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Nonlinear relationship between triglyceride-glucose index and cardiovascular mortality with competing risk analysis on populations aged 18–80 years

Jianchun Yao[3†], Jinping Lu[2†], Linfen Li[1] and Liangping Huang[1*]

Abstract

Background The existing evidence regarding the relationship between the triglyceride-glucose index (TyG index) and cardiovascular mortality risk remains relatively limited and controversial, particularly within the context of competing risk scenarios. This study seeks to investigate this relationship, while further incorporating the impact of non-cardiovascular mortality as a competing risk event to this association.

Methods Data of eligible participants were extracted from National Health and Nutrition Examination Surveys (NHANES) 1999–2018. Traditional Cox proportional hazards regression and Fine-Gray sub-distribution hazard models were applied to assess the TyG index and cardiovascular mortality relationship. Restricted cubic splines were used to estimate possible non-linearity, while segmented regression and log-likelihood ratio tests were used to identify threshold values and model fit.

Results The final analysis compromised a number of 23,800 participants, with a mean age of 47.75 ± 18.06 years, and female prominent (51.72%). After fully adjusted, it revealed a positive relationship between the TyG index and cardiovascular mortality risk (HR = 1.24, 95%CI 1.08–1.41, $P = 0.0017$). Furthermore, upon considering non-cardiovascular mortality as competing risk event, the result of Fine-Gray sub-distribution hazard model analysis attenuated but remained significantly positive (sHR = 1.11, 95%CI 1.11–1.11, $P < 0.0001$). Besides, a non-linear reversed L-shaped relationship was revealed, with a cutoff value determined as 9.4. Below 9.4, the relationship was insignificant (HR = 1.10, 95%CI 0.92–1.31, $P = 0.2866$), whereas beyond 9.4, the relationship became positive (HR = 1.64, 95%CI 1.21, 2.22, $P = 0.0014$), and the log-likelihood ratio test confirmed the threshold effect ($P = 0.049$). Significant interaction was observed in age and body mass index (BMI) subgroups, respectively, with individuals ≤ 65 years and normal BMI category exhibited higher risk in the relationship (P for interaction < 0.05).

Conclusions The present study reveals a robust positive relationship between the TyG index and cardiovascular mortality among individuals aged 18–80 years despite the influence from non-cardiovascular mortality event. Additionally, the relationship was non-linear with the risk intensifying when TyG index beyond a specific threshold. Besides, individuals younger than 65 years old with normal BMI may be more susceptible in this relationship.

[†]Jianchun Yao and Jinping Lu contributed equally to this work and shared first authorship.

*Correspondence:
Liangping Huang
Liangping83447@163.com
Full list of author information is available at the end of the article

Clinical trial number Not applicable.

Keywords TyG index, Cardiovascular mortality, Nonlinear relationship, Competing risk model, NHANES

Background

Cardiovascular mortality continues to pose a significant public health challenge worldwide. According to the Global Burden of Disease (GBD) Study, the number of deaths due to cardiovascular diseases (CVDs) has increased consistently over time, from 12.1 million in 1990 to 18.6 million in 2019 [1]. This highlights the urgent need for reliable predictors that can facilitate early detection and effective intervention strategies [1].

Among the various biomarkers under investigation, the biomarkers of insulin resistance, a condition closely associated with incidence of CVDs [2, 3] and risk of mortality [4, 5] has emerged as one of the hot spots. As one of the indicators for insulin resistance, the triglyceride-glucose index (TyG index) has become one of the promising candidate in this realm for its low-cost and easily accessibility. Besides, studies have shown the TyG index has better performance in predicting metobolic syndromes (Mets) than traditional homeostasis model assessment (HOMA) [6, 7]. The TyG index is calculated from fasting triglycerides and fasting plasma glucose, and reflects both lipid and glucose metabolic disorder, and thus represents the joint effects of hyperglycemia and dyslipidemia [8]. Elevated TyG index levels have been consistently linked to an increased risk of cardiovascular events and mortality across diverse populations, including both diabetic and non-diabetic cohorts [9–11].

Despite a growing body of research that supports the TyG index as a potential prognostic marker, the existing evidence regarding its relationship with cardiovascular mortality risk remains relatively limited and controversial. For instance, the result of a meta-analysis involving 12 cohort studies with altogether 6,354,990 participants showed that a higher TyG index was associated with an increased incidence of CVDs, but not significantly associated with risk of cardiovascular mortality [12]. On the contrary, the pooled results of another meta-analysis showed that the TyG index was positively associated with an increased incidence of major adverse cardiovascular events (MACE) and cardiac-specific death [13]. Thus, the complexity of cardiovascular mortality necessitates further investigations to address this conflicting evidence by exploring non-linear relationships. Besides, considering the fact that some individuals may be censored due to non-cardiovascular mortality, such as asthma, infection, cancer, etc., the estimated cardiovascular mortality risk may be confounded by the presence of non-cardiovascular mortality.

The traditional Cox proportional hazards model is a widely statistical tool in survival analysis, valued for its flexibility and ability to handle censored data. However, it has challenges in managing competing risks, which may apply underestimation or overestimation of the risk of a specific. The Fine-Gray sub-distribution hazard model [14] was developed to address this issue by effectively incorporating competing risks and estimating sub-distribution hazard ratios (sHR), enabling a more accurate risk assessment for cardiovascular cause and other causes. As of now, a growing body of research has utilized the Fine-Gray model to analyze estimates of the event of interest by incorporating competing events [15–17]. Nevertheless, the integration of competing risks in the assessment of cardiovascular mortality risk related to the TyG index has not been sufficiently investigated.

Therefore, this study seeks to examine the association of TyG index and cardiovascular mortality risk among US adults aged 18–80 years from the National Health and Nutrition Examination Surveys (NHANES) 1999–2018 cycles, through combining Cox proportional hazards model and competing risk model. This approach will enhance the scientific understanding of the relationship between the TyG index and cardiovascular mortality risk, and offer valuable insights for clinical management.

Methods

Study design and participants

This is a longitudinal cohort study using data from ten cycles of NHANES, spanning from 1999 to 2018. NHANES is a publicly available database (https://wwwn.cdc.gov/nchs/nhanes/Default.aspx). It contains data from a programme that is comprehensively designed to collect health data from representative U.S. population. According to the statements (https://www.cdc.gov/nchs/nhanes/irba98.htm), NHANES have received ethical approval from the Institutional Review Board of the National Center for Health Statistics, and all participants' written informed consents.

