 30-min interview at baseline was performed to collect data on demographic and socioeconomic factors. Patients were also asked about their medical (including dyslipidemia, DM, HTN, and medications) and lifestyle factors.

Height, weight, systolic (SBP) and diastolic blood pressure (DBP) were measured during physical examination. A12 h fasting blood sample was gathered from all participants. The samples were analyzed at the central laboratory of the Isfahan Cardiovascular Research Center, following strict quality control measures set by national and international standards. An autoanalyzer made by Eppendorf in Hamburg, Germany was used to measure levels of FPG, TG, and total cholesterol through
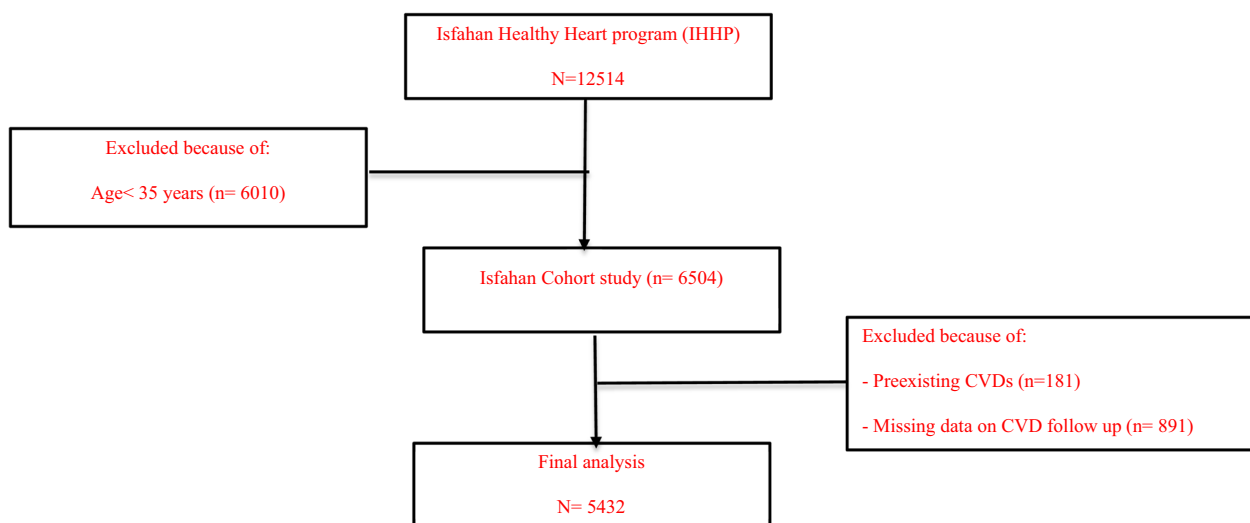
Fig. 1 Folow of participants through the study

enzymatic methods. To measure HDL-C, low-density and very low-density lipoproteins were removed from the blood using dextran sulfate magnesium before analysis [21]. Diabetes was characterized by a fasting plasma glucose (FPG) equal to or exceeding 126 mg/dL, a 2-h post-prandial glucose (2hpp) equal to or exceeding 200 mg/dL, or the use of anti-diabetic medications [22]. The global dietary index (GDI) was determined by assessing food quality. 29 food items were grouped into seven categories and given scores of 0, 1, or 2 based on how often they were eaten. Healthier food groups received higher scores while unhealthy ones received lower scores. The scores for all seven categories were added to calculate the GDI, with lower values indicating a healthier diet. Weight (Kg) divided by square of height (m2) was used to compute the body mass index (BMI). The TyG index was calculated as Ln (fasting TG (mg/dl) × FPG (mg/dl)/2) [23]. Individuals with SBP ≥ 140 mmHg and\or DBP ≥ 90 or those who were taking antihypertensive drug were considered HTN. Dyslipidemia was described as if LDL-C ≥ 130 mg/dL, TC ≥ 200 mg/dL, TG ≥ 150 mg/dL or HDL-C < 40 mg/dL in men or < 50 mg/dL in women.

Follow-up
Participants were interviewed biannually over the phone. Data regarding mortality was collected by conducting verbal autopsies with family members who survived the deceased individual. The approach involved a structured primary interview wherein the initial inquiry was whether the person in question was still alive. The study under consideration defined cardiovascular mortality as the occurrence of fatal myocardial infarction, fatal strokes (i.e., death resulting from cerebrovascular disease), and

sudden cardiac death. For the purposes of the study, sudden cardiac death was characterized as death occurring within one hour after onset, witnessed cardiac arrest, or abrupt collapse without preceding symptoms lasting longer than 41 h.

Statistical analysis
Participants were categorized into three groups based on the tertile of TyG index. We compared the baseline characteristics of male and female participants using independent sample t-tests (or Mann–Whitney tests if necessary) for continuous variables and chi-square tests for categorical variables. We also compared the baseline characteristics of participants across the tertiles of the TyG index using analysis of variance (ANOVA) (or Kruskal–Wallis tests if assumptions were not met) and chi-square tests, for continuous and categorical variables, respectively. We presented continuous variables as mean ± SD and categorical variables as number (percent).

