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The role of Triglyceride-Glucose index in predicting pre-DM risk among Chinese adults

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The triglyceride-glucose (TyG) index, a key indicator of insulin resistance, acts as a predictive factor for diabetes; however, its potential role as a prognostic marker for prediabetes (Pre-DM) remains to be elucidated. This retrospective cohort study enrolled 100,309 Chinese adults from a hospital in China between January 2010 and December 2014. We employed Cox regression, generalized additive models (GAMs), and smooth curve fitting, supplemented by a series of sensitivity analyses, to evaluate the relationship between the TyG index and pre-DM (Pre-DM). To investigate the potential mediating effect of BMI on the association between the TyG index and Pre-DM, a mediation analysis was performed. The prevalence of Pre-DM was 12.3% over 6.0 years. After adjusting for the covariates, the results showed a positive relationship between the triglyceride-glucose (TyG) index and no pre-DM. (HR = 2.1, 95%CI 2.0-2.1). Furthermore, the TyG index level exhibited a non-linear correlation with the incidence of Pre-DM, and sensitivity analysis confirmed the robustness of these findings. Subgroup analysis revealed a more pronounced association between the TyG index and Pre-DM among females and individuals aged 60 years or younger with a body mass index (BMI) of 24 kg/m² or less. Both the TyG index and BMI level were notably correlated with Pre-DM, with BMI significantly mediating 30.7% of the relationship between the TyG index and Pre-DM. Our research confirms that the TyG index serves as an independent predictor for pre-DM among the Chinese population. The body mass index (BMI) partially mediates the correlation between the TyG index and pre-DM. It is particularly important for individuals with normal weight to pay close attention to their TyG index to prevent the progression towards pre-DM.

Diabetes Mellitus (DM) is one of the most common chronic and serious diseases worldwide, which causes disabling complications and life threatening. In 2021, the International Diabetes Federation (IDF) estimated that approximately 537 million individuals were living with diabetes. Alarmingly, the prevalence of DM is projected to escalate to 643 million (11.3%) by 2030 and to 783 million (12.2%) by 2045[1,2]. Furthermore, it is estimated that 541 million individuals experienced impaired glucose tolerance in 2021[3]. An expert panel from the American Diabetes Association (ADA) suggests that up to 70% of those with pre-DM will eventually progress to diabetes, with an annual conversion rate ranging from 5 to 10%[4]. pre-DM affects approximately 35.7% of adults in China[5]. Compared to individuals with normal blood glucose levels, preventing or delaying the onset of diabetes can also help avoid numerous specific complications, including microvascular[6] and macrovascular diseases[7], as well as depression[8] and certain types of tumors[9] and so on, which seem to be more common among individuals with pre-DM Consequently, early detection of pre-DM and timely intervention in its progression are essential for preventing diabetes and its associated complications.

Currently, numerous risk factors for pre-DM have been identified, encompassing overweight or obesity, advanced age, physical inactivity, an unhealthy diet, hypertriglyceridemia, and genetic susceptibility[10]. Among these, overweight and obesity, which are closely correlated with pre-DM, are highly concerning as they represent a major risk factor that can be controlled. The US Preventive Services Task Force recommends screening for pre-

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DM every three years in adults aged 35 to 70 who have overweight or obesity[11]. The timely identification of pre-DM through cost-effective routine assessments is fundamental to preventing the progression of diabetes and its associated complications, with studies indicating a relative risk reduction of 40–70%[12]. Overweight and obesity can induce insulin resistance, which is one of the main pathophysiological mechanisms of type 2 diabetes onset, playing a significant role in the occurrence and development of Pre-DM and type 2 diabetes[13,14].

The Triglyceride glucose index (TyG Index) is a novel and early indicator of insulin resistance (IR)[15]. This index, which combines fasting blood glucose and triglyceride levels, serves as a surrogate measure of insulin sensitivity and β-cell function. It can be consistently applied in large-scale observational and/or interventional studies[16]. Numerous studies have confirmed that the TyG Index is an independent risk factor for diabetes. One such study identified a significant and independent correlation between an elevated TyG index and an increased risk of incident diabetes among adults[17]. In complementary research, a longitudinal cohort study demonstrated a positive correlation between baseline TyG-BMI and the risk of incident type 2 diabetes mellitus (T2DM) in Japanese individuals with normal glycemic levels[18]. Furthermore, research has revealed that an elevated TyG index is not only a precursor but also a robust predictor of type 2 diabetes, particularly among community-dwelling middle-aged and elderly individuals who are lean[19]. Additionally, several studies conducted in the American population have found an association between the TyG Index and the occurrence of cardiovascular disease in patients with diabetes or Pre-DM[20,21].

