

Association Between Triglyceride Glucose Index and Risk of New-onset Diabetes Among Chinese Adults: Findings From the China Health and Retirement Longitudinal Study

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Research

Keywords: Triglyceride glucose index, Diabetes mellitus, Association, CHARLS

Posted Date: September 23rd, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-80124/v1>

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Abstract

Background

The triglyceride glucose (TyG) index has been proposed to be a simple surrogate of insulin resistance. We aimed to examine the relationship between TyG index and risk of incident diabetes in middle-age and elderly adults in China.

Methods

Nationally representative data from the China Health and Retirement Longitudinal Study 2011-2015 were used. Sociodemographic, medical, anthropometric, and laboratory information were collected following a standard protocol. Cox proportional hazards models and restricted cubic spline regression were performed to estimate hazard ratio (HR) with 95% confidence interval (CI) of diabetes for TyG index. Subgroup analyses were also conducted to examine potential interactions.

Results

Of 7428 participants without at baseline diabetes, 791 (10.6%) participants developed diabetes over 3.4 years of follow-up. The multivariate HR for every SD increase in TyG index was 1.22 (95% CI, 1.14-1.31). When dividing TyG index into quartiles, the multivariate HRs for new-onset diabetes were 1.22 (0.96-1.54) for Q2, 1.61 (1.28-2.01) for Q3, and 1.73 (1.38-2.16) for Q4 (P for trend < 0.001) compared with Q1. The restricted cubic spline regression confirmed a linear association. No interaction was found between subgroup variables and association of TyG index with risk of diabetes.

Conclusion

TyG index was significantly and positively associated with risk of new-onset diabetes in middle-aged and elderly adults. TyG index may be a useful predictive marker for predicting new-onset diabetes.

Introduction

Diabetes is associated with increased risk of cardiovascular morbidity and all-cause mortality, imposing a huge public burden owing to its high prevalence [1]. In the past few decades, the number of adults with diabetes as well as the prevalent rate has considerably increased, especially in low and middle-income countries [2]. According to data from the International Diabetes Federation, China has the largest number of diabetic patients, which has reached 114.4 million in 2017, with a national rate of 10.9% [3]. Therefore, identifying individuals at high risk for developing diabetes is of major importance to reduce the incidence rate and related complications.

Insulin resistance (IR) is a major pathophysiological pathway of type 2 diabetes development and appears about two decades prior to the formal diagnosis [4, 5]. A recent study indicated that IR was more closely associated with risk of incident diabetes than β -cell dysfunction, another pivotal pathological

features of diabetes, among Chinese adults [6]. Additionally, in the past four decades, China has experienced disruptive transitions of dietary patterns and witnessed a massive rise in the number of individuals with obesity, which is major etiological factor for the diabetes epidemic by promoting the progression and severity of IR [7, 8]. Thus, assessment of IR status is essential to prevent diabetes incidence. However, the traditional way to measure IR such as the homeostasis model assessment of IR (HOMA-IR) is time-consuming, complex, and costly for daily practice and in large epidemiological studies.

Recently, the triglyceride glucose (TyG) index, the product of triglyceride (TG) and fasting blood glucose (FBG), has attracted attention as a simple surrogate of IR owing to its good correlation with HOMA-IR and better performance for examining insulin sensitivity [9]. A few studies have examined the association of TyG index and diabetes in Asia and western populations [10-15]. However, the results were inconclusive and limited due to either the cross-sectional design [14], small sample size [12] or the geographically regional and selected population [11, 15]. Therefore, we designed a prospective cohort study using nationally representative data from the China Health and Retirement Longitudinal Study (CHARLS) to explore the relationship between TyG index and risk of new-onset diabetes.

