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Relationship between changes in the triglyceride glucose-body mass index and frail development trajectory and incidence in middle-aged and elderly individuals: a national cohort study

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Abstract

Background Insulin resistance is linked to an increased risk of frailty, yet the comprehensive relationship between the triglyceride glucose-body mass index (TyG-BMI), which reflects weight, and frailty, remains unclear. This relationship is investigated in this study.

Methods Data from 9135 participants in the China Health and Retirement Longitudinal Study (2011–2020) were analysed. Baseline TyG-BMI, changes in the TyG-BMI and cumulative TyG-BMI between baseline and 2015, along with the frailty index (FI) over nine years, were calculated. Participants were grouped into different categories based on TyG-BMI changes using K-means clustering. FI trajectories were assessed using a group-based trajectory model. Logistic and Cox regression models were used to analyse the associations between the TyG-BMI and FI trajectory and frail incidence. Nonlinear relationships were explored using restricted cubic splines, and a linear mixed-effects model was used to evaluate FI development speed. Weighted quantile regression was used to identify the primary contributing factors.

Results Four classes of changes in the TyG-BMI and two FI trajectories were identified. Individuals in the third (OR = 1.25, 95% CI: 1.10–1.42) and fourth (OR = 1.83, 95% CI: 1.61–2.09) quartiles of baseline TyG-BMI, those with consistently second to highest (OR = 1.49, 95% CI: 1.32–1.70) and the highest (OR = 2.17, 95% CI: 1.84–2.56) TyG-BMI changes, and those in the third (OR = 1.20, 95% CI: 1.05–1.36) and fourth (OR = 1.94, 95% CI: 1.70–2.22) quartiles of the cumulative TyG-BMI had greater odds of experiencing a rapid FI trajectory. Higher frail risk was noted in those in the fourth quartile of baseline TyG-BMI (HR = 1.42, 95% CI: 1.28–1.58), with consistently second to highest (HR = 1.23, 95% CI: 1.12–1.34) and the highest TyG-BMI changes (HR = 1.58, 95% CI: 1.42–1.77), and those in the third (HR = 1.10, 95%

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CI: 1.00-1.21) and fourth quartile of cumulative TyG-BMI (HR = 1.46, 95% CI: 1.33–1.60). Participants with persistently second-lowest to the highest TyG-BMI changes ($\beta = 0.15$, 0.38 and 0.76 respectively) and those experiencing the third to fourth cumulative TyG-BMI ($\beta = 0.25$ and 0.56, respectively) demonstrated accelerated FI progression. A U-shaped association was observed between TyG-BMI levels and both rapid FI trajectory and higher frail risk, with BMI being the primary factor.

Conclusion A higher TyG-BMI is associated with the rapid development of FI trajectory and a greater frail risk. However, excessively low TyG-BMI levels also appear to contribute to frail development. Maintaining a healthy TyG-BMI, especially a healthy BMI, may help prevent or delay the frail onset.

Keywords TyG-BMI, Frailty index, Group-based trajectory model, Cohort study, K-means clustering

Introduction

Frailty is a complex, age-related clinical condition characterized by a decline in physiological capacity across multiple organ systems, which increases susceptibility to stressors [1]. The overall prevalence of frailty in the Chinese population is approximately 3.1% [2], with higher rates observed among middle-aged and elderly individuals, ranging from 15–25% [1, 3]. Once frail status is established, it progresses naturally and is associated with an increased likelihood of other geriatric syndromes, including falls, incontinence, rapid functional decline, pressure ulcers, mild cognitive impairment, and delirium [4]. Moreover, frailty is strongly correlated with both all-cause mortality and cause-specific mortality, and this correlation is independent of age [2]. Given the large base of the elderly population in China and the high prevalence of frailty among this group, it is imperative to prioritize the prevention of the onset and progression of frailty in this population. The gradual and continuous nature of frailty-related functional decline, which begins years before death [5], provides an opportunity to implement measures to halt or delay the onset and progression of frailty, thereby preventing adverse outcomes and extending the years of healthy life in the elderly population. However, current interventions for frailty have been generally ineffective [6], highlighting the need to bridge the gap between evidence and practice, identify more precise biomarkers, and develop more targeted treatment strategies for frailty.