The association between the TyG index and diabetes, along with its cardiovascular complications, has been well-established. Nevertheless, the connection between the Triglyceride-Glucose Index and pre-DM remains unclear, despite its importance for disease prevention and the reduction of related health risks. The current study aims to investigate the role of the TyG index in predicting pre-DM risk within a large cohort of the Chinese population, and further examines the interplay of BMI in the relationship between the TyG index and pre-DM.

Methods

Data source

In our study, we conducted a secondary analysis of a medical examination program using publicly available data. The raw data was downloaded from the following source: https://datadryad.org/stash/dataset/doi:10.5061%2Fdryad. ft8750v, which was uploaded by Chen et al.[22].

Study population

The data were extracted from a computerized database established by the Rich Healthcare Group in China, which spans across 32 sites in 11 cities. This database encompasses 685,277 Chinese adults aged over 20 years, each with a minimum of two visits. Participants were excluded based on the following criteria[1]: a diagnosis of diabetes at baseline or during follow-up[2]; a BMI exceeding 55 kg/m² or falling below 15 kg/m²[3]; missing baseline data for sex, weight, height, triglycerides (TG), or fasting plasma glucose (FPG), or missing FPG data during follow-up. Ultimately, 100,309 eligible individuals were included in the analysis. A flowchart detailing the participant selection process is presented in Figure S1.

The initial study had already been granted approval by the Rich Healthcare Group Review Board, thereby eliminating the need for additional ethical approval for this subsequent analysis. Moreover, the primary research was carried out in strict compliance with the principles stipulated in the Declaration of Helsinki.

Variables

Triglyceride glucose index (TyG index)

The Triglyceride Glucose Index (TyG Index) is calculated using the following formula: TyG Index = Ln (fasting glucose (mg/dL) ×triglycerides (mg/dl)/2)[23]).

Outcomes

The definition of pre-DM is characterized by impaired fasting glucose levels, specifically an FPG ranging from 6.1 to 6.9 mmol/l.

Covariates

In this study, covariates were meticulously chosen based on clinical expertise and existing literature. Data collection was conducted by well-trained personnel. The covariates encompassed anthropometric and biochemical measurements: height, weight, and blood pressure were meticulously recorded by trained staff, with Body Mass Index (BMI) calculated as weight in kilograms divided by the square of height in meters (kg/m²). Blood pressure was measured using standard mercury sphygmomanometers. Serum levels of total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were quantified using an autoanalyzer (Beckman 5800). Fasting blood samples were obtained after a minimum 10-hour fast during each visit. Plasma glucose concentrations were determined by the glucose oxidase method, also using the Beckman 5800 autoanalyzer. Demographic information, including age, sex, smoking status, drinking status, sex(1, male; 2, female), smoking status(1,current smoker;2, ever smoker;3,never smoker), drinking status(1,current drinker;2, ever drinker;3,never drinker).and family history of diabetes (1, Yes;0, No), was collected by skilled personnel through detailed questionnaires administered during each visit to the health check center. Medical history and family history of chronic diseases were similarly obtained, ensuring a comprehensive assessment of participant health and lifestyle factors. This standardized approach facilitated the accurate and reliable collection of data essential for our analysis.

Statistical analysis

In the present study, the TyG index was categorized into tertiles to facilitate analysis. Variables that followed a normal distribution were characterized by their mean and standard deviation, whereas those with a skewed distribution were represented by their median and interquartile range. Categorical variables were reported as percentages. We employed one-way ANOVA or the Kruskal-Wallis test to compare continuous variables, and chi-square tests for categorical variables. Initially, a univariate Cox regression model was applied to evaluate the effect of each covariate on the risk of pre-DM. The relationship between the TyG index and the risk of pre-DM was subjected to further scrutiny using multivariate Cox regression analysis, incorporating various levels of covariate adjustment to precisely delineate this association. Multiple sensitivity analyses were performed to reinforce the robustness of our findings. The TyG index was considered both categorically and continuously, with the P value for trend computed to confirm the validity of the results and to evaluate for any potential nonlinearity.

There were 13 (0.013%), 13 (0.013%), 162 (0.161%), 1 (0.001%), 2307 (2.289%), 1216 (1.205%), and 372 (0.369%) individuals with missing data for SBP, DBP, LDL-C, TC, BUN, Scr, and ALT, respectively. Our study used the interpolation model to deal with missing.

data for multiple variables, including age, gender, BMI, alcohol drinking status, smoking status, DBP, SBP, TC, LDL-C, AST, ALT, Scr, BUN, FPG and family history of diabetes.We used linear regression and 10 iterations to create the interpolation model. Analysis of missing data was based on the assumption of random missingness.