A total of 101,316 individuals took part in the NHANES survey from 1999 to 2018. The exclusion criteria was as follows: (i) Participants' age not within 18–80 years at baseline (N = 45,832); (ii) Participants without fasting triglyceride value (N = 5,919); (iii) Participants without fasting plasma glucose value (N = 25,531); (iii) Participants without mortality status record (N = 41); (iv) Participants' follow-up duration < 12 months (N = 193). Ultimately, a number of 23,800 participants was included in final

analysis (Fig. 1). In addition, the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines was adopted during our analysis [18].

Assessment of cardiovascular mortality

The outcome of the present study was cardiovascular mortality. Mortality status was determined using the NHANES publicly linked mortality file, updated through December 31, 2019, which is in combination with the National Death Index (NDI) providing by the National Center for Health Statistics (NCHS). This was achieved through a probability matching algorithm [19, 20]. The cause of death was classified based on the 10 th Revision of International Statistical Classification of Diseases (ICD- 10). Cardiovascular mortality was defined as death resulting from cardiac diseases (I00-I09, I11, I13, I20-I51) or cerebrovascular diseases (I60-I69).

Assessment of TyG

The exposure factor in present study was the TyG index. The TyG index was calculated by utilizing formula [8]:

$$TyG = Ln[\text{fasting triglycerides (mg/dL)} \times \text{fasting glucose (mg/dL)}/2].$$

During statistical analysis, the TyG index was treated as a continuous variable, as well as quartile categories for subgroup evaluation.

Covariates

The covariates were chosen on the basis of previous research that identifies risk factors for cardiovascular mortality, consisting age, gender, race/ethnicity, body mass index (BMI), estimated glomerular filtration rate (eGFR), educational level, poverty to income ratio (PIR), smoking status, drinking status, low-density lipoprotein cholesterol (LDL), C-reactive protein, lipid-lowering medications, anti-diabetic medications, and self-reported history of diabetes.

The educational level was classified as: below high school, high school, and above high school. PIR was categorized into three groups: <1.3, 1.3–1.85, and >1.85, with lower PIR values indicating a higher likelihood of poverty. Smoking status was generated by two questionnaires: SMQ020"Smoked at least 100 cigarettes in life?", and SMQ040"Do you now smoke cigarettes"(SMQ040), and classified as: never, former, and current. Drinking status was derived from questionnaires: ALQ101"Had at least 12 alcohol drinks/1 yr", and classified into two groups based on whether annual consumption of at least 12 alcohol drinks or not, in which one alcohol drink represents 12 oz of beer, 5 oz of wine, or 1.5 oz of liquor. The usage of lipid-lowering medications was derived from questionnaires: BPQ090D "Told to take prescriptn for cholesterol", and BPQ100D "Now taking prescribed medicine". The usage of anti-diabetic medications was derived from questionnaires: DIQ050 "Taking insulin now", and DIQ070 "Take diabetic pills to lower blood sugar". Self-reported diabetes was derived from DIQ010 questionnaire. The eGFR was measured by adopting the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [21].

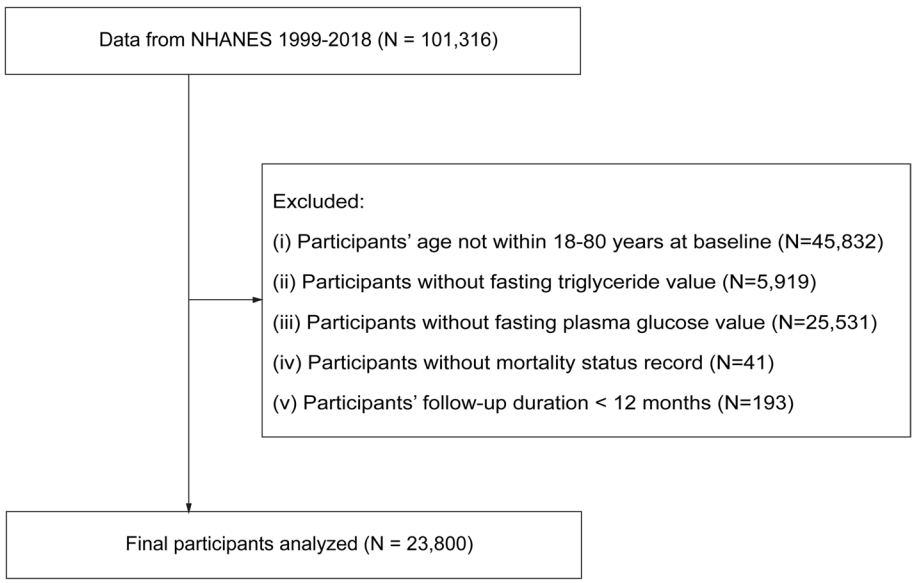

Fig. 1 The inclusion of study participants

Statistical analysis

All statistical analyses were conducted to evaluate the association between the TyG index and cardiovascular mortality. Continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were presented as frequencies and percentages. Differences in baseline characteristics and follow-up outcomes across TyG index quartiles were assessed using one-way analysis of variance (ANOVA) for continuous variables and the chi-square test for categorical variables.

The primary outcome of interest was cardiovascular mortality, and non-cardiovascular mortality was treated as a competing risk in certain analyses. Multivariate Cox proportional hazards regression models were constructed to evaluate the association between the TyG index (as both a continuous variable and in quartiles) and cardiovascular mortality. Hazard ratios (HRs) and their 95% confidence intervals (CIs) were calculated. Four models were applied: (i) a non-adjusted model; (ii) Adjust I, adjusted for gender, age, and race/ethnicity; (iii) Adjust II, further adjusted for BMI and eGFR; and (iv) Adjust III, adjusted for gender, age, race/ethnicity, BMI, eGFR, education, smoking status, drinking status, LDL, diabetes, taking lipid-lowering medications, and taking antidiabetic medications.

The cumulative mortality functions were calculated to estimate the probability of experiencing a cardiovascular-specific death when competing risks were present between the two groups. To account for competing risks, competing risk analysis based on the Fine-Gray sub-distribution hazard model [22, 23] was applied, with non-cardiovascular mortality treated as a competing risk. Sub-distribution hazard ratios (sHRs) and their 95% CIs were calculated for the TyG index in both continuous and quartile forms. Same adjustment strategies using in the Cox models (non-adjusted, Adjust I, Adjust II, and Adjust III) were applied in the competing risk models.