Methods

Study design and participants

Participants enrolled in this study were from the CHARLS, which is an ongoing longitudinal survey for accessing the social, economic and health status of community residents aged 45 years or older in China. Details of the study design of CHARLS have been described elsewhere [16]. Briefly, the CHARLS adopted a multistage probability sampling and investigated 17708 individuals in 28 provinces through random selection of 10257 households to cover the overall population in China in the first wave (W1, 2011-2012), making the sample nationally representative. The response rate was up to 81% in the baseline survey. Well-trained interviews collected sociodemographic, physical, biological, and health-related information of study participants complying with the standard study plan. To date, the follow-up surveys have been conducted twice, including the second wave (W2) in 2013 and the third wave (W3) in 2015. For the present study, 10111 individuals with laboratory measurement at W1 were initially enrolled. Participants aged less than 45y, missing TG, FBG, and glycated hemoglobin were excluded, leaving 9663 participants. Of those, 1760 with diabetes at baseline were further excluded. Next, we excluded subjects who died (n=103) or lost follow-up (n=372) in the subsequent waves (W2 and W3) of the study. Finally, 7428 participants were enrolled for the final analysis (Figure 1). The Ethics Review Committee of Peking University approved CHARLS (IRB00001052–11015) and all participants gave informed consent before participation.

Data collection and definitions

After taking a rigorous training program, the researchers visited and interviewed participants in their homes using computer-assisted personal interview technology to collect sociodemographic information [including age, gender, education level (primary school or lower, secondary school, and higher), and

marriage status (current married or not)], health behavior (including current smoking and drinking), medical history [including self-reported hypertension, diabetes, and cardiovascular disease (CVD)] and medication usage (including antihypertensive drugs, antidiabetic drugs, and lipid-lowering drugs).

Anthropometric indicators included systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters), and waist circumference (WC). Blood pressure were measured three times in a seated position by trained nurses using the HEM-7200 electronic monitor (Omron, Dalian, Japan). Hypertension was defined as SBP \geq 140 mmHg or DBP \geq 90 mmHg or self-reported prior diagnosis of hypertension by a doctor or using antihypertensive drugs in the past two weeks [17]. Height and WC were accurate to 0.1 cm and weight was accurate to 0.1 kg.

For biomarkers assessment, the CHARLS researcher collected fasting blood samples from every participant. These samples were transported from all over the country to Beijing and were stored at minus 80°C at the Chinese Center for Disease Control and Prevention. The biological determination of FBG, Hemoglobin A1c, TG, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were conducted by professional staff. TyG index was calculated as $\ln [TG \text{ (mg/dl)} \times \text{FBG (mg/dl)}/2]$ [18]. At baseline and follow-up, diabetes was defined as FBG > 125 mg/dL or Hemoglobin A1c > 6.5% or self-reported prior diagnosis of hypertension by a doctor or using antidiabetic medications. Non-diabetic participants whose FBG was at 100–125 mg/dL or Hemoglobin A1c was at 5.7–6.4% were classified as having prediabetes [19]. Participants without diabetes and prediabetes were normoglycemic.

Statistical Analysis

Data were presented as mean standard deviation (SD) for continuous variables and percentage for categorical variables. Baseline characteristics between groups according to quartiles of TyG index (Q1, Q2, Q3, Q4) or developing diabetes or not were reported and compared using the One-Way ANOVA, Kruskal-Wallis H test and chi-square tests, as appropriate. We initially conducted Cox proportional hazards models to estimate HR with 95% confidence interval (CI) of diabetes for per SD increase as well as quartiles of TyG index. Three models were fitted. Model 1 was univariate. Models adjusted for age and gender. Fully adjusted model (Model 3) incorporated covariates including age, gender, education, marriage, smoking, drinking, BMI, WC, SBP, history of hypertension, history of CVD, and usage of lipid-lowering drugs. Next, the shape of association between TyG index and incident diabetes was examined by multivariate adjusted Cox restricted cubic spline regression model. We choose three knots at quartiles 25th, 50th, and 75th. Finally, we conducted subgroup analyses (multivariate Cox proportional hazards models) including age (< 65 or \geq 65 years), gender (male or female), BMI (< 25 or \geq 25 kg/m²), and glycemic status (normoglycemia or prediabetes). $P < 0.05$ was considered statistically significant. R version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria) was used for all statistical analyses.