We utilized Cox proportional hazards regression with cubic spline functions to investigate the nonlinear relationship between the TyG index and pre-DM. Our method for tackling nonlinearity is methodologically sound, incorporating a recursive algorithm to pinpoint the inflection point, succeeded by a two-piece Cox regression model for distinct analysis on both sides of the inflection point. The log-likelihood ratio test was employed to determine the optimal model.

To address nonlinearity, our methodology was rigorously methodical, employing a recursive algorithm to pinpoint the inflection point, and subsequently utilizing a two-piece Cox regression model for distinct analysis on both sides of this point. The log-likelihood ratio test was utilized to determine the optimal model.

We evaluated the model's performance and discrimination by comparing the C statistic (area under the curve [AUC]), calculating the integrated discrimination improvement (IDI), and net reclassification improvement (NRI) indices for censored data.

Subgroup analyses were performed, stratified by age, sex, family history of diabetes, BMI, SBP, DBP, drinking status, and smoking status. Each stratification underwent a fully adjusted analysis, and a likelihood ratio test was used to evaluate interactions. Statistical significance was established at P values ≤ 0.05. Acknowledging the higher incidence of pre-DM in the obese populations, Regression models were compared among BMI ≤ 25, BMI > 25, and total population groups to assess prevalence variations across BMI strata. Furthermore, E-values were computed to evaluate the potential influence of unmeasured confounding factors on the relationship between the TyG index and pre-DM risk[24].

A mediation analysis was executed to ascertain whether BMI mediates the effect of the TyG index on pre-DM risk, quantifying the total effect, natural direct effect, and natural indirect effect. Potential confounding factors were accounted for in the adjusted mediation analysis. Statistical analyses were performed using R software version 3.6.1 and EmpowerStats (R) version 2.2. GraphPad Prism (v10) were used for professional formatting.

Results

In this cohort study involving 100,309 Chinese adults, we monitored the progression to pre-DM in 12.34% of the participants over a median follow-up period of 3.12 years. The baseline characteristics, as outlined in Table 1, indicated that individuals who developed pre-DM had significantly elevated levels of diastolic blood pressure (DBP), body mass index (BMI), systolic blood pressure (SBP), triglycerides (TG), fasting plasma glucose (FPG), age, total cholesterol (TC), aspartate aminotransferase (AST), low-density lipoprotein cholesterol (LDL-C), alanine aminotransferase (ALT), and were more often male, smokers, and had a family history of diabetes (all $P < 0.05$). Conversely, those who did not develop pre-DM had higher levels of high-density lipoprotein cholesterol (HDL-C).

Univariate analysis

The results of the univariate analysis are presented in Table 2. The risk of prediabetes was positively associated with age, DBP, BMI, ALT, TG, LDL-C, TC, TyG and FPG. There was a negative association between HDL-C and the risk of prediabetes. (Table 2).

Nonlinear relationship between TyG index and pre-DM

Figure 1 illustrates the results of a Cox proportional hazards regression analysis, which employed cubic spline functions to elucidate a nonlinear relationship between the TyG index and the risk of pre-DM. Upon adjusting for potential confounders, the TyG index exhibited a pivotal inflection point at a value of 8.8. Below this threshold, there was a robust positive correlation with pre-DM risk (Hazard Ratio [HR]: 5.0, 95% Confidence Interval [CI]: 2.0–12.7, $P < 0.0001$). However, for TyG index values exceeding 8.8, while the association persisted, its impact was attenuated (HR: 1.4, 95% CI: 1.3–1.5, $P < 0.001$).

Comparison of predictive efficacy between two predictive models

Incorporating the TyG index into the pre-DM risk prediction model substantially improved its predictive accuracy. The area under the curve (AUC) rose from 0.695 (95% CI 0.680–0.710) to 0.731 (95% CI 0.717–0.746) following the substitution of fasting blood glucose and triglycerides with the TyG index(Figure2).