Insulin resistance (IR) manifests as a reduced sensitivity or inadequate response to insulin, leading to a range of abnormalities in energy metabolism and lipid metabolism [7, 8], which seems to be the underlying pathomechanism in frailty and metabolic syndromes [9]. Currently, the triglyceride-glucose (TyG) index is widely used to measure IR [10], and elevated TyG indices are associated with various metabolic diseases, such as diabetes, cardiovascular diseases, acute kidney injury, and heart failure [11–13]. Furthermore, another study proposed a new metric that combines IR with body mass index (BMI), known as the triglyceride glucose-body mass index (TyG-BMI) [14]. This index, especially in the context of studies considering the impact of obesity on health, provides a more comprehensive perspective on metabolic health and is a more sensitive predictor of metabolic diseases than the TyG alone [15]. For instance, a high TyG-BMI may promote the incidence and progression of various diseases through impacts on muscle function, energy utilization, and inflammation levels [14], thereby facilitating the development of frailty. A cross-sectional study in Japan revealed a strong correlation between elevated TyG-BMI levels and hypertension [16]. In the United States, the TyG-BMI is useful for the early screening of non-alcoholic fatty liver disease (NAFLD) and metabolic associated fatty liver disease (MAFLD), and both the TyG-BMI and homeostatic model assessment of IR (HOMA-IR) are more suitable for assessing metabolic risk and monitoring disease progression in patients with NAFLD [17]. A longitudinal study in China revealed that persistently high TyG-BMI levels were associated with an increased incidence of stroke [18]. These diseases play a significant role in the onset of frailty among middle-aged and elderly people.

However, no studies have directly explored the relationship between changes in the TyG-BMI and the frail onset and progression. Only two smaller-scale studies have investigated the relationship between the TyG index and frailty. One retrospective study from Turkey among 430 elderly nondiabetic patients revealed that a high TyG was associated with an increased frailty index, generated using five items [19]. Another study from China involving 1,866 elderly individuals revealed that a persistently high TyG level was highly correlated with an increased frail risk, and this correlation was only present in participants with a high BMI. Unfortunately, that study did not explore the relationship between changes in the TyG and the frail progression [20]. Therefore, the purpose of the present study was to use the TyG-BMI, which incorporates BMI, to further explore the relationship between the TyG-BMI and changes in the risk of frailty onset and its progression, providing a reference for developing more precise frail treatment strategies and addressing the issue of poor intervention outcomes.

Methods

Study design and population

This study utilized a nationwide longitudinal cohort study conducted in China targeting middle-aged and elderly individuals, known as the China Health and Retirement Longitudinal Study (CHARLS). The design of this study has been extensively described in previous literature [21]. The cohort recruited a total of 17,708 participants from 150 districts in 28 provinces during the baseline survey (Wave 1), spanning the period from June 2011 to March 2012, primarily focusing on individuals aged 45 and above. Standardized questionnaires were used, and trained interviewers conducted face-to-face interviews with participants. Subsequently, new participants were enrolled in 2013 (Wave 2: 3,426), 2015 (Wave 3: 3,824), 2018 (Wave 4: 628), and 2020 (Wave 5: 297), totalling 25,583 surveyed participants (eFigure 12). Measurements of height, weight, blood samples, and blood pressure were collected at baseline and Wave 3. Our study included individuals aged 45 and older who completed all five surveys. Participants with missing data for triglycerides, glucose, or BMI at baseline and follow-ups were excluded, resulting in 9,135 participants who provided informed consent. Figure 1 shows the participant inclusion process. To analyze the relationship between TyG-BMI and frailty incidence, 950 participants who were frail at baseline were excluded. The CHARLS study was approved by the Ethics Review Committee of Peking University (IRB00001052–11,015).

Assessment of TyG-BMI

BMI formula is weight (kg) divided by height (m^2). The TyG-BMI was calculated using the formula Ln [Triglyceride (mg/dl) × Glucose (mg/dl)/2] × BMI (kg/m^2) [18] in wave 1 and wave 3. Furthermore, the cumulative TyG-BMI index was computed as $(TyG\text{-}BMI_{r1} + TyG\text{-}BMI_{r3})/2 \times time\ (r3-r1)$ [18].

Changes in the TyG-BMI were determined through K-means clustering analysis based on the TyG-BMI from wave 1 and wave 3. This unsupervised machine learning method allowed unbiased analysis without prior knowledge of the outcome variable. The optimal number