Results

Baseline characteristics of study participants

The baseline characteristics of all the participants according to quartiles of TyG index and developing diabetes or not were summarized in **Table 1** and **Table 2**, respectively. The present study included 7428 participants (male: 46.5% and mean age: 59.3 years). The mean value TyG index was 8.56. Among groups of TyG index quartiles, we observed significant differences in all baseline covariates except for marriage status and education level (**Table 1**). Compared with participants remaining non-diabetic during follow-up, subjects developed diabetes were older, having lower education level, less likely to be married, having higher levels of SBP, DBP, BMI, WC, TG, TC, LDL-C, HDL-C, FBG, Hemoglobin A1c, and TyG index, more likely to have hypertension and CVD, and more likely to use lipid-lowering drugs (**Table 2**).

Hazard ratios for incident diabetes

Over a median of 3.4 years of follow-up, 791 (10.6%) participants developed diabetes. After controlling for age, gender, education, marriage, smoking, drinking, BMI, WC, SBP, history of hypertension, history of CVD, and usage of lipid-lowering drugs, every SD increase in TyG index was associated with 22% higher risk of developing diabetes (HR 1.22, 95% CI, 1.14-1.31). When dividing TyG index into quartiles, the multivariate HRs for new-onset diabetes were 1.22 (0.96-1.54) for Q2, 1.61 (1.28-2.01) for Q3, and 1.73 (1.38-2.16) for Q4 (P for trend < 0.001) (**Table 3**). In the restricted cubic spline regression models with full adjustment, the relationship between TyG index and risk of incident diabetes was linear (**Figure 2**).

Subgroup analyses

We performed subgroups analyses stratified by age gender, BMI and glycemic status, as provided in **Table 4**. No interaction was found between subgroup variables and association of TyG index with risk of diabetes. The positive relationship remained consistent in both men and women, younger and elderly participants, lean and overweight/obese participants, and normoglycemic and prediabetic participants (**Table 4**).

Discussion

We derived nationally representative data from the CHARLS and found an independent and positive relationship between the simple surrogate of IR (TyG index) and risk of new-onset diabetes in middle-aged and elderly Chinese adults. Additionally, the effects of TyG index on diabetes were not interacted by age, gender, BMI and glycemic status. The associations between TyG index and incident diabetes were more pronounced in the elderly, women, individuals with obesity, and prediabetic subjects.

Our results were consistent with previous studies that indicated a linear relationship between TyG index and risk of diabetes. A recent study involving 4,285 middle-aged and elderly Korean adults with BMI < 25 kg/m² found a positive association of TyG index and diabetes after 12 years of follow-up. Similarly, in

lean Chinese individuals, Zhang et al. suggested that TyG index was predictive of incident diabetes. The authors claimed that lean people were more likely to be comorbid with hypertriglyceridemia because of lacking subcutaneous fat, leading to subsequent IR and β -cell dysfunction [20]. In a White European population, Navarro-Gonzalez et al. reported that the risk of developing diabetes was increased by 54% for per SD increase of TyG index, and the authors also suggested that TyG index was a better predictor of diabetes than TG or FBG separately [12].

In the subgroup analyses, we found that the positive relationship between TyG index and diabetes was more evident in elderly, women, obese or prediabetic individuals. The reasons could be explained as follows. Visceral adiposity tissue increases with age and may lead to the higher incidence and risk of diabetes [21]. In addition, the higher hepatocellular lipids in women may contribute to the increased risk of diabetes [22]. Moreover, a recent study showed that TyG was an important mediator in the BMI-related diabetes development in both obese and non-obese individuals [23]. Another retrospective study of 2,900 Korean adults reported that TyG index of 8.8 or higher significantly increased the risk of type 2 diabetes regardless of BMI range [13]. Finally, prediabetes is more likely related to IR than normoglycemia, which explains the more pronounced risk of developing diabetes in this population [24-26].

Several mechanisms have been reported to explain the predictive value of TyG index for the development of diabetes. On the one hand, increased TG level in the blood contributes to the inhibitory insulin activity, production of inflammatory cytokines, and muscle catabolism while overloaded TG in the pancreatic islet cells disrupts the β -cell function [27]. On the other hand, elevated glucose concentrations exert toxic effects on β -cells by raising reactive oxygen species [28]. These mechanisms have been confirmed in an intervention study indicating that the capacity of insulin secretion and IR status were improved by reduce TG and FBG level [29]. As the product of TG and FBG, high TyG index reveals both seriously decreased β -cells and increased IR, which are considered to be the major events of incident diabetes [30]. Despite this, more mechanistic researches need to be conducted in different ethnic populations to reveal the difference and consistency of the role of TyG in the development of diabetes in order to better guide clinical practice.