We calculated person-years of follow-up from recruitment until the occurrence of death. We calculated crude and multiple-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) to determine the association between the TyG index and mortality using Cox proportional hazards regression. Model 1 was unadjusted, and model 2 was adjusted for age at baseline and sex. Model 3 included additional adjustments for education, marital status, and residency area (rural vs. urban). Model 4 included adjustments for GDI, smoking status, and total daily physical activity. The final model further adjusted for BMI, hypertension, and elevated total cholesterol. We additionally controlled the mediating effect of diabetes in model 6. All statistical analyses were performed using

SPSS (v. 26) and STATA (v 14.0), considering a p ≤ 0.05 to be statistically significant.

Results

During a median follow-up of 11.25 years, 487 cases of ACM (overall incidence of 7.76 per 1000 person-years), 181 cases of CVM (overall incidence of 2.88 per 1000 person-years) and 306 cases of non-cardiovascular mortality (overall incidence of 4.88 per 1000 person-years) were recorded. There was no evidence for interaction between diabetes and TyG either in the whole population or in men and women separately.

Baseline characteristics of participants according to the tertiles of TyG index is illustrated in Table 1. Participants in the higher TyG index group were older than the first group (51.75 ± 11.08 vs. 49.38 ± 11.88; p < 0.001) and were more likely to be physically inactive, live in rural areas, and have lower diet quality (GD). Moreover, HTN, DM, dyslipidemia, and overweight (BMI ≥ 25) were more frequent in individuals in the third tertile of the TyG index compared with the first one (p < 0.001). SBP (126.59 ± 21.61 vs 117.04 ± 19.64; p < 0.001) and DBP (80.72 ± 11.74 vs 75.86 ± 10.70; p < 0.001) were higher in participants in the third tertile of the TyG index in comparison with the first one. Similar trends were observed for FPS, TC, HDL-c, LDL-c, TG and TG:HDL (p < 0.001).

Table 2 highlights multivariate-adjusted HRs (and 95% CIs) for CVM, non-cardiovascular mortality and ACM across the tertiles of TyG index in the whole population. In the crude model, risk of ACM was higher in the highest

Table 1 Baseline characteristics of the participants by tertiles of triglyceride glucose index

	Overall N = 4973	Triglyceride glucose index			P value[†]
		Tertile 1 (TyG < 8.58) N = 1810	Tertile 2 (8.585 ≤ TyG < 9.09) N = 1811	Tertile 3 (9.09 ≤ TyG) N = 1811	
Males, n (%)	2648 (48.7)	864 (47.7)	885 (48.9)	899 (49.6)	0.514
Age, years (Mean ± SD)	50.69 (11.62)	49.38 (11.88)	50.96 (11.77)	51.75 (11.08)	< 0.001
Education					0.923
≤ 5 years	3861 (71.2)	1290 (71.4)	1277 (70.6)	1294 (71.6)	
6–12 years	1230 (22.7)	411 (22.7)	419 (23.2)	400 (22.1)	
≥ 13 years	333 (6.1)	106 (5.9)	113 (6.2)	114 (6.3)	
Married, n (%)	4951 (91.1)	1665 (92.0)	1659 (91.6)	1627 (89.8)	0.052
Urban, n (%)	1501 (27.6)	565 (31.2)	503 (27.8)	433 (23.9)	< 0.001
Physical activity (MET.min/wk) (Mean ± SD)	872.38 (548.62)	898.53 (548.11)	883.33 (557.70)	835.28 (538.19)	0.001
Global dietary index	1.02 (0.27)	1.06 (0.24)	1.02 (0.27)	0.98 (0.28)	< 0.001
Smoking status, n (%)					0.628
Current	292 (16.1)	267 (14.7)	287 (15.8)	846 (15.6)	
Former	353 (6.5)	120 (6.6)	110 (6.1)	123 (6.8)	
Never	4233 (77.9)	1398 (77.2)	1434 (79.2)	1401 (77.4)	
Hypertension, n (%)	1510 (27.8)	344 (19.0)	514 (28.4)	652 (36.0)	< 0.001
Diabetes, n (%)	459 (8.4)	16 (0.9)	46 (2.5)	397 (21.9)	< 0.001
Dyslipidemia, n (%)	4735 (87.2)	1202 (66.4)	1729 (95.5)	1804 (99.6)	< 0.001
BMI (kg/m^2) (Mean ± SD)	26.77 (4.68)	25.07 (4.46)	26.90 (4.56)	28.35 (4.43)	< 0.001
Waist to hip ratio	0.93 (0.08)	0.91 (0.09)	0.93 (0.08)	0.95 (0.08)	< 0.001
Systolic blood pressure, mm Hg	121.64 (20.95)	117.04 (19.64)	121.28 (20.44)	126.59 (21.61)	< 0.001
Diastolic blood pressure, mm Hg	78.40 (11.52)	75.86 (10.70)	78.61 (11.57)	80.72 (11.74)	< 0.001
Fasting glucose, mg/dL	88.67 (32.84)	76.83 (10.77)	81.79 (14.08)	107.38 (32.84)	< 0.001
Total cholesterol, mg/dL	214.12 (52.25)	187.86 (40.98)	212.57 (44.88)	241.91 (55.08)	< 0.001
LDL cholesterol, mg/dL	128.96 (43.42)	119.05 (38.31)	131.41 (42.22)	136.42 (47.39)	< 0.001
HDL cholesterol, mg/dL	46.91 (10.36)	47.99 (10.17)	46.59 (10.04)	46.16 (10.77)	< 0.001
TG, mg/dL	191.28 (103.26)	104.37 (24.90)	172.80 (33.00)	296.62 (106.24)	< 0.001
TG:HDL	4.31 (2.63)	2.29 (0.78)	3.88 (1.15)	6.77 (2.91)	< 0.001