To address non-linear relationship and threshold effect, restricted cubic splines and segmented Cox proportional hazards regression model was conducted using adjust III strategy. The inflection point (K) of the TyG index was determined using a log-likelihood ratio test to compare the one-line and two-line models.

To examine the robustness of the results, sensitivity analyses were conducted. The utilization of dummy variables served to denote absent covariate values, which was executed in instances where continuous variables were lacking in more than 1% of their values [24]. Stratified analyses were performed to examine the association between the TyG index and cardiovascular mortality in predefined subgroups, including age (≤ 65 years and > 65 years), gender, race/ethnicity, BMI categories (≤ 18.5, 18.5–25, > 25 kg/m^2), and diabetes status. The models incorporated interaction terms to assess the potential for effect modification, with the *P* values for these interactions being documented. The Adjust III adjusting strategy were applied, while in each subgroup analysis, the stratification variable was excluded from the adjustment.

All statistical analyses were performed using R software (version 4.2.0) and Empower Stats (www.empowerstats.com; X&Y Solutions, Inc., Boston, MA). A two-sided *P* value < 0.05 was considered statistically significant.

Results

Baseline characteristics and follow-up mortality status of study participants

As shown in Table 1, a total of 23,800 participants were enrolled in the baseline of the study. Following a mean follow-up duration of 119.46 ± 66.45 months, 910 deaths (3.82%) were attributed to cardiovascular related causes and 2,070 (8.70%) to non-cardiovascular related causes. Stratified by TyG index quartiles (Q1-Q4), it revealed significant differences across multiple variables (all $P < 0.001$ except drinking status). Participants among the higher TyG quartiles (Q3 and Q4) were older, had higher BMI, glycohemoglobin levels, total cholesterol, LDL, and C-reactive protein, but lower eGFR with comparison to those among the lower quartiles (Q1 and Q2). The proportion of male increased progressively across quartiles, with Q4 having the highest percentage (54.58%). Racial distribution showed a higher prevalence of Mexican ethnicity in Q4, while Black participants were more concentrated in Q1. Education level and family PIR also varied, with a greater proportion of participants below high school education and lower family PIR in Q4. Smoking status showed a higher prevalence of current smokers in Q4, while never smokers were more common in Q1. The prevalence of comorbidities, including stroke, heart attack, and diabetes, increased significantly from Q1 to Q4. Mortality analysis indicated that participants in Q4 had the highest rates of both non-cardiovascular death (11.65%) and cardiovascular death (5.81%), while those in Q1 had the lowest (5.00% and 1.90%, respectively).

Association of the TyG index and cardiovascular mortality

As illustrated in Table 2, when the TyG index was treated as a continuous variable, it exhibited a significantly positive correlation with the risk of cardiovascular mortality in the non-adjusted model (HR = 1.79, 95% CI 1.65–1.94, $P < 0.0001$). After adjusting for gender, age, and race/ethnicity (Adjust I), the association remained significant but attenuated (HR = 1.42, 95% CI 1.29–1.56, $P < 0.0001$). Further adjustment for BMI and eGFR (Adjust II) slightly strengthened the association (HR = 1.51, 95% CI 1.34–1.70, $P < 0.0001$). In the fully adjusted model (Adjust III), additionally adjusting for education, smoking, drinking,

Table 1 Baseline characteristics and follow-up mortality status of participants

	Total	TyG quartile				
		Q1 (5.85–8.16)	Q2 (8.16–8.59)	Q3 (8.59–9.04)	Q4 (9.05–13.35)	*P* value
N	23,800	5,940	5,951	5,953	5,956	
Age, years	47.75 ± 18.06	39.86 ± 17.00	47.54 ± 18.32	50.64 ± 17.73	52.95 ± 16.38	< 0.001
Follow-up duration, Person-Months	119.46 ± 66.45	125.33 ± 65.90	119.22 ± 66.60	118.08 ± 66.80	115.22 ± 66.10	< 0.001
BMI (kg/m^2)	28.87 ± 6.81	26.23 ± 6.29	28.24 ± 6.66	29.76 ± 6.74	31.24 ± 6.49	< 0.001
Glycohemoglobin (%)	5.69 ± 1.08	5.31 ± 0.46	5.47 ± 0.58	5.64 ± 0.75	6.36 ± 1.70	< 0.001
eGFR (mL/min/1.73 m^2)	96.96 ± 30.83	101.33 ± 28.46	96.08 ± 30.08	95.40 ± 31.07	95.00 ± 33.13	< 0.001
Total cholesterol (mg/dL)	194.21 ± 42.58	175.32 ± 34.88	190.19 ± 37.76	199.71 ± 40.49	211.57 ± 47.59	< 0.001
LDL (mg/dL)	114.72 ± 35.82	101.64 ± 29.77	115.47 ± 33.61	121.89 ± 36.29	120.40 ± 39.66	< 0.001
C-reactive protein (mg/L)	0.45 ± 0.82	0.32 ± 0.76	0.45 ± 0.93	0.51 ± 0.90	0.52 ± 0.65	< 0.001
Gender (%)						< 0.001
Male	11,491 (48.28%)	2,403 (40.45%)	2,834 (47.62%)	3,003 (50.45%)	3,251 (54.58%)	
Female	12,309 (51.72%)	3,537 (59.55%)	3,117 (52.38%)	2,950 (49.55%)	2,705 (45.42%)	
Race/ethnicity (%)						< 0.001
Mexican	4,418 (18.56%)	795 (13.38%)	1,016 (17.07%)	1,194 (20.06%)	1,413 (23.72%)	
White	10,268 (43.14%)	2,255 (37.96%)	2,564 (43.09%)	2,721 (45.71%)	2,728 (45.80%)	
Black	4,874 (20.48%)	1,936 (32.59%)	1,342 (22.55%)	905 (15.20%)	691 (11.60%)	
Other	4,240 (17.82%)	954 (16.06%)	1,029 (17.29%)	1,133 (19.03%)	1,124 (18.87%)	
Education (%)						< 0.001
Below high school	6,449 (27.13%)	1,237 (20.84%)	1,530 (25.73%)	1,724 (29.00%)	1,958 (32.94%)	
High school	5,549 (23.34%)	1,329 (22.39%)	1,397 (23.49%)	1,395 (23.47%)	1,428 (24.02%)	
Above high school	11,774 (49.53%)	3,369 (56.76%)	3,020 (50.78%)	2,826 (47.54%)	2,559 (43.04%)	
Family PIR categorical (%)						< 0.001
< = 1.3	6,851 (31.56%)	1,667 (30.62%)	1,654 (30.45%)	1,700 (31.18%)	1,830 (34.01%)	
> 1.3, < = 1.85	2,895 (13.34%)	684 (12.56%)	728 (13.40%)	757 (13.88%)	726 (13.49%)	
> 1.85	1,1963 (55.11%)	3,094 (56.82%)	3,049 (56.14%)	2,996 (54.94%)	2,824 (52.49%)	
Smoking status (%)						< 0.001
Never	12,511 (54.24%)	3,478 (62.71%)	3,187 (55.18%)	3,017 (51.60%)	2,829 (47.97%)	
Former	5,701 (24.72%)	1,028 (18.54%)	1,339 (23.18%)	1,585 (27.11%)	1,749 (29.66%)	
Current	4,854 (21.04%)	1,040 (18.75%)	1,250 (21.64%)	1,245 (21.29%)	1,319 (22.37%)	
Drinking status (%)						0.271
Yes	10,866 (71.04%)	2,719 (71.84%)	2,767 (71.65%)	2,701 (70.58%)	2,679 (70.09%)	
No	4,430 (28.96%)	1,066 (28.16%)	1,095 (28.35%)	1,126 (29.42%)	1,143 (29.91%)	
Diabetes (%)						< 0.001
Yes	3,195 (13.43%)	235 (3.96%)	445 (7.48%)	747 (12.55%)	1,768 (29.71%)	
No	20,590 (86.57%)	5,701 (96.04%)	5,503 (92.52%)	5,203 (87.45%)	4,183 (70.29%)	
Taking lipid-lowering medications (%)						0.079
Yes	3,899 (78.48%)	410 (81.35%)	823 (80.21%)	1,081 (78.28%)	1,585 (77.05%)	
No	1,069 (21.52%)	94 (18.65%)	203 (19.79%)	300 (21.72%)	472 (22.95%)	
Taking anti-diabetic medications [a] (%)						< 0.001
Yes	2,506 (10.79%)	151 (2.62%)	307 (5.29%)	578 (9.96%)	1,470 (25.08%)	
No	20,720 (89.21%)	5,612 (97.38%)	5,491 (94.71%)	5,225 (90.04%)	4,392 (74.92%)	
Mortality status (%)						< 0.001
Alive	20,820 (87.48%)	5,530 (93.10%)	5,240 (88.05%)	5,134 (86.24%)	4,916 (82.54%)	
Non-cardiovascular cause of death	2,070 (8.70%)	297 (5.00%)	507 (8.52%)	572 (9.61%)	694 (11.65%)	
Cardiovascular cause of death	910 (3.82%)	113 (1.90%)	204 (3.43%)	247 (4.15%)	346 (5.81%)	