Our findings have a few clinical implications. First, TyG index was recently reported to be superior to traditional predictors of IR and diabetes such as TG/HDL-C and HMOA-IR [31]. Second, several studies have shown that TyG index improved prediction of diabetes compared with FBG or TG itself, as well as single other lipid markers such as TC, LDL-C, and HDL-C cross different ethnic groups [12, 32, 33]. Third, TyG index is a simple, inexpensive and routine indicator and is suitable for clinical practice. Finally, and most importantly, monitoring the TyG index can help identify people at high risk of developing diabetes, even though their FBG or TG is not high or is at a borderline high level. For this group of people, timely lifestyle and diet adjustments are crucial [34].

Study limitations

The strength of the current research was to include a nationally representative sampling design, rigorous and standard protocol for data collection and follow-up, which made our results of prospective relationship more reliable. However, some limitations should be considered for cautious interpretation.

First, despite we have fully adjusted for many risk factors, residual confounding might exist due to unrecognized confounders such as physical activity and family history of diabetes. Second, 2h oral glucose tolerance test was not included to detect cases of diabetes, which might underestimate the incidence of diabetes. Third, the follow-up time was relatively short. Longer duration of follow-up is needed to further verify our results. Finally, all participants were Chinese people aged 45 years or older, caution should be made when interpreting our findings in younger individuals and in other ethnic populations.

Conclusion

In conclusion, TyG index was significantly and positively associated with risk of new-onset diabetes in middle-aged and elderly adults. TyG index might be a useful predictive marker for predicting new-onset diabetes.

Abbreviations

TyG, triglyceride glucose; TG, triglyceride; FBG, fasting blood glucose; BMI, body mass index. SBP, systolic blood pressure; DBP, diastolic blood pressure; CVD, cardiovascular disease

Declarations

Acknowledgements

We thank the Institute of Social Science Survey of Peking University and the National School of Development of Peking University for providing the data. We also acknowledge all the participants in the survey design and data collection as well as the CHARLS research team for collecting high-quality, nationally representative data.

Authors' contributions

Chao-lei CHEN, Yu-qing HUANG, and Ying-qing FENG designed the study, interpreted the data and contributed to critically revising the manuscript. Chao-lei CHEN and Lin-LIU analyzed the data and drafted the manuscript. Kenneth LO, Jia-yi HUANG, and Yu-ling YU helped manuscript editing and data analysis. All authors read and approved the final manuscript.

Funding

This work was supported by the Science and Technology Program of Guangzhou (No.201604020143, No.201604020018, No.201604020186, and No.201803040012), the National Key Research and Development Program of China (No.2017YFC1307603, No.2016YFC1301305), and the Key Area R&D Program of Guangdong Province (No.2019B020227005).

Availability of data and materials

Detailed examination methods, questionnaire information, and mortality data can be referred to <http://charls.pku.edu.cn/en>.

Ethics approval and consent to participate

Our study complied with the Declaration of Helsinki and was approved by the Ethics Review Committee of Peking University.

Consent for publication

Not applicable.

Competing Interests

The authors declare that they have no conflicts of interest.

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Tables

Table 1 Baseline characteristics of study participants according to quartiles of triglyceride glucose index