Values are n (%) for categorical variables and mean (SD) for continuous variables

BMI body mass index, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *TG* Triglycerides

[†] Derived from either an analysis of variance (ANOVA) or a Kruskal–Wallis test for continuous variables, and a chi-squared test for categorical variables

Table 2 Multiple-adjusted HRs (and 95% CIs) for all-cause, CVD and non-CVD mortality across tertiles of triglyceride glucose index

	Case/ person year	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
All-cause mortality							
Tertile 1	140	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
Tertile 2	155	1.14 (0.90, 1.43)	1.06 (0.84, 1.33)	1.06 (0.84, 1.34)	1.09 (0.87, 1.38)	1.12 (0.88, 1.42)	1.09 (0.86, 1.40)
Tertile 3	192	1.36 (1.10, 1.69)	1.27 (1.02, 1.58)	1.28 (1.03, 1.60)	1.31 (1.05,1.64)	1.41 (1.11, 1.81)	1.14 (0.88, 1.49)
P for trend		0.005	0.029	0.026	0.015	0.005	0.329
Cardiovascular mortality							
Tertile 1	41	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
Tertile 2	61	1.53 (1.03, 2.27)	1.46 (0.98, 2.17)	1.47 (0.99, 2.18)	1.53 (1.03, 2.28)	1.38 (0.91, 2.10)	1.31 (0.86, 2.00)
Tertile 3	79	1.91 (1.31, 2.78)	1.82 (1.25, 2.66)	1.78 (1.21, 2.61)	1.85 (1.26, 2.71)	1.64 (1.07, 2.50)	1.11 (0.70, 1.75)
P for trend		0.001	0.002	0.003	0.002	0.024	0.732
Non-cardiovascular mortality							
Tertile 1	99	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
Tertile 2	94	0.97 (0.73, 1.29)	0.90 (0.68, 1.19)	0.90 (0.67, 1.19)	0.92 (0.69, 1.22)	1.00 (0.74, 1.36)	1.00 (0.74, 1.35)
Tertile 3	113	1.13 (0.86, 1.48)	1.04 (0.80, 1.37)	1.07 (0.81, 1.41)	1.10 (0.83, 1.44)	1.32 (0.97, 1.79)	1.18 (0.85, 1.64)
P for trend		0.359	0.732	0.603	0.511	0.072	0.318

Model 1: crude

Model 2: Adjusted for age (years) and sex (man/woman)

Model 3: Additionally adjusted for education level (0–5 years/6–12 years/ > 12 years), marital status (married/not married), residency location (urban/rural)

Model 4: Additionally adjusted for global dietary index (GDI), smoking status (never have smoked/have ever smoked), and total daily physical activity (METs-min/day)

Model 5: Additionally adjusted for BMI (kg/m^2), hypertension (yes/no), and high total cholesterol (yes/no)

Model 6: Additionally adjusted for diabetes mellitus (DM) (yes/no)

tertile of the TyG index in the crude model (HR = 1.36, 95% CI 1.10, 1.69; P for trend = 0.005) and after adjustment for potential confounders in model 5 (HR = 1.41, 95% CI 1.11, 1.81; P for trend = 0.005). Similarly, individuals in the top tertile of TyG compared with those in the bottom tertile had 91% increased risk of CVM in the crude model (HR = 1.91, 95% CI 1.31, 2.78; P for trend = 0.001). Further adjustment for potential cofounding variables slightly weakened the association but did not affect its significance in model 5 (HR = 1.64, 95% CI 1.07, 2.50; P for trend = 0.024). However, there was no increased risk in non-cardiovascular mortality following the rise in the TyG index in crude model (HR = 1.13, 95% CI 0.86, 1.48; P for trend = 0.359). After full adjustment for potential confounding variables in model 5, there was a marginally significant increase in non-cardiovascular mortality in participants with the highest TyG index compared to those with those in the lowest tertile (HR = 1.32, 95% CI 0.97, 1.79; P for trend = 0.072). However, adjustment for diabetes as a mediator disappeared significance for both ACM (HR = 1.14, 95% CI 0.88, 1.49; P for trend = 0.329) and CVM (HR = 1.11, 95% CI 0.70, 1.75; P for trend = 0.732), and weakened the association for non-cardiovascular mortality (HR = 1.18, 95% CI 0.85, 1.64; P for trend = 0.318).