Prediabetes	0	1	Standardize diff.	*P*-value*
N	87,957	12,352		
age	42.05 ± 12.04	49.00 ± 13.59	0.54 (0.52, 0.56)	< 0.001
BMI	22.91 ± 3.17	24.38 ± 3.25	0.46 (0.44, 0.48)	< 0.001
SBP	117.08 ± 15.61	125.17 ± 17.52	0.49 (0.47, 0.51)	< 0.001
DBP	73.21 ± 10.57	77.61 ± 11.38	0.40 (0.38, 0.42)	< 0.001
TyG	8.30 ± 0.57	8.58 ± 0.59	0.48 (0.46, 0.50)	< 0.001
ALT	22.57 ± 21.29	26.78 ± 22.45	0.19 (0.17, 0.21)	< 0.001
AST	23.45 ± 11.78	25.22 ± 17.08	0.12 (0.09, 0.15)	< 0.001
BUN	4.61 ± 1.15	4.84 ± 1.16	0.20 (0.18, 0.22)	< 0.001
TG	1.32 ± 1.02	2.09 ± 1.50	0.89(−0.38,0.32)	< 0.001
TC	4.7 ± 0.90	5.05 ± 0.95	0.90(−0.38,0.32)	< 0.001
HDL	1.37 ± 0.31	1.29 ± 0.34	1.03(−0.80,−0.74)	< 0.001
LDL	2.77 ± 0.68	2.90 ± 0.70	0.31(0.07,0.09)	< 0.001
Sex			0.25 (0.23, 0.27)	-=<0.001
1	44,395 (50.47%)	7735 (62.62%)		
2	43,562 (49.53%)	4617 (37.38%)		
Smoking			0.18 (0.14, 0.21)	< 0.001
1	4509 (18.54%)	840 (25.32%)		
2	935 (3.84%)	155 (4.67%)		
3	18,877 (77.62%)	2322 (70.00%)		
Drink			0.08 (0.04, 0.11)	< 0.001
1	539 (2.22%)	100 (3.01%)		
2	3944 (16.22%)	604 (18.21%)		
3	19,838 (81.57%)	2613 (78.78%)		
Family history			0.02 (0.00, 0.04)	< 0.001
0	86,059 (97.84%)	12,042 (97.49%)		
1	1898 (2.16%)	310 (2.51%)		

Table 1. Characteristics of 100309 participants

	HR	95%CI		*P* value
Age	1.0142	1.0090	1.0194	0.0000
BMI	1.0563	1.0361	1.0769	0.0000
DBP	1.0121	1.0064	1.0179	0.0000
FPG	5.5540	4.7589	6.4820	0.0000
ALT	1.0034	1.0011	1.0058	0.0038
BUN	1.0356	0.9881	1.0854	0.1447
TG	1.36	0.29	0.32	0.000
TC	1.46	0.35	0.41	0.000
HDL	0.39	1.07	0.81	0.000
LDL	1.31	0.22	0.32	0.000
Family history	1.2614	1.0400	1.5299	0.0184
TyG(continue)	2.1	2.0	2.1	< 0.001

Table 2. Hazard ratios and 95% confidence intervals for incident prediabetes

Development of the nomogram

We developed a nomogram that incorporates age, sex, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), alanine aminotransferase (ALT), blood urea nitrogen (BUN), and a family history of diabetes to estimate the 5-year risk of pre-DM (refer to Fig. 3). This instrument assigns scores to various factors, aggregating them into a total that indicates an individual's risk for pre-DM, thereby aiding in clinical evaluation and the formulation of intervention strategies(Figure3).

Results of sensitivity analysis

Sensitivity analysis affirmed the resilience of our results. Converting TyG into a categorical variable and applying the P for trend indicated a nonlinear association with pre-DM risk. The results of the generalized additive

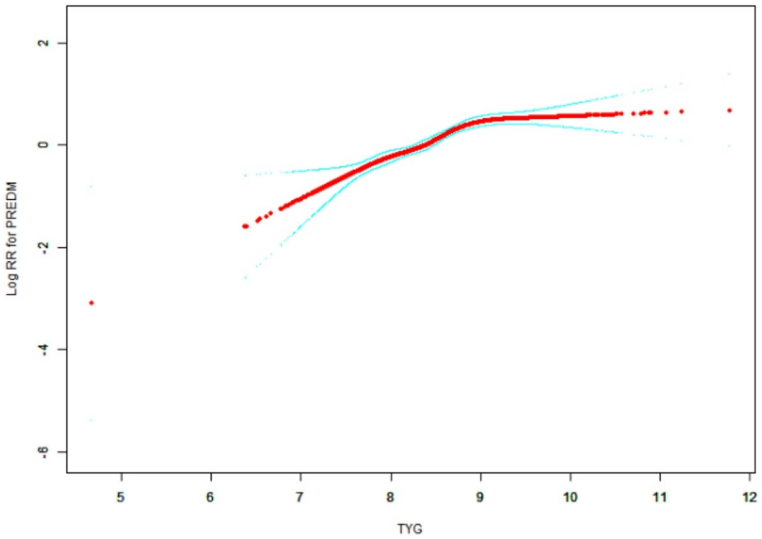

Fig. 1. Restricted spline curve (weighted) examining the association of TyG and Pre-DM in all participants