	Q1	Q2	Q3	Q4	<i>P</i> -value
Number	1857	1857	1857	1857	
Age, years	59.56 ± 9.83	59.36 ± 9.36	59.60 ± 9.12	58.67 ± 9.11	0.008
Gender					<0.001
Male	1007 (54.2)	921 (49.6)	782 (42.1)	747 (40.2)	
Female	850 (45.8)	936 (50.4)	1075 (57.9)	1110 (59.8)	
Education					0.338
Primary school or lower	1325 (71.4)	1307 (70.4)	1332 (71.7)	1281 (69.0)	
Secondary school	358 (19.3)	362 (19.5)	342 (18.4)	400 (21.5)	
Higher	173 (9.3)	187 (10.1)	183 (9.9)	176 (9.5)	
Current married	1639 (88.3)	1644 (88.5)	1632 (87.9)	1649 (88.8)	0.843
Current smoking	808 (43.5)	753 (40.5)	681 (36.7)	663 (35.7)	<0.001
Current drinking	548 (29.5)	498 (26.8)	403 (21.7)	441 (23.7)	<0.001
SBP, mmHg	126.70 ± 21.07	128.29 ± 20.75	131.30 ± 22.03	133.00 ± 21.63	<0.001
DBP, mmHg	73.69 ± 12.10	74.59 ± 11.96	76.34 ± 12.40	77.70 ± 12.52	<0.001
BMI, kg/m ²	22.01 ± 3.18	22.83 ± 3.73	23.61 ± 3.67	24.78 ± 3.67	<0.001
WC, cm	80.06 ± 10.74	82.55 ± 11.74	84.59 ± 12.75	87.71 ± 12.49	<0.001
TC, mg/dL	178.15 ± 33.52	188.61 ± 33.88	196.85 ± 36.74	205.84 ± 39.63	<0.001
TG, mg/dL	59.72 ± 13.51	86.81 ± 13.01	121.10 ± 18.03	217.93 ± 88.01	<0.001
LDL-C, mg/dL	107.93 ± 29.13	117.54 ± 30.86	124.06 ± 33.99	118.19 ± 39.17	<0.001
HDL-C, mg/dL	60.47 ± 14.97	55.65 ± 13.98	50.28 ± 12.89	42.27 ± 11.38	<0.001
FBG, mg/dL	93.57 ± 13.31	99.16 ± 10.40	101.03 ± 10.40	106.14 ± 9.98	<0.001
Hemoglobin A1c, %	5.05 ± 0.38	5.08 ± 0.39	5.11 ± 0.41	5.16 ± 0.40	<0.001
TyG index	7.90 ± 0.25	8.35 ± 0.10	8.70 ± 0.11	9.29 ± 0.33	<0.001
Hypertension	568 (30.8)	652 (35.5)	784 (42.7)	888 (48.2)	<0.001
Cardiovascular	197 (10.6)	233 (12.6)	249 (13.5)	265 (14.3)	0.006

disease					
Lipid-lowering drugs	34 (1.8)	52 (2.8)	76 (4.1)	107 (5.8)	<0.001
New-onset diabetes	123 (6.6)	166 (8.9)	232 (12.5)	270 (14.5)	<0.001

Data are presented as mean \pm standard deviation or number (%).

Q, quartiles; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WC, waist circumference; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FBG, fasting blood glucose; TyG, triglyceride glucose.

Table 2 Comparison of baseline characteristics of study participants who developed diabetes or not

	Overall	Not developed DM	Developed DM	<i>P</i> -value
Number	7428	6637	791	
Age, years	59.30 ± 9.36	59.14 ± 9.37	60.68 ± 9.20	<0.001
Gender				0.210
Male	3457 (46.5)	3106 (46.8)	351 (44.4)	
Female	3971 (53.5)	3531 (53.2)	440 (55.6)	
Education				0.018
Primary school or lower	5245 (70.6)	4656 (70.2)	589 (74.6)	
Secondary school	1462 (19.7)	1319 (19.9)	143 (18.1)	
Higher	719 (9.7)	661 (10.0)	58 (7.3)	
Current married	6564 (88.4)	5888 (88.7)	676 (85.5)	0.008
Current smoking	2905 (39.1)	2595 (39.1)	310 (39.2)	0.993
Current drinking	1890 (25.4)	1709 (25.7)	181 (22.9)	0.088
SBP, mmHg	129.82 ± 21.51	129.29 ± 21.42	134.25 ± 21.78	<0.001
DBP, mmHg	75.58 ± 12.34	75.29 ± 12.24	77.98 ± 12.92	<0.001
BMI, kg/m ²	23.31 ± 3.71	23.16 ± 3.62	24.52 ± 4.23	<0.001
WC, cm	83.72 ± 12.28	83.31 ± 12.13	87.18 ± 12.94	<0.001
TC, mg/dL	192.36 ± 37.44	191.85 ± 37.38	196.62 ± 37.70	0.001
TG, mg/dL	121.39 ± 75.40	119.39 ± 73.93	138.21 ± 84.99	<0.001
LDL-C, mg/dL	116.93 ± 34.00	116.63 ± 33.98	119.46 ± 34.07	0.027
HDL-C, mg/dL	52.17 ± 14.98	52.46 ± 14.87	49.74 ± 15.68	<0.001
FBG, mg/dL	99.98 ± 11.98	99.54 ± 11.84	103.65 ± 12.47	<0.001
Hemoglobin A1c, %	5.10 ± 0.40	5.08 ± 0.39	5.25 ± 0.44	<0.001
TyG index	8.56 ± 0.56	8.54 ± 0.55	8.72 ± 0.56	<0.001
Hypertension	2892 (39.3)	2483 (37.7)	409 (52.1)	<0.001
Cardiovascular disease	944 (12.8)	807 (12.2)	137 (17.4)	<0.001
Lipid-lowering drugs	269 (3.6)	222 (3.3)	47 (5.9)	<0.001