Abbreviation: *TyG* triglyceride to glucose index; *BMI* body mass index; *eGFR* estimated glomerular filtration rate; *LDL* low-density lipoprotein; *PIR* poverty to income ratio

[a] Anti-diabetic medications include insulin, and diabetic pills

Among the 23,800 participants, the number of missing values for the covariates were 322 (1.35%) for BMI, 41 (0.17%) for glycohemoglobin, 2293 (9.63%) for eGFR, 1037 (4.36%) for total cholesterol, 15 (0.06%) for LDL, 9887 (41.54%) for C-reactive protein, 28 (0.12%) for education, 2,091 (8.79%) for PIR, 734 (3.08%) for smoking, 8,504 (35.73%) for drinking, 18,832 (79.13%) for taking lipid-lowering medications, 574 (2.41%) for taking anti-diabetic medications, and 15 (0.06%) for diabetes

Table 2 The association between TyG index and cardiovascular mortality

	Non-adjusted HR (95%CI) *P* value	Adjust I HR (95%CI) *P* value	Adjust II HR (95%CI) *P* value	Adjust III HR (95%CI) *P* value
TyG continuous	1.79 (1.65, 1.94) < 0.0001	1.42 (1.29, 1.56) < 0.0001	1.51 (1.34, 1.70) < 0.0001	1.24 (1.08, 1.41) 0.0017
TyG quartile				
Q1	1.0	1.0	1.0	1.0
Q2	1.98 (1.57, 2.49) < 0.0001	1.09 (0.86, 1.37) 0.4754	1.13 (0.87, 1.48) 0.3488	1.09 (0.84, 1.43) 0.5093
Q3	2.45 (1.96, 3.07) < 0.0001	1.20 (0.96, 1.50) 0.1167	1.29 (0.99, 1.67) 0.0549	1.20 (0.92, 1.56) 0.1732
Q4	3.64 (2.94, 4.50) < 0.0001	1.57 (1.27, 1.96) < 0.0001	1.63 (1.26, 2.11) 0.0002	1.27 (0.97, 1.66) 0.0831
P for trend	< 0.0001	< 0.0001	< 0.0001	0.0533

Non-adjusted model adjusted for: None

Adjust I model adjusted for: Gender; Age; Race/ethnicity

Adjust II model adjusted for: Gender; Age; Race/ethnicity; BMI; eGFR

Adjust III model adjusted for: Gender; Age; Race/ethnicity; BMI; eGFR; Education; Smoking; Drinking; LDL; Diabetes; Taking lipid-lowering medications; Taking anti-diabetic medications

Abbreviation: *TyG* triglyceride to glucose index; *HR* hazard ratios, *CI* confidence interval; *Q* quartile; *BMI* body mass index; *eGFR* estimated glomerular filtration rate; *LDL* low-density lipoprotein

LDL, diabetes, taking lipid-lowering medications, and taking anti-diabetic medications, the risk weaken but remained significant (HR = 1.24, 95% CI 1.08–1.41, P= 0.0017), indicating that for every one increment of the TyG index, the risk of cardiovascular mortality increased by 24%.

Upon analysis of the TyG index using quartiles, a robust dose–response correlation was evident in the non-adjusted, adjusted I, and adjusted II models. The elevated quartiles exhibited a marked increase in cardiovascular mortality risk (P for trend < 0.0001). Moreover, the associations in the Q4 for each model were consistently significant (all P< 0.05). However, in the fully adjusted model (Adjust III), the association in the Q4 was attenuated with marginally statistical significance (HR = 1.27, 95% CI 0.97–1.66, P= 0.0831), and the trend across quartiles remained significant (P for trend = 0.0533). This finding indicates the presence of a probable non-linear relationship between the TyG index and cardiovascular mortality.