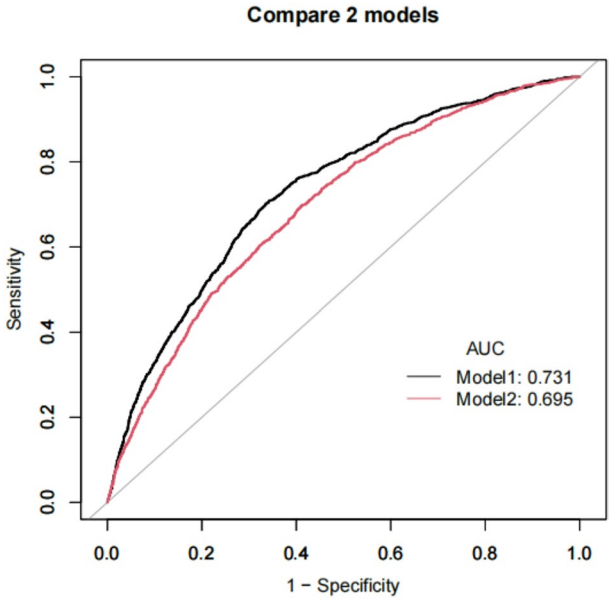

Fig. 2. Receive operating characteristic curve (ROC) analyses for the prediction of pre-DM events. Model 2 (red) includes the basic model; model 1 (black) adds the TyG variables;

model (GAM) were consistent with those of the fully adjusted model, with a hazard ratio (HR) of 2.0 and a 95% confidence interval (CI) ranging from 1.70 to 2.40.Additionally(Table 3), Higher TyG index tertiles consistently showed increased.

prediabetes risk across all BMI groups, with hazard ratios (HRs) rising from low to high tertiles (non-adjusted HR for high tertile: total population HR = 2.6, BMI ≤ 25 HR = 2.9, BMI > 25 HR = 1.8), and associations remained significant after multivariable adjustments (Adjust I/II).Notably, BMI ≤ 25 individuals exhibited steeper risk gradients (non-adjusted high-tertile HR = 2.9 vs. BMI > 25 h = 1.8) (Table 4). An E-value was computed to assess the vulnerability of the study results to potential unobserved confounding factors. The resulting E-value (3.62) demonstrated a higher level of statistical significance in comparison to the relative risk (2.1) associated with unmeasured confounders and TyG. This suggests that the impact of unmeasured or unidentified confounders on the relationship between TyG and the occurrence of prediabetes was negligible. Subgroup analyses were performed to further investigate factors that might influence the association between the TyG index and pre-DM risk, with stratification by age, smoking status, alcohol consumption, family history of diabetes, hypertension, and body mass index (BMI). Notably, a more robust correlation was identified among individuals aged 60 years or younger, those without hypertension, and those with a BMI of 25 kg/m² or less Figure4.

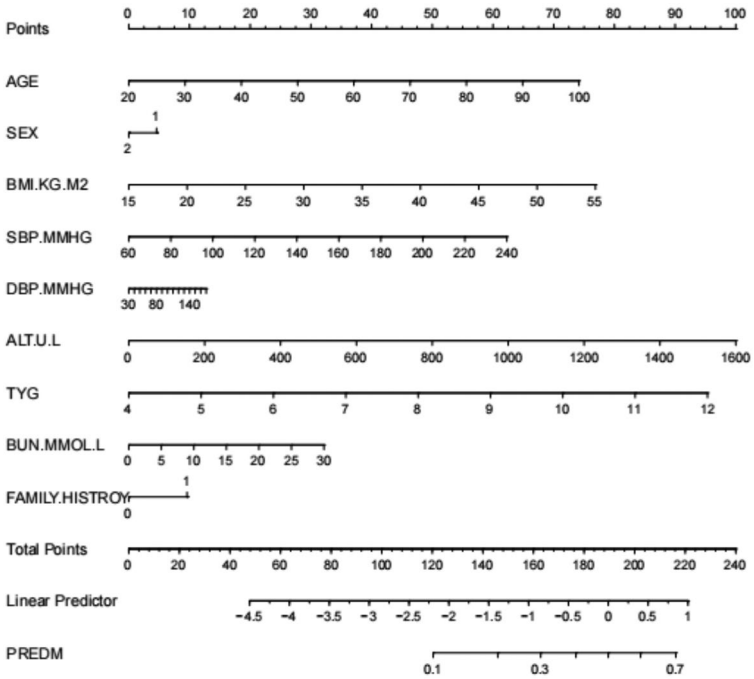

Fig. 3. Nomogram to predict the risk of pre-DM.The patient's score for each risk predictor is plotted on the appropriate scale. Te patient's score for each risk predictor is plotted on the appropriate scale and vertical lines are drawn from that value to the top Points scale to obtain the corresponding scores. All scores are summed to obtain the total points score. Te total points score is plotted on the bottom Total Points scale. The corresponding value shows the predicted probability of incident pre-DM