Data are presented as mean ± SD or n (%).

Q, quartiles; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WC, waist circumference; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FBG, fasting blood glucose; TyG, triglyceride glucose.

Table 3 Cox-proportional hazard models for the association between triglyceride glucose index and incident diabetes

	Case/total	Model 1	Model 2	Model 3
TyG index				
Per SD increase		1.34 (1.25, 1.43)	1.35 (1.26, 1.44)	1.22 (1.14, 1.31)
Quartiles				
Q1	123/1857	ref	ref	ref
Q2	166/1857	1.37 (1.08, 1.73)	1.37 (1.08, 1.73)	1.22 (0.96, 1.54)
Q3	232/1857	1.91 (1.54, 2.38)	1.90 (1.53, 2.37)	1.61 (1.28, 2.01)
Q4	270/1857	2.27 (1.84, 2.81)	2.32 (1.87, 2.87)	1.73 (1.38, 2.16)
<i>P</i> for trend		< 0.001	< 0.001	< 0.001

Data are presented as hazard ratio (95% confident interval). TyG, triglyceride glucose; SD, standard deviation; Q, quartiles.

Model 1 adjust for none.

Model 2 adjust for age and gender.

Model 3 adjust for age, gender, education, marriage, smoking, drinking, body mass index, waist circumference, systolic blood pressure, history of hypertension, history of cardiovascular disease, and usage of lipid-lowering drugs.

Table 4 Multivariable-adjusted hazard ratios for the association between quartiles of triglyceride glucose index and incident diabetes by subgroups

	Case/total	Q1	Q2	Q3	Q4	<i>P</i> for trend	<i>P</i> for interaction
Age, years							0.74
≥ 65	258/2029	ref	1.22 (0.81, 1.83)	1.66 (1.13, 2.43)	1.82 (1.23, 2.69)	<0.001	
< 65	533/5399	ref	1.20 (0.89, 1.61)	1.55 (1.17, 2.05)	1.66 (1.26, 2.19)	<0.001	
Gender							0.14
Male	351/3457	ref	1.15 (0.84, 1.58)	1.33 (0.97, 1.82)	1.56 (1.14, 2.14)	0.004	
Female	440/3971	ref	1.34 (0.93, 1.94)	1.96 (1.40, 2.75)	1.99 (1.42, 2.79)	0.001	
BMI, kg/m ²							0.66
≥ 24	405/2822	ref	1.53 (1.01, 2.33)	1.85 (1.25, 2.74)	2.03 (1.39, 2.97)	<0.001	
< 24	377/4493	ref	1.08 (0.80, 1.46)	1.55 (1.17, 2.06)	1.63 (1.20, 2.21)	<0.001	
Glycemic status							0.41
Normoglycemia	528/3888	ref	1.16 (0.82, 1.63)	1.54 (1.12, 2.11)	1.38 (1.01, 1.89)	0.03	
Prediabetes	263/3540	ref	1.17 (0.84, 1.65)	1.35 (0.95, 1.90)	1.80 (1.25, 2.60)	0.002	

Data are presented as hazard ratio (95% confident interval). Q, quartiles; BMI, body mass index.