Competing risk analysis of the TyG index on cardiovascular and non-cardiovascular mortality

Figure 2 and Table 3 displays the competing risk analysis of the TyG index on cardiovascular and non-cardiovascular mortality. The cumulative incidence of cardiovascular mortality and non-cardiovascular mortality across quartiles (Q1–Q4) of TyG index over the follow-up period was shown in Fig. 2. Higher TyG levels (Q3 and Q4) were associated with a greater cumulative incidence of both cardiovascular mortality and non-cardiovascular mortality, as indicated by the steeper slopes for Q3 and Q4 compared to Q1 and Q2. Over time, particularly after following-up for approximately 150 months, the cumulative incidence of non-cardiovascular death surpasses that of cardiovascular death across all TyG quartiles. This underlined the TyG index is a potential risk predictor for cardiovascular mortality in the context of competing non-cardiovascular death risks.

Additionally, the sHR for cardiovascular was presented in Table 3. After fully adjusted (Adjust III), the TyG index was positively and significantly associated with cardiovascular (sHR = 1.11, 95%CI 1.11–1.11, P< 0.0001). This indicated that considering the presence of non-cardiovascular mortality, the positive association of cardiovascular mortality risk linked to the TyG index remained significant. Besides, comparing to the Q1 group, cardiovascular mortality risk increased across the Q3 and Q4 groups albeit without statistical significance, but the trend was significant (P for trend < 0.001) independent of non-cardiovascular mortality influence.

Nonlinear association of TyG index and cardiovascular mortality

Figure 3 and Table 4 demonstrate the non-linear relationship and threshold effect between the TyG index and cardiovascular mortality. As shown in Fig. 3, the fully-adjusted Cox proportional hazards model with restricted cubic splines analysis fitted a reversed L-shape curve between the TyG index and the log-relative risk (log RR) of cardiovascular mortality, suggesting a threshold effect. Additionally, the segmented Cox regression revealed a potential threshold effect with an inflection point (K) of the TyG index at 9.4. Below 9.4,

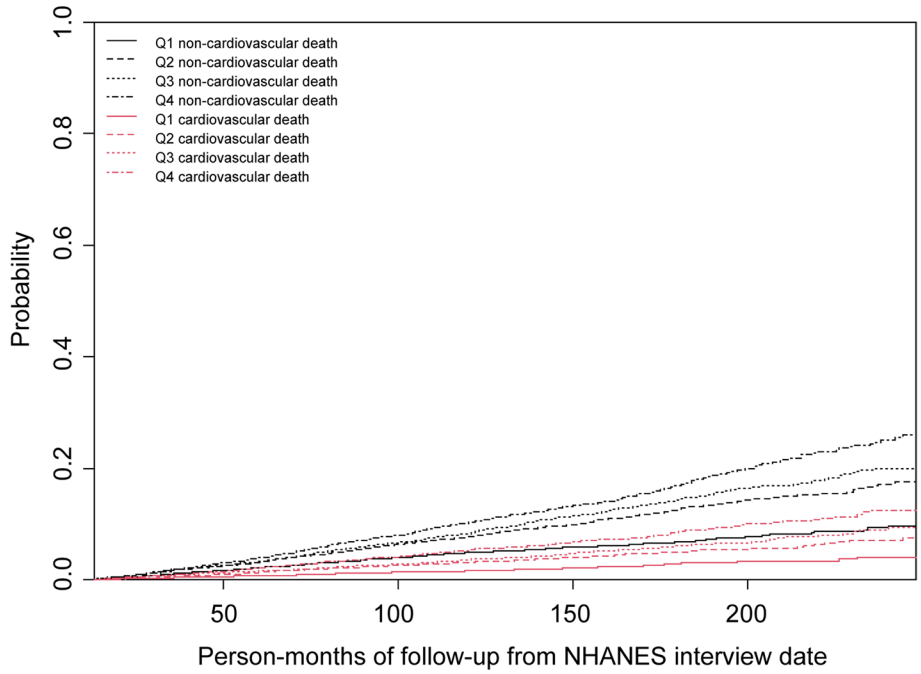

Fig. 2 Cumulative incidence of cardiovascular mortality and non- cardiovascular mortality across quartiles (Q1–Q4) of the TyG index. Higher TyG levels (Q3 and Q4) were associated with a greater cumulative incidence of cardiovascular mortality, as indicated by the steeper slopes for Q3 and Q4 compared to Q1 and Q2. Over time, particularly after following-up for approximately 150 months, the cumulative incidence of non-cardiovascular death surpasses that of cardiovascular death across all TyG quartiles, underlining the importance of TyG as a potential risk predictor for cardiovascular mortality in the context of competing death risks

Table 3 The association between TyG index and cardiovascular mortality with competing risk from non-cardiovascular mortality

	Non-adjusted sHR (95%CI) *P* value	Adjust I sHR (95%CI) *P* value	Adjust II sHR (95%CI) *P* value	Adjust III sHR (95%CI) *P* value
TyG index continuous	1.56 (1.43,1.70) < 0.0001	1.28 (1.14, 1.45) < 0.0001	1.13 (1.02, 1.26) 0.0223	1.11 (1.11, 1.11) < 0.0001
TyG index quartile				
Q1	1.0	1.0	1.0	1.0
Q2	1.81 (1.44, 2.28) < 0.0001	1.02 (0.78, 1.32) 0.8866	1.00 (0.76, 1.32) 0.9809	1.14 (1.14, 1.14) < 0.0001
Q3	2.21 (1.76, 2.76) < 0.0001	1.08 (0.82, 1.41) 0.5770	1.01 (0.76, 1.32) 0.9685	1.15 (1.15, 1.15) < 0.0001
Q4	3.14 (2.55, 3.87) < 0.0001	1.32 (1.03, 1.71) 0.0309	1.19 (0.92, 1.55) 0.1861	1.29 (1.29, 1.29) < 0.0001
P for trend	< 0.0001	< 0.0001	< 0.0001	< 0.0001

Non-adjusted model adjusted for: None

Adjust I model adjusted for: Gender; Age; Race/ethnicity

Adjust II model adjusted for: Gender; Age; Race/ethnicity; BMI; eGFR

Adjust III model adjusted for: Gender; Age; Race/ethnicity; BMI; eGFR; Education; Smoking; Drinking; LDL; Diabetes; Taking lipid-lowering medications; Taking anti-diabetic medications

Abbreviation: *TyG* triglyceride to glucose index; *sHR* sub-distribution hazard ratios, *CI* confidence interval; *Q* quartile; *BMI* body mass index; *eGFR* estimated glomerular filtration rate; *LDL* low-density lipoprotein

the association was non-significant (HR = 1.10, 95% CI 0.92–1.31, $P = 0.2866$); whereas above 9.4, the risk of cardiovascular mortality accelerated significantly (HR = 1.64, 95%CI 1.21–2.22, $P = 0.0014$). The result of log-likelihood ratio test confirmed the non-linear dose-dependent manner better fit the relationship, by comparing the standard Cox regression and segmented Cox regression models ($P = 0.049$).