Exposure	Non-adjusted	Adjust I	Adjust II
TyG tertile			
Low	1.0	1.0	1.0
Middle	1.7 (1.6, 1.8) < 0.001	1.4 (1.2, 1.5) < 0.001	1.4 (1.2, 1.7) < 0.001
High	3.0 (2.9, 3.2) < 0.001	2.0 (1.8, 2.3) < 0.001	2.0 (1.7, 2.4) < 0.001

Table 3. Hazard ratios and 95% confidence intervals for pre-DM according to TyG index quartiles Non-adjusted model adjust for: None. Adjust I model adjust for: Age; Sex; SBP.DBP.Family history, Smoking. Drinking. Adjust II model adjust for: Age; Sex; SBP.DBP.Family history, Smoking. Drinking, ALT. AST; BUN. CCR.

Mediated effect of BMI on the association between TyG and pre-DM

Upon investigation, it was discovered that both the TyG index and BMI exhibited a positive correlation with pre-DM. Furthermore, the TyG index was also positively correlated with BMI, suggesting that BMI may serve as a mechanistic bridge connecting the TyG index to pre-DM. To explore their intrinsic relationship, we conducted a mediation analysis to ascertain the role of BMI in mediating the link between the TyG index and pre-DM.

Our mediation analysis uncovered that body mass index (BMI) significantly mediates the relationship between the TyG index and the risk of pre-DM. The TyG index exerted a substantial direct influence on the risk of pre-DM (β = 5, 95% CI: 2–12.7), and BMI was identified as a partial mediator of this effect (β = 1.4, 95% CI: 1.3–1.5), accounting for approximately 30.7% of the TyG index's impact on pre-DM risk(Figure5).

Discussion

To our knowledge, the present study is the first to provide robust evidence of a significant correlation between elevated TyG index levels and an increased risk of pre-DM among adults. This association followed a nonlinear pattern, with each increment in the TyG index corresponding to a 2.1-fold increase in the risk of pre-DM. Notably, the association was stronger among younger participants, those without hypertension, and individuals with a normal BMI. The TyG index was found to mediate 30% of the effect on pre-DM risk. Leveraging these insights, we developed a personalized prediction tool that estimates the 5-year risk of pre-DM by incorporating the TyG index and other significant risk factors. This novel approach offers greater predictive precision than conventional metrics such as fasting blood glucose and HbA1c. Our findings suggest that the TyG index is a powerful predictor of pre-DM risk in specific demographic groups, emphasizing the importance of tailored

Exposure	BMI < = 25	BMI = > 25	Total
Non-adjusted			
TyG tertile			
Low	1.0	1.0	1.0
Middle	1.7 (1.6, 1.8) < 0.001	1.2 (1.1, 1.3) < 0.001	1.6 (1.5, 1.7) < 0.001
High	2.9 (2.8, 3.1) < 0.001	1.8 (1.7, 2.0) < 0.001	2.6 (2.5, 2.8) < 0.001
Adjust I			
TyG tertile			
Low	1.0	1.0	1.0
Middle	1.4 (1.2, 1.6) < 0.001	1.4 (1.1, 1.8) 0.005	1.4 (1.3, 1.6) < 0.001
High	2.1 (1.9, 2.4) < 0.001	2.1 (1.7, 2.7) < 0.001	2.2 (2.0, 2.4) < 0.001
Adjust II			
TyG tertile			
Low	1.0	1.0	1.0
Middle	1.5 (1.3, 1.9) < 0.001	1.1 (0.7, 1.6) 0.714	1.5 (1.2, 1.8) < 0.001
High	2.2 (1.8, 2.7) < 0.001	1.7 (1.2, 2.5) 0.003	2.2 (1.8, 2.6) < 0.001

Table 4. Hazard ratios and 95% confidence intervals for pre-DM according to TyG index quartiles and BMI Non-adjusted model adjust for: None. Adjust I model adjust for: Age; Sex; SBP.DBP.Family history, Smoking. Drinking. Adjust II model adjust for: Age; Sex; SBP.DBP.Family history, Smoking. Drinking, ALT. AST; BUN. CCR.