Models adjust for age, gender, education, marriage, smoking, drinking, body mass index, waist circumference, systolic blood pressure, history of hypertension, history of cardiovascular disease, and usage of lipid-lowering drugs except the subgroup variable itself.

Figures

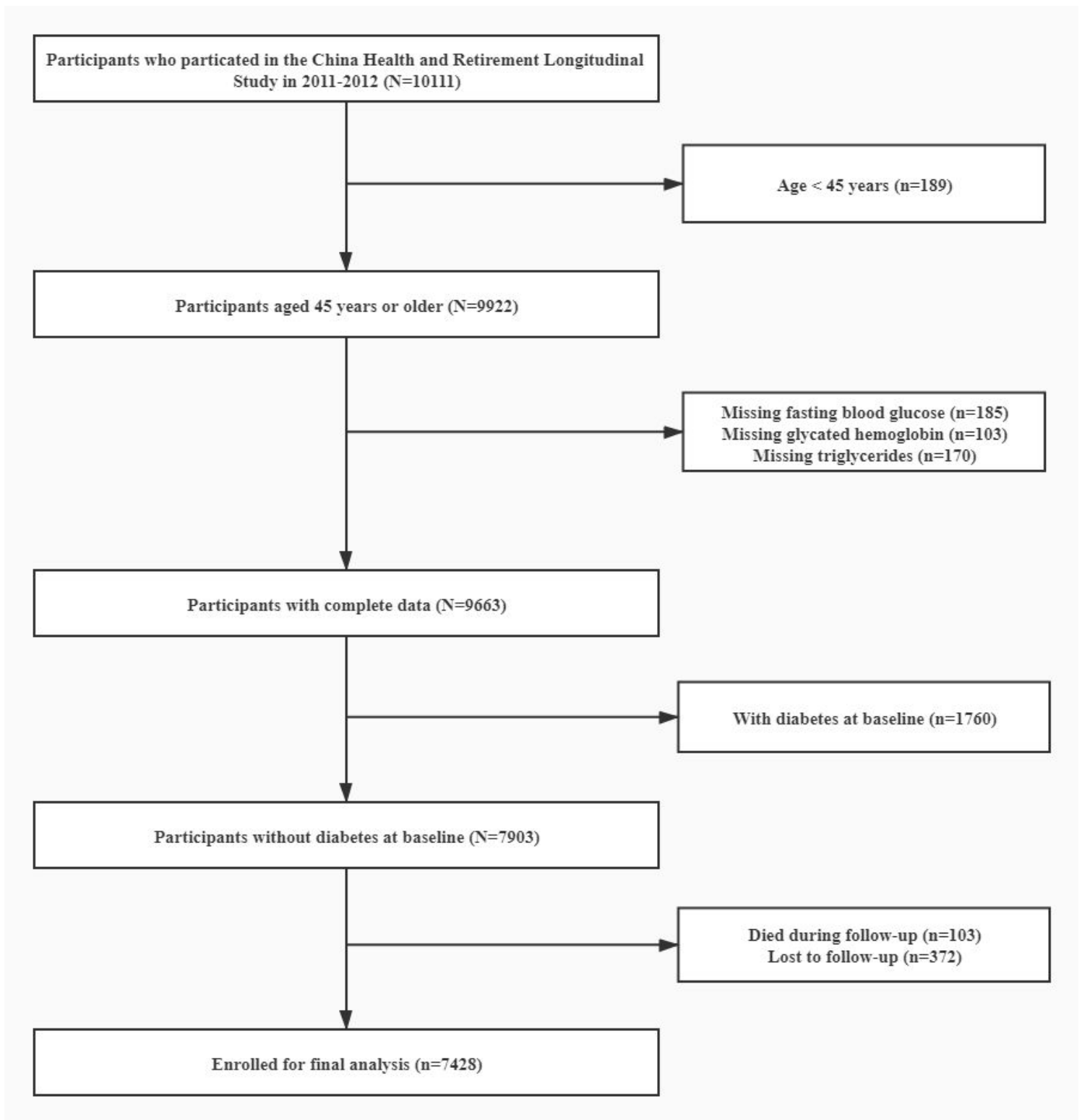


Figure 1

Flow chart of study participants.