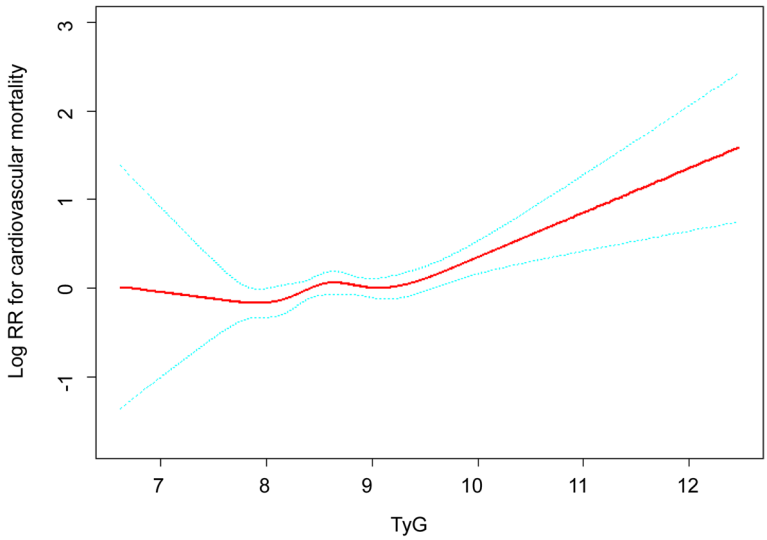

Fig. 3 The association between the TyG index and log-relative risk (log RR) of cardiovascular mortality. The red line represents the estimated log RR of cardiovascular mortality, and the blue dashed lines show the 95% confidence intervals. A non-linear reversed L-shape relationship is observed, with stable log RR at TyG levels of 7 to 9 and a progressive increase beyond 9, indicating higher cardiovascular mortality risk

Table 4 Threshold effect analysis of TyG index on cardiovascular mortality

	HR(95% CI) *P* value
Fitting model by standard Cox regression	1.24 (1.08, 1.41) 0.0017
Fitting model by two-piecewise Cox regression	
Inflection point (K) of TyG index	9.4
< K	1.10 (0.92, 1.31) 0.2866
> K	1.64 (1.21, 2.22) 0.0014
P for log-likelihood ratio test	0.049

Adjusted for: Gender; Age; Race/ethnicity; BMI; eGFR; Education; Smoking; Drinking; LDL; Diabetes; Taking lipid-lowering medications; Taking anti-diabetic medications

Abbreviation: *TyG* triglyceride to glucose index; *HR* hazard ratios, *CI* confidence interval; *BMI* body mass index; *eGFR* estimated glomerular filtration rate; *LDL* low-density lipoprotein

Stratified associations of TyG index and cardiovascular mortality risk in exploratory subgroups

Table 5 explores the stratified associations of the TyG index and cardiovascular mortality risk across various subgroups. All models were adopted the adjust III strategy in the Cox regression model (see Table 2), and the stratification variable were excluded in the adjustment for each subgroup. Significant interaction was observed between TyG index and age (*P* for interaction = 0.0048), race/ethnicity (*P* for interaction = 0.0445), and BMI categorical (*P* for interaction = 0.0144). Specifically, for age, higher risk of cardiovascular mortality was observed in participants aged ≤65 years (HR = 1.87, 95%CI 1.58–2.21, *P* < 0.0001), while no significant association was found in those aged >65 years (HR = 0.93, 95%CI 0.79–1.10, *P* = 0.4073). For Race/ethnicity, the association was significant in Black participants (HR = 1.49, 95%CI 1.19–1.86, *P* = 0.0006) and Mexican participants (HR = 1.40, 95%CI 1.08–1.81, *P* = 0.0111), but the association was not significant in White (HR = 1.05, 95% CI 0.88–1.25, *P* = 0.6001) or Other participants (HR = 1.38, 95%CI 0.92–2.07, *P* = 0.1185). For BMI status, the strongest effect was observed in individuals with normal BMI (HR = 1.75, 95%CI 1.37–2.24, *P* < 0.0001), and a weaker but significant association in those overweight or obesese (BMI > 25 $kg/m^{2)}$ (HR = 1.18, 95%CI 1.02–1.37, *P* = 0.0240), but no significant association in participants underweight (BMI ≤18.5 $kg/m^{2)}$ (HR = 0.73, 95%CI 0.20–2.69, *P* = 0.6362). On the other hand, the risk was consistent in both genders and diabetes status, but no significant modification was observed in these subgroups (*P* for interaction = 0.9198 for gender and 0.4779 for diabetes status).

Discussion

The present study investigated the association of the TyG index and cardiovascular mortality, incorporating the consideration of competing risk from non-cardiovascular mortality with the employment of advanced statistical techniques. Upon analysis on 23,800 U.S. adults aged 18–80 years enrolling from NHANES 1999–2018 datasets, the results demonstrated a significant positive relationship between the TyG index and cardiovascular mortality risk after applying various adjusting strategies for potential confounding variate. This relationship

Table 5 Stratified associations between TyG index and cardiovascular mortality risk in exploratory subgroups

	N	HR, 95%CI, *P* value	*P* for interaction
Age (years) categorical			
< = 65	19,000	1.87 (1.58, 2.21) < 0.0001	0.0048
> 65	4800	0.93 (0.79, 1.10) 0.4073	
Gender			0.9198
Male	11,491	1.23 (1.05, 1.44) 0.0103	
Female	12,309	1.25 (1.03, 1.50) 0.0224	
Race/ethnicity			0.0445
Mexican	4418	1.40 (1.08, 1.81) 0.0111	
White	10,268	1.05 (0.88, 1.25) 0.6001	
Black	4874	1.49 (1.19, 1.86) 0.0006	
Other	4240	1.38 (0.92, 2.07) 0.1185	
BMI (kg/m^2) categorical			0.0144
< = 18.5	414	0.73 (0.20, 2.69) 0.6362	
> 18.5, < = 25	6830	1.75 (1.37, 2.24) < 0.0001	
> 25	16,234	1.18 (1.02, 1.37) 0.0240	
Diabetes			0.4779
Yes	3195	1.30 (1.08, 1.58) 0.0068	
No	20,590	1.20 (1.01, 1.41) 0.0358	