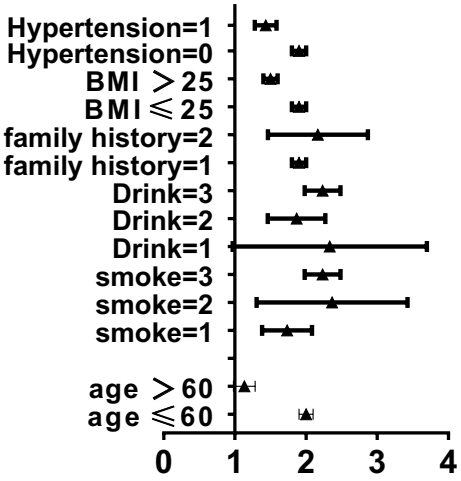

Fig. 4. Stratifed analyses on the association between TyG and the risk of Pre-DM. Adjustment for Age; BMI, Hypertension. Family history, Smoking. Drinking

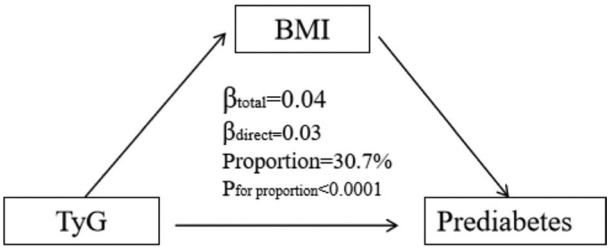

Fig. 5. Mediation effect of BMI between TyG index prediabetes.

risk assessment and intervention strategies. It has been reported that the TyG index has a higher sensitivity in predicting pre-DM than fasting glucose or HbA1c, due to its inclusion of both triglyceride and glucose levels[25]. The ease of obtaining parameters from routine laboratory tests makes it a promising first-line screening tool for pre-DM, especially in resource-limited settings. This advancement could be crucial for clinicians in identifying and intervening with high-risk individuals in a timely manner.

Our research offers fresh insights into the correlation between the TyG index and pre-DM. A cross-sectional investigation among non-obese individuals with normal LDL-C levels revealed a positive correlation between TG/HDL-C and pre-DM[26]. In a separate study, three innovative markers of insulin resistance were identified to differentiate pre-DM/diabetes within the general German population, with TyG and LAP demonstrating effective discrimination among individuals with pre-DM/diabetes[27]. In our study, we have advanced beyond previous research by resolving the nonlinear relationship of the TyG index with pre-DM and broadened the spectrum of covariates to include a wider array of biochemical indicators such as Scr, AST, ALT, and family history of diabetes. Research indicates that these parameters are associated with the risk of pre-DM[28,29]. By incorporating these factors into our analysis, we have introduced a novel perspective on the intricate interrelation between biochemical markers and the risk of pre-DM. This method not only enhances the robustness of our results but also contributes to the creation of more precise and effective strategies for the prevention and intervention of pre-DM.

Current research is exploring the mechanism of action of the TyG index in the context of glucose metabolism abnormalities. Chen et al. discovered that an elevated TyG index correlates with compromised β-cell function, irrespective of glucose metabolism status[30]. Further research has indicated that an excess of nutrients disrupts lipid metabolism, resulting in the formation of advanced glycation and lipoxidation end products. These compounds are responsible for inducing β-cell dysfunction[31]. Furthermore, within the islet cells, an excess of triglycerides disrupts the function of β-cells. Elevated levels of fatty acids and glucose result in the accumulation of esterified fatty acid metabolites, which in turn causes dysfunction in the islet cells[32]. These studies suggest a strong correlation between glucolipid metabolism and β-cell function. It has also been observed that elevated blood triglyceride levels suppress insulin activity in muscles and disrupt glucose uptake[33]. The TyG index may specifically mirror muscle-related insulin resistance, indicating that it could function as a more precise biomarker for evaluating the risk of pre-DM[34–36]. These insights are derived from cross-sectional studies and have yet to be confirmed in cohort studies. Consequently, the objective of this cohort study is to explore the relationship between the TyG index and pre-DM by analyzing retrospective data.

The TyG index has been shown to correlate with the risk of pre-DM, with a particularly strong association observed in women, individuals under 60 years of age, those with systolic blood pressure below 140 mmHg, and individuals with a BMI under 25 kg/m^2. This finding is consistent with recent studies that have investigated the link between the TyG index and the risk of non-alcoholic fatty liver disease (NAFLD) and diabetes[37,38]. Research indicates that the TyG index is a reliable predictor for evaluating insulin resistance in patients with type 2 diabetes, and its predictive accuracy in children and adolescents even surpasses that of the Homeostasis Model Assessment for Insulin Resistance (HOMA-IR)[39]. For each standard deviation increase in the TyG index among adults, the risk ratio for diabetes increases to 1.22, and this ratio is even higher in subgroup analyses involving women and individuals over 65 years of age[40]. The interplay between the TyG index, BMI, and metabolic diseases, particularly their varying impacts on specific populations, underscores the intricate relationship between obesity and metabolic disorders. The reasons behind these population-specific correlations are not entirely clear. The swift pace of urbanization and the growing dependence on digital devices have resulted in reduced physical activity for many, making them more susceptible to metabolic disorders. The modern trend towards sedentary lifestyles likely contributes to the increased prevalence of metabolic issues[41]. Additionally, the rapid development of social informatization has encouraged unhealthy lifestyle choices among the youth, leading to premature metabolic problems[42,43].