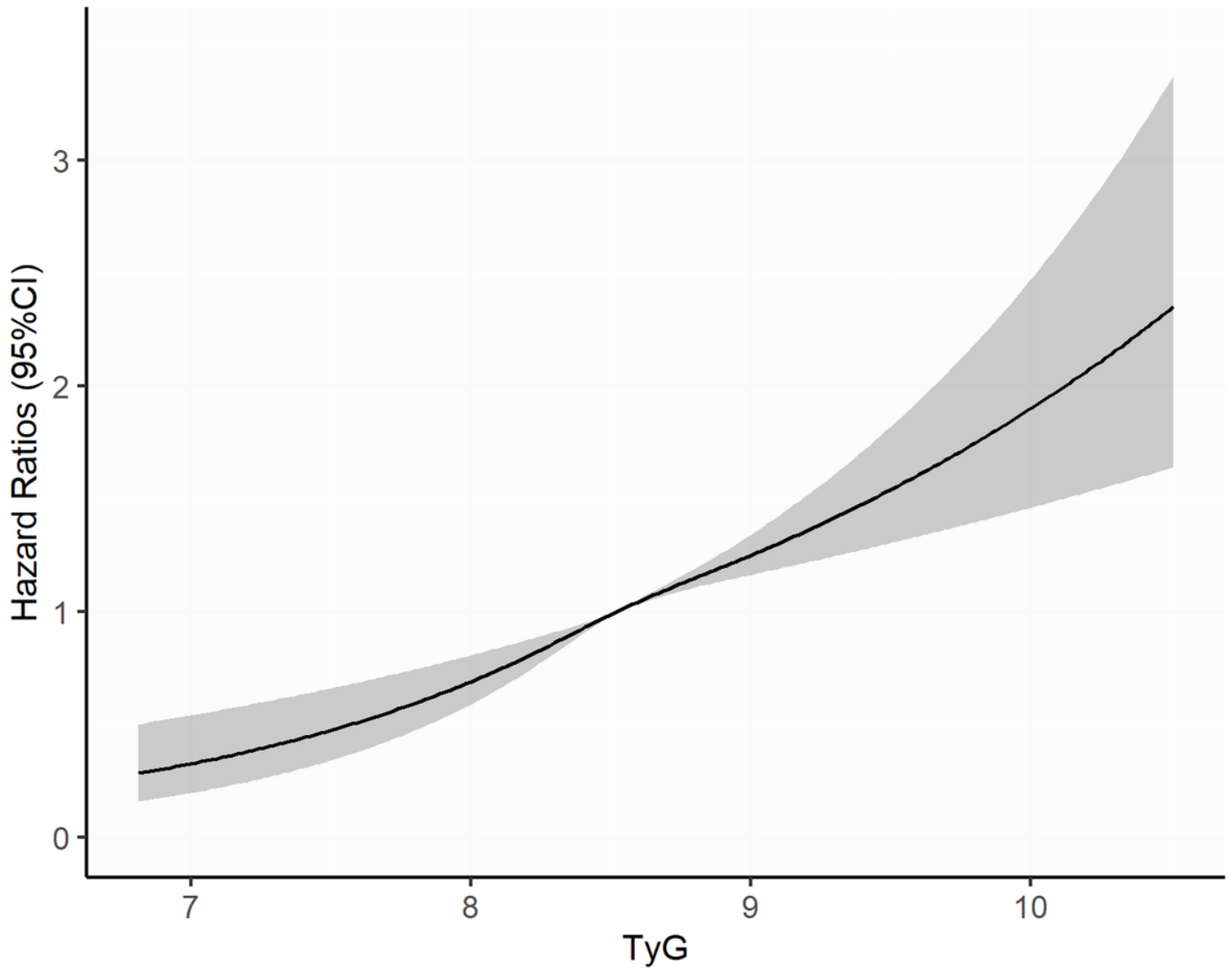


Figure 2

Adjusted cubic spline model of the association between triglyceride glucose index and risk of new-onset diabetes. TyG, triglyceride glucose.