Table 3 highlights the association between TyG index tertiles and mortality stratified by sex. In females, despite a significant positive association between the TyG index and ACM in the crude model (HR = 1.74, CI 1.23, 2.46; P for trend = 0.002), no statistically significant association was observed in any of the adjusted model. In males, higher TyG index was not associated with higher risk of ACM in the crude model (HR = 1.13, 95% CI 0.85, 1.50; P for trend = 0.378) but tended to be higher in model 5 after adjustment for various potential confounders (HR = 1.38, 95% CI 0.99, 1.92; P for trend = 0.056). however, adjustment for diabetes mellitus led to a null association (HR = 1.06, 95% CI 0.74, 1.51; P for trend = 0.760). Similarly, CVM was significantly higher in females in the top tertile of the TyG index in comparison with those in the first tertile in the crude model but not in the fully adjusted model including diabetes mellitus. In males, in the crude model, a significant association was found between TyG and CVM risk (HR = 1.60, 95% CI 1.00, 2.55; P for trend = 0.043) and adjustment for age strengthened it (HR = 1.91, 95% CI 1.20, 3.06; P for trend < 0.001) and other confounders adjustment did not change it substantially except for mediators in model 5 and diabetes mellitus in model 6 (HR = 1.01, 95% CI 0.56, 1.83; P for trend = 0.995). Non-cardiovascular mortality

Table 3 Multiple-adjusted HRs (and 95% CIs) for all-cause, CVD and non-CVD mortality across tertiles of triglyceride glucose index stratified by sex

All-cause mortality		Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Females	Tertile 1	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
	Tertile 2	1.49(1.04,2.14)	1.01(0.70, 1.45)	0.99(0.69, 1.42)	1.01(0.70, 1.45)	1.15(0.78, 1.68)	1.13(0.77, 1.66)
	Tertile 3	1.74(1.23,2.46)	1.14(0.80, 1.61)	1.11(0.79, 1.58)	1.14(0.80, 1.62)	1.37(0.94, 2.00)	1.18(0.79, 1.76)
	P trend	0.002	0.430	0.502	0.419	0.094	0.424
Males	Tertile 1	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
	Tertile 2	0.93(0.69, 1.25)	1.06(0.79, 1.44)	1.08(0.80, 1.46)	1.11(0.82, 1.50)	1.06(0.77, 1.45)	1.02(0.74, 1.41)
	Tertile 3	1.13(0.85,1.50)	1.34(1.01, 1.78)	1.39(1.04, 1.86)	1.42(1.06, 1.90)	1.38(0.99, 1.92)	1.06(0.74, 1.51)
	P trend	0.378	0.042	0.024	0.018	0.056	0.760
CVD mortality							
Females	Tertile 1	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
	Tertile 2	2.19(1.13, 4.25)	1.47(0.75,2.85)	1.45(0.75, 2.83)	1.44(0.74, 2.80)	1.39(0.69, 2.81)	1.35(0.67,2.74)
	Tertile 3	2.49(1.30,4.76)	1.63(0.85,3.13)	1.59(0.83, 3.03)	1.57(0.82, 3.02)	1.58(0.78, 3.18)	1.17(0.56,2.47)
	P trend	0.007	0.151	0.185	0.189	0.217	0.773
Males	Tertile 1	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
	Tertile 2	1.21(0.73, 1.99)	1.41(0.85,2.32)	1.45(0.88, 2.40)	1.51(0.91, 2.50)	1.30(0.76, 2.20)	1.20(0.70,2.04)
	Tertile 3	1.60(1.00, 2.55)	1.91(1.20,3.06)	1.90(1.18, 3.06)	1.96(1.21, 3.17)	1.58(0.92, 2.71)	1.01(0.56,1.83)
	P trend	0.043	<0.001	0.008	0.006	0.099	0.995
Non-CVD mortality							
Females	Tertile 1	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
	Tertile 2	1.25(0.81, 1.93)	0.85(0.55, 1.31)	0.83(0.54, 1.29)	0.86(0.55, 1.32)	1.04(0.66, 1.66)	1.04(0.66, 1.65)
	Tertile 3	1.48(0.98, 2.24)	0.97(0.64, 1.47)	0.95(0.63, 1.44)	0.98(0.65, 1.49)	1.27(0.81, 2.01)	1.19(0.73, 1.92)
	P trend	0.063	0.955	0.894	0.988	0.271	0.471
Males	Tertile 1	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
	Tertile 2	0.80(0.55, 1.17)	0.91(0.62, 1.33)	0.91(0.62, 1.33)	0.93(0.64, 1.36)	0.94(0.63, 1.40)	0.93(0.62, 1.38)
	Tertile 3	0.91(0.64, 1.30)	1.08(0.75, 1.54)	1.15(0.80, 1.66)	1.16(0.80, 1.68)	1.28(0.84, 1.96)	1.11(0.71, 1.75)
	P trend	0.613	0.700	0.470	0.440	0.265	0.681

Model 1: crude

Model 2: adjusted for age (years)

Model 3: Additionally adjusted for education level (0–5 years/6–12 years/ > 12 years), marital status (married/not married), residency location (urban/rural)

Model 4: Additionally adjusted for global dietary index (GDI), smoking status (never have smoked/have ever smoked), and total daily physical activity (METs-min/day)

Model 5: Additionally adjusted for BMI (kg/m^2), hypertension (yes/no), and high total cholesterol (yes/no)

Model 6: Additionally adjusted for diabetes mellitus (DM) (yes/no)

was related to the tertiles of TyG neither in females nor in males in any of the models.