The model was adjusted for: Gender; Age; Race/ethnicity; BMI; eGFR; Education; Smoking; Drinking; LDL; Diabetes; Taking lipid-lowering medications; Taking anti-diabetic medications. In each subgroup, the model was not adjusted for the stratification variable

Abbreviation: *TyG* triglyceride to glucose index; *HR* hazard ratios, *CI* confidence interval; *BMI* body mass index; *eGFR* estimated glomerular filtration rate; *LDL* low-density lipoprotein

remained robustly positive even after accounting for the competing risk from non-cardiovascular mortality utilizing Fine-Gray models. Additionally, a remarkable reversed L-shaped association between the TyG index and cardiovascular mortality risk was identified, with a threshold value of 9.4. Specifically, the risk was insignificant below 9.4, while significantly accelerated beyond 9.4. Moreover, the effect was modified by some demographic and lifestyle factors, such as age, race/ethnicity, and BMI status.

Competing risks are a frequent challenge in traditional survival analyses, especially when dealing with irreversible events such as death. Conventionally, Cox regression models are based on the assumption that the observation period is long enough for the individual under scrutiny to eventually experience the event of interest, while ignoring the likelihood that a competing event occurs in the first place. Therefore, in the context of survival analysis, Cox regression models primarily focus on a single event, such as cardiovascular-specific mortality. However, when assessing the mortality risks arising from other causes (such as asthma, infection, malignancy, accident, etc.), they do not adequately account for the influence of competing events. This may result in an overestimation or underestimation of the risk of the event of interest. This issue is addressed by the Fine-Gray sub-distribution hazard model using cumulative incidence functions (CIFs), which takes into account the effect of the competing event on the likelihood of the main event, thus improving the precision of the estimated risk.

In our study, the cardiovascular death risk was estimated using the Cox proportional hazard models and Fine-Gray sub-distribution hazard models. In Cox model, after adjusting for gender, age, race/ethnicity, BMI, and eGFR in Adjust II, the HR of TyG linked cardiovascular mortality risk was 1.51 (95%CI 1.34, 1.70), while with considering competing event of non-cardiovascular mortality, the sHR was 1.13 (95%CI 1.02–1.26). After fully adjusted (Adjust III), the HR was 1.24 in Cox model, which indicates that with one increment of the TyG index, the cardiovascular mortality risk increases 24%. In contrast, with further consideration of competing event in Fine-Gray model, the sHR was 1.11, which indicates that considering the influence of non-cardiovascular mortality event, with every one increment of the TyG index, the cardiovascular mortality risk increases by 11%. This suggests that by incorporating competing event, the Fine-Gray model provides a more conservative risk estimate (sHR = 1.11) comparing to the traditional Cox model (HR = 1.24), and the impact of competing event somewhat weakens the effect of the exposure on the event, indicating traditional Cox model may slightly overestimate the risk. Nevertheless, despite the impact of non-cardiovascular mortality event, the positive relationship between the TyG index and cardiovascular mortality risk remains robust. Moreover, the finding of our study is supported by published literature. For incidence, Lee J et al. [25] performed analysis in a cohort of 233,546 adults aged ≥ 19 years from the Korea National Health Insurance Service-National Sample, and discovered that a rising trajectory of TyG index from baseline to follow-up independently correlates with increased cardiovascular mortality risks after accounting for non-cardiovascular causes of death. Hei J et al. [26] included 5,559 adult participants with arthritis from the 1999–2018 NHANES, and reported that in comparison to the lowest TyG index

quartile, higher TyG index quartiles were significantly and positively associated with cardiovascular mortality risk using Fine-Gray model to address competing risk effect from non-cardiovascular mortality. Taken together, accounting for competing risks from cause-specific mortality through competing risk analysis offers advanced evidence in the literature, highlighting that the TyG index is a valuable predictor for assessing cardiovascular mortality risk.

Moreover, we demonstrated a non-linear relationship between the two variables in a reverse L-shape manner with a inflecting point at 9.4. This finding is inline with current literature. For incidence, Liu X et al. [27], in an analysis on 19,420 individuals from NHANES 1999–2014 with an average followed-up period of 98.2 months, presented that the relationship between TyG index and cardiovascular mortality was non-linear inflecting at TyG = 9.52. Beyond 9.52, the risk of cardiovascular cause of death increased dramatically by 1.35 times (HR = 2.35), while below the threshold, the relationship was insignificant [27]. Feng X et al. [28] demonstrated a reverse L-shape relationship with cutting value at 9.37 by studying 3,349 diabetes mellitus patients from the 1999–2014 NHANES during 82 months follow-up. In addition, not only the reserve L-shape correlation manner was observed in diabetes mellitus population [28], or general participants [27], it was also reported in patients with arthritis [26], metabolic dysfunction-associated steatotic liver disease (MASLD) [29], and cardiometabolic syndrome [11]. Altogether, these findings reveals that the reverse L-shape relationship between the TyG index and cardiovascular mortality may persist consistently across various populations. This offers a vital foundation and cost-effective tool for early screening and risk stratification in cardiovascular prevention. Additionally, it supports clinical decision-making and health education by enhancing awareness and encouraging healthier behaviors to reduce risks. Also, it serves the exploration of therapeutic targets and interventions, such as anti-inflammatory or antioxidant strategies triggered by insulin resistance.

However, some inconsistent results have been reported. For incidence, Chen J et al. [5] included 20,194 participants from NHANES 2009–2018 with 105 months follow-up duration in the analysis and found that the TyG index showed a U-shape relationship with cardiovascular mortality with the lowest risk being TyG index at 8.975 (non-linear P = 0.034), which means both lower and higher TyG levels possess hazardous effect on the risk of cardiovascular mortality. On the other hand, Chen Y et al. [30] performed an analysis on 17,118 individuals from NHANES 1999–2018 with 125-month follow-up, and demonstrated that the TyG index alone was not significantly associated with cardiovascular mortality. Yu S et al. [31] observed no significant correlation between the TyG index and cardiovascular mortality in 3,918 rural Chinese patients with baseline MetS from Northeast China Rural Cardiovascular Health Study. This discrepancies may result from variations in study population, with Yu S et al. [31] et al. studying rural Chinese patients with MetS. Also, variations in inclusion–exclusion criteria may contribute to the discrepancy, with Chen J [5] and Chen Y et al. [30] applying different inclusion–exclusion criteria for NHANES cohort. Besides, the follow-up duration, or statistical models may contribute to the controversy. Thus, further research is needed to clarify the impact of population and methodological differences on the TyG-cardiovascular mortality relationship.