Our research findings suggest that a high Body Mass Index (BMI) is indeed a significant risk factor for pre-DM. However, the TyG index also offers valuable insights, underscoring the necessity to take both indicators into account when performing a thorough risk evaluation for pre-DM[44]. Especially for non-obese Asian populations, the TyG index provides distinctive predictive value. The potential reason behind this phenomenon is that, on the one hand, BMI is not the sole reliable indicator of obesity[45]. Compared to other ethnic groups, Asians are more susceptible to metabolically abnormal abdominal obesity, even when their body mass index (BMI) falls within a relatively normal range[46]. Conversely, individuals with lower body weight tend to have reduced subcutaneous fat, rendering them more vulnerable to hypertriglyceridemia. This condition can result in ectopic fat accumulation in the liver and skeletal muscles, fostering insulin resistance and elevating the risk of pre-DM[47].

Our findings that BMI mediates 30.7% of the TyG-prediabetes association suggest intertwined biological pathways. Elevated TyG index reflects systemic insulin resistance (IR), which may originate from adipose tissue dysfunction. In individuals with high BMI, hypertrophic adipocytes release excess free fatty acids (FFAs), promoting hepatic TG accumulation and gluconeogenesis – directly captured by the TyG index[48]. Conversely, in normal-weight individuals (BMI ≤ 24 kg/m^2), the steeper TyG-prediabetes gradient (HR = 2.9 vs. 1.8 in BMI > 25) implies distinct mechanisms. Ectopic fat deposition in liver/skeletal muscle may drive IR without overt obesity, making TyG a sensitive marker of subclinical metabolic dysregulation[49].

This study boasts several key strengths. To begin with, it represents the inaugural large-scale, multicenter, prospective investigation into the correlation between the TyG index and pre-DM. Secondly, we utilized stringent statistical methodologies to mitigate the influence of confounding variables, thereby bolstering the study's reliability. In parallel, to further validate the robustness of our findings, we undertook sensitivity analyses, encompassing the stratification of the TyG index, the application of Generalized Additive Models (GAMs) for managing continuous covariates, and the computation of the E-value to gauge the impact of unobserved confounding factors. Lastly, we explored the role of BMI within the relationship between the TyG index and pre-

DM, elucidating the interplay among the three within specific demographic groups, thus furnishing a foundation for the development of more targeted intervention and prevention strategies.

Our research has its inherent limitations. The omission of the oral glucose tolerance test (OGTT) could result in an underestimation of the prevalence of pre-DM. Nevertheless, the substantial sample size of our study population, the broad sampling scope, and the robust representativeness somewhat mitigate these deficiencies. It is also important to acknowledge that our dataset lacks details on atherosclerosis, the utilization of lipid-lowering medications, and the condition of hyperlipidemia, which restricts more detailed subgroup analyses on the incidence of complications associated with pre-DM. Like all observational studies, even after accounting for known confounding variables, we cannot eliminate the influence of unquantified factors such as diet and physical activity. E-value analysis indicates that unmeasured confounding factors are unlikely to completely account for our results. Future research should aim to gather more comprehensive data, which may necessitate joint research endeavors. Furthermore, the initial study only assessed triglycerides and HDL-C at baseline, without monitoring their variations over time. Future investigations should document these changes to examine their dynamic influence on the risk of pre-DM in conjunction with the TyG index.

Conclusion

In conclusion, the Triglyceride Glucose (TyG) index has established itself as a powerful and independent predictor for identifying pre-DM, especially among individuals with a normal Body Mass Index (BMI). Interestingly, BMI seems to partially mediate the relationship between the TyG index and pre-DM risk. This discovery highlights the importance of monitoring the TyG index in individuals with normal weight as a preventive measure against the development of pre-DM. Conversely, for those categorized as overweight or obese, clinical attention should not only focus on the TyG index but also encompass proactive steps to attain and maintain a healthy BMI range. This comprehensive strategy is justified, considering the intricate interrelation between metabolic disorders, as suggested by elevated TyG index levels, and the increased adiposity linked to higher BMI categories, both of which elevate the risk of pre-DM.

Data availability

Data is provided within the manuscript or supplementary information files.

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Author contributions

The study conception and design were performed by Z.S. and H.L. Data collection and analysis were performed-by Z.W., C.L., and Q.W. Data verification and the first draft of the manuscript were written by Z.W. Y.O, C.L and L.T were responsible for statistical analysis. All authors approved the final manuscript and taking final responsibility for the paper.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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