Figures 2, 3, 4 display Kaplan–Meier survival analysis curves, illustrating the occurrence of ACM, CVM, and non-cardiovascular mortality, respectively across tertiles of TyG index in total population, men and women.

Additional file 1: Table S1 reveals the association of ACM, CVM and non-cardiovascular mortality with TG and FPG separately. Higher TG levels were not associated with increased risk of ACM and non-cardiovascular mortality in any of the model. However, although it was directly related to the risk of CVM, it was dependent on some mediators and disappeared after controlling their mediating effect. Regarding FPG, the higher FPG levels, the higher risk of ACM and CVM in all models except

for the adjusted model for DM. Nevertheless, it was not related to the risk of non-cardiovascular mortality.

Discussion

In the current cohort study, which involved 5432 Iranian adults from the general population, we observed a significant direct relationship between the baseline TyG index and CVM and ACM after 11.25 years of follow-up. This association was independent of various demographic, lifestyle and metabolic variables. Nevertheless, DM emerged as a significant confounding variable in the connection between TyG index and both CVM and ACM. In stratified analysis by sex, the increased risk of ACM and CVM with an increase in the TyG index was evident in males, but not females, though it depended on metabolic
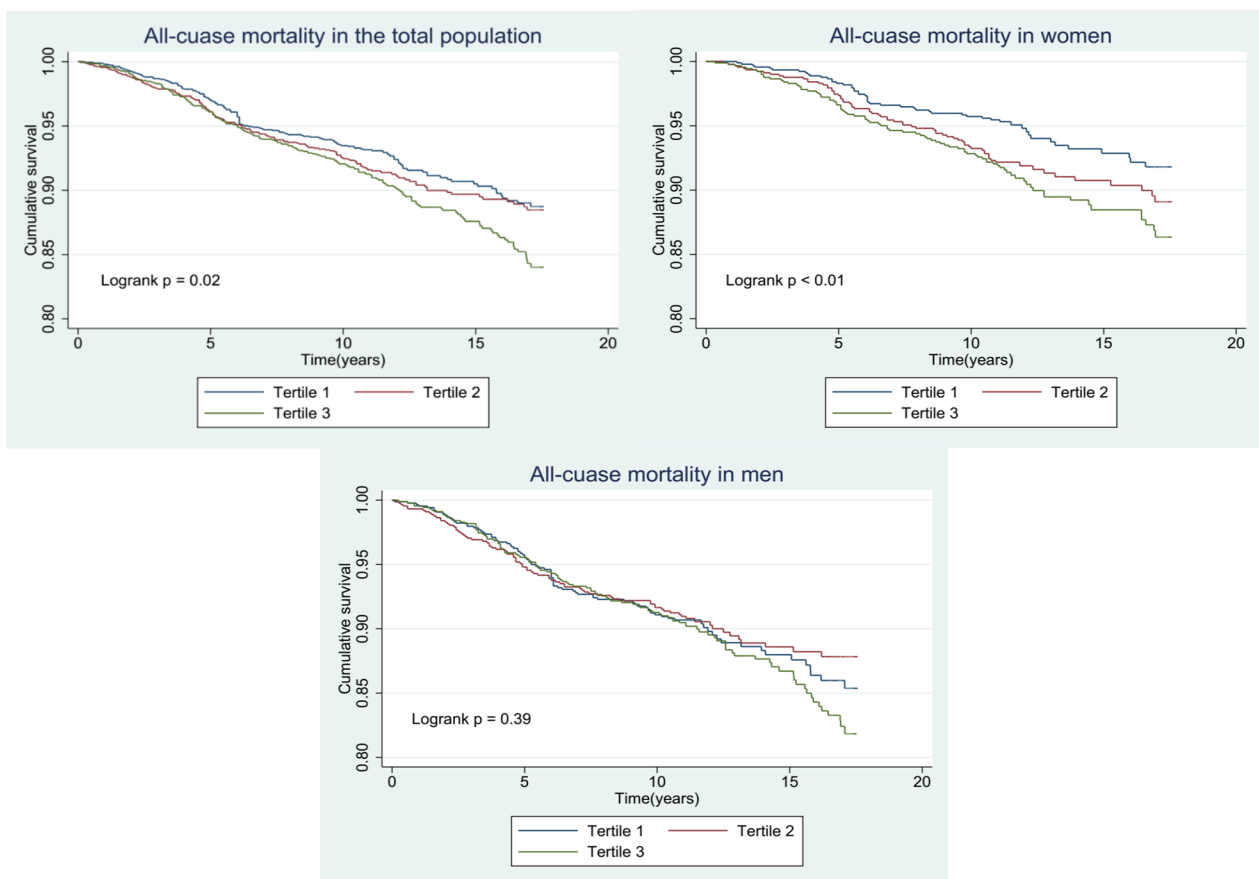
Fig. 2 Kaplan–Meier curves to estimate cumulative hazard for the development of all-cause mortality by baseline triglyceride glucose index tertiles in total population, male participants, and female participants

risk factors. Non-CVD mortality was not significantly related to the TyG index.