Several demographic or lifestyle factors are frequently reported modifiers on the TyG index and cardiovascular mortality relationship. Among them, age, race, and BMI status are among the strongest modifiers. In our study, we observed participants that are younger (aged <= 65 years old), Mexican or African background, or normal weight (BMI 18.5–25 kg/m^2) exhibited higher risk of cardiovascular mortality linked to the TyG index, comparing to their respective counterparts. This indicates that younger individuals and normal weight individuals are more susceptible to the TyG-linked cardiovascular mortality risk. This is supported by published literature [5, 28, 32]. Collectively, this underscores an important clinical implication that younger individuals with a normal BMI, who may lack obvious traditional cardiovascular risk factors but exhibit persistent metabolic derangements, should receive closer attention in insulin resistance screening. This approach would enable earlier identification and management of cardiovascular mortality risks, preventing delays in preventive or therapeutic interventions and reducing the likelihood of adverse outcomes.

The exact mechanism connecting changes in the TyG index to higher mortality rates remains to be elucidate. The core mechanism is insulin resistance. As a surrogate of insulin resistance, higher TyG index indicates higher insulin resistance. Insulin resistance is a known trigger of chronic inflammation and oxidative stress, laying a pathophysiological foundation in promoting the development and progress of cardiovascular events. Recent studies have demonstrated that inflammatory markers, such as C-reactive protein and the systemic inflammatory response index (SIRI), mediate the relationship between TyG and cardiovascular mortality risk, with a significant impact [33]. Besides, insulin resistance leads to endothelial dysfunction. Studies have showed that elevated TyG index is associated with endothelial dysfunction estimated via flow-mediated dilation (FMD) [34], and contributed to arterial stiffness [35]. Accordingly, the finding of a reverse L-shaped non-linear relationship highlights the

clinical importance of a"high-risk threshold,"indicating that lower levels of the TyG index pose minimal or insignificant risk due to the retention of certain compensatory mechanisms, such as partially preserved insulin sensitivity, lower grade of inflammatory response and oxidative stress, which help maintain a relatively low risk of cardiovascular mortality. However, once the TyG index reaches or exceeds the threshold, reflecting a marked increase in insulin resistance, the combined burden of elevated triglycerides and hyperglycemia may intensify insulin resistance, exacerbate chronic inflammation, and promote oxidative stress. These pathological processes collectively contribute to the development of cardiovascular events, such as atherosclerosis, hypertension, coronary heart disease, stroke, etc. [36–38], leading to a sharp escalation in the risk of cardiovascular mortality.

Limitations

There are limitations in our study. Firstly, in the Adjust III model, there appeared the anomalies that the upper and lower limits of the 95%CI for continuous variables and quartiles of the TyG index were exactly the same as their respective effect sizes. This may be due to overfitting of the model, low event number, or computational accuracy problems, so it is still necessary to validate the results in prospective studies with larger sample sizes. Secondly, given that the present study exclusively involved U.S. civilians from the NHANES dataset, it is possible that the findings may have restricted applicability to populations in other regions with diverse ethnicities and lifestyles, necessitating further validation. Thirdly, selection bias might have influenced the outcomes due to the exclusion of participants without triglyceride, fasting glucose, or survival status data, as well as those omitted from the adjusted models for missing information. Finally, while covariates were adjusted, the potential of unmeasured or residual confounding factors cannot be entirely excluded.

Conclusion

In conclusion, the present study reveals a robust positive relationship between the TyG index and the risk of cardiovascular mortality among U.S. individuals aged 18–80 years after accounting for potential confounding factors and the competing risk influence from non-cardiovascular mortality. Moreover, the relationship presents as a reverse L-shape non-linear nature, which suggests that, in addition to its role as an effective indicator of insulin resistance, the TyG index may serve as an valuable tool in the assessment of risk with respect to cardiovascular mortality. Particularly, individuals that are younger than 65 years old and normal BMI may be more susceptible in this relationship, underscoring the need for focused attention on high-risk groups in risk stratification, screening, prevention, and clinical management.

Abbreviations

TyG index	Triglyceride-glucose index
NHANES	National Health and Nutrition Examination Surveys
BMI	Body mass index
GBD	Global Burden of Disease
CVD	Cardiovascular diseases
Mets	Metobolic syndromes
HOMA	Homeostasis model assessment
MACE	Major adverse cardiovascular events
sHR	Sub-distribution hazard ratios
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
NDI	National Death Index
NCHS	National Center for Health Statistics
ICD- 10	International Statistical Classification of Diseases
eGFR	Estimated glomerular filtration rate
PIR	Poverty to income ratio
LDL	Low-density lipoprotein cholesterol
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
SD	Standard deviation
ANOVA	Analysis of variance
HR	Hazard ratios
CI	Confidence intervals
CIFs	Cumulative incidence functions
MASLD	Metabolic dysfunction-associated steatotic liver disease
SIRI	Systemic inflammatory response index
FMD	Flow-mediated dilation

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Authors' contributions

JCY & JPL: Conceptualization, Statistical analysis, Interpretation of the results and Writing - original draft; LFL: Conceptualization, Data extraction and verification; LPH: Conceptualization, Supervision, Methodology, Statistical analysis, Interpretation of the results and Writing – review & editing manuscript. All authors have read and approved the final manuscript.

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Data availability

The NHANES data are available on the NHANES website (https://www.cdc.gov/nchs/nhanes/index.htm).

Declarations

Ethics approval and consent to participate

The NHANES has been approved by the National Center for Health Statistics Ethics Review Board, and all participants were provided informed written consent at enrollment.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details
[1]Office of Drug Clinical Trial Institution, The Second Affiliated Hospital of Shantou University Medical College, No. 69 North Dongxia Road, Jinping District, Shantou, Guangdong 515000, China. [2]Department of Pediatrics, The Second Affiliated Hospital of Shantou University Medical College, No. 69 North Dongxia Road, Jinping District, Shantou, Guangdong 515000, China. [3]Department of Anesthesiology, The First Affiliated Hospital of Shantou University Medical College, No. 57 Changping Road, Jinping District, Shantou, Guangdong 515000, China.

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