Atherosclerosis, type 2 DM, metabolic syndrome, and nonalcoholic fatty liver are just a few modern debilitating diseases that are thought to be triggered by IR [24]. Additionally, IR and ACM association in different populations and not only in diabetic patients has gained attention in recent years. TyG index, as an indicator of FPG and TG, is a more suitable indicator of IR state than the FPG and TG alone [25]. Prior research suggests that TyG index has a positive correlation with arterial stiffness [26], coronary artery calcification progression [27], DM incidents [28], LDL-C, TG, and estimated glomerular filtration rate [29]. All of which are traditional risk factors for CAD and this correlation can rationalize the prognostic value of the TyG index with CVM.

Our results are in line with previous studies regarding the increased rate of CVM and ACM among those with higher TyG index [29–32]. For example, after 7.6 years of follow-up, a higher TyG index was linked to an 18% greater risk of ACM in a study on 9254 American men

over the age of 45 [32]. In another observational study on acute coronary syndrome patients with DM, individuals in the top tertile of the TyG index had an HR of 1.44 for ACM compared to the first tertile in a dose–response manner [29]. The precise predictive significance of TyG index regarding ACM is still controversial. In light of this, Lopez-Jaramillo et al. reported significant association between the higher TyG index and cardiovascular incidence and CVM, especially in LMIC in the PURE study. However, their results differ from ours as they did not find a significant association between the TyG index and non-cardiovascular mortality and ACM, while we observed an increased risk of ACM with higher TyG index [19]. Liu et al. also reported inconsistent results when it comes to ACM and CVM, and based on their systematic review and meta-analysis of 12 cohort studies, there was no association between the TyG index and ACM and CVM [6]. The inconsistent findings in various studies could be due to disparities in location and economic status. Our study of the Iranian population, which is considered a middle-income country, showed an increased risk for
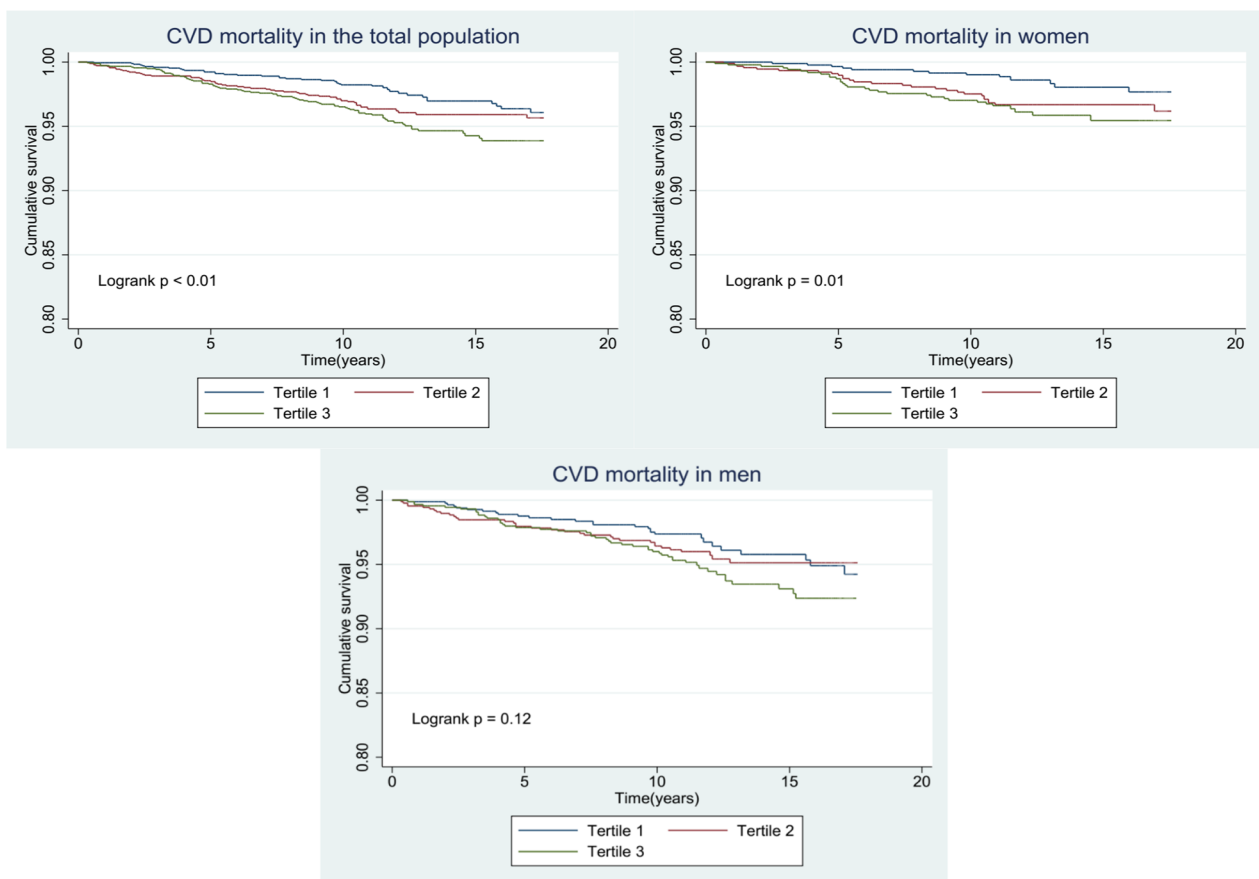
Fig. 3 Kaplan–Meier curves to estimate cumulative hazard for the development of cardiovascular mortality by baseline triglyceride glucose index tertiles in **A** Total population, **B** Male, and **C** Female

ACM and CVM. This may be explained by the fact that LMIC are more susceptible to insulin resistance, which is possibly caused by poor maternal nutrition resulting in low birthweight babies and exposure to obesogenic modern lifestyles in adulthood [19]. Additionally, as a result of habits developed through rapid urbanization leading to a sedentary lifestyle and consumption of high-energy foods, obesity and overweight rates are high among these populations [33]. Another key factor that can explain the heterogeneity between high income countries and LMIC is the level of education. The research suggests that people with lower levels of education in LMIC are at a significantly higher risk of experiencing serious cardiovascular events compared to those with higher levels of education [34].

Inconsistencies in findings regarding the impact of the TyG index on mortality with respect to sex have been documented previously [35–37]. Upon stratifying our outcomes by sex, we showed no statistically significant association between the TyG index and ACM or CVM in males and females after adjustment for metabolic mediators. However, in other adjusted models, the associations were evident in males, but not females. Sex differences found in our study was in line with another analysis in US adults which suggested the higher TyG, the higher mortality in males but not females [36]. Consistently, while higher TyG was a risk factor for atherosclerosis in only males in one study [38], some others failed to find a sex-specific association for various cardiovascular events [39, 40]. These variations may be attributed to an insufficient participant pool, underscoring the necessity for more expansive sex-specific studies with a larger participant cohort to precisely elucidate sex-based differences in the clinical implications of the TyG index. However, there is scarce data directly on TyG index and ACM and CVM. Exploring sex-specific association with respect to TyG and mortality is relevant due to the effect of sex on IR and mortality [41, 42].

More extensive observational and interventional studies are required to authenticate the effectiveness of using this index to forecast ACM and CVM in both the general population and diabetic patients. Nevertheless,
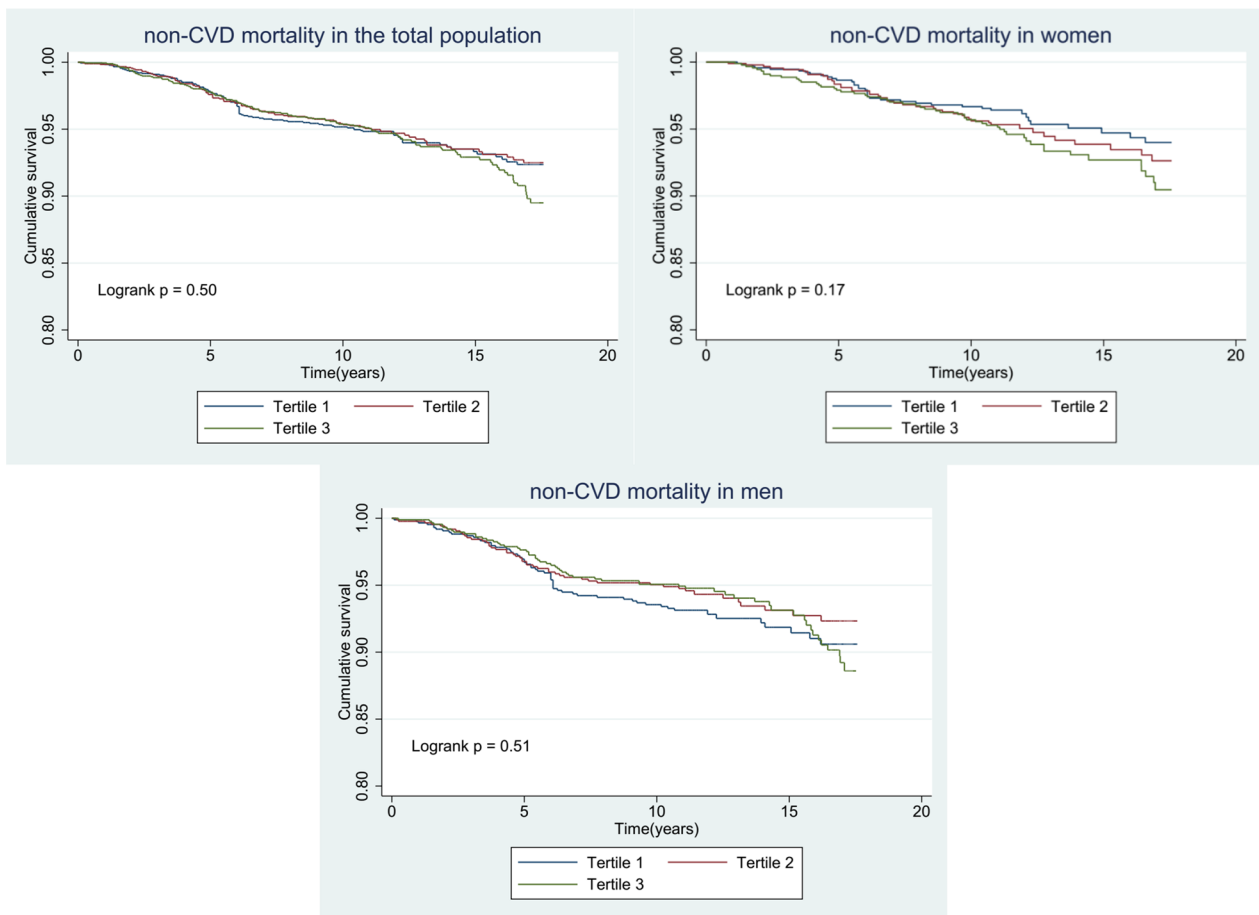
Fig. 4 Kaplan–Meier curves to estimate cumulative hazard for the development of non-cardiovascular mortality by baseline triglyceride glucose index tertiles in **A** Total population, **B** Male, and **C** Female

the mechanism behind predictive value of the TyG index could be elaborated as follows. Firstly, increased mortality may be caused by several metabolic disorders including hyperglycemia, dyslipidemia, and HTN, all of which are strongly associated with a poor prognosis for CVD events [43]. Secondly, IR may be associated with enhanced oxidative stress, inflammatory response, impaired endothelial function, and consequently greater vascular lesion [44]. Moreover, IR and the state of chronic hyperinsulinemia lead to increased sodium retention and sympathetic activity, which in turn raise blood pressure and renal and vascular damage [45]. And lastly, chronic illnesses have been observed to be more prevalent among patients with higher TyG index which can further complicate patients' conditions [32]. Although FPG was a strong predictor of CVM in our analysis, for ACM, its predictive value was considerably affected by adjustment for confounders and therefore TyG might outweigh FPG to predict ACM.

The main strength of our study was that we confirmed that predicting value of high TyG index for mortality from all-cause and CVD in the general Iranian population was dependent on the status of diabetes. Other strengths of our investigation included the large number of people who participated, the prospective design, and the long follow-up period. Another supremacy of our study was that we included participants from both rural and urban areas of Iran and therefore our results can be extrapolated to similar areas in the country. Moreover, as highlighted by previous PURE studies [19, 37], fundamental differences exist between LMIC and high-income countries regarding risk factors for cardiovascular disease outcomes and mortality. This contextual specificity adds a novel dimension to our investigation. Finally, our analysis delves into the sex-specific differences of the TyG index, contributing to the ongoing discourse in the literature. Our study, however, had a number of flaws. The TyG index could not be compared to other IR gold standard

measurements, such as the HOMA-IR and HIEC, duet to the lack of measurements for fasting plasma insulin. Additionally, residual confounding factors might have an impact on the patients' prognosis. Finally, we only measured the baseline TyG index and did not evaluate this index throughout the years and its transition.

In summary, the predicting value of TyG index for ACM and CVM might be mediated by diabetes status. Further comprehensive investigations are imperative to ascertain the precise association of the TyG index with mortality and to delineate whether diabetes plays a mediator role in this relationship. This may be considered a promising aspect of using TyG index in clinical practice. Due to its feasibility, this index has the potential to aid in detecting individuals at increased risk for developing cardiovascular events and mortality early on.

Abbreviations

CVD	Cardiovascular disease
CVM	Cardiovascular mortality
ACM	All-cause mortality
TyG index	Triglyceride glucose index
CAD	Coronary artery disease
PAD	Peripheral artery disease
HIEC	Hyper insulinemic-euglycemic
HOMA-IR	Hemostasis model assessment of insulin resistance
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
DM	Diabetes mellitus
HTN	Hypertension
FPG	Fasting plasma glucose
TG	Triglyceride
HDL-c	High density lipoprotein cholesterol
GDI	Global dietary index

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-024-02148-8.

Additional file 1: Table S1. Multiple-adjusted HRs (and 95% CIs) for triglyceride and fasting blood sugar and all-cause, CVD and non-CVD mortality.

Declaration of generative AI and AI-assisted technologies in the writing process

Following the completion of the manuscript preparation, the authors used chatGPT-3.5 to ensure the grammar and language correctness. The authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Author contributions

FH, GA, and HR conceptualized the study, interpreted the results, and drafted the manuscript. FN, AM, HR and MT managed and analyzed the data. NM, MS, JN, MB, HR, and NS were involved in the study design and data collection. All authors reviewed and approved the final version of the manuscript.

Availability of data and materials

All data generated or analyzed during this study are included in the published article titled, the Isfahan cohort study rationale, methods, and main findings [20].

Declarations

Ethics approval and consent to participate

After being informed about the study's specifics, each participant provided their signed consent. The Declaration of Helsinki's guidelines were followed throughout the investigation. This study was approved by the Ethic Committee of the Research Council of the Isfahan Cardiovascular Research Center, an Isfahan, Iran facility that is a partner facility of the World Health Organization (#1402114).

Consent for publication

Not applicable.

Competing interests

The authors declare that there are no competing interests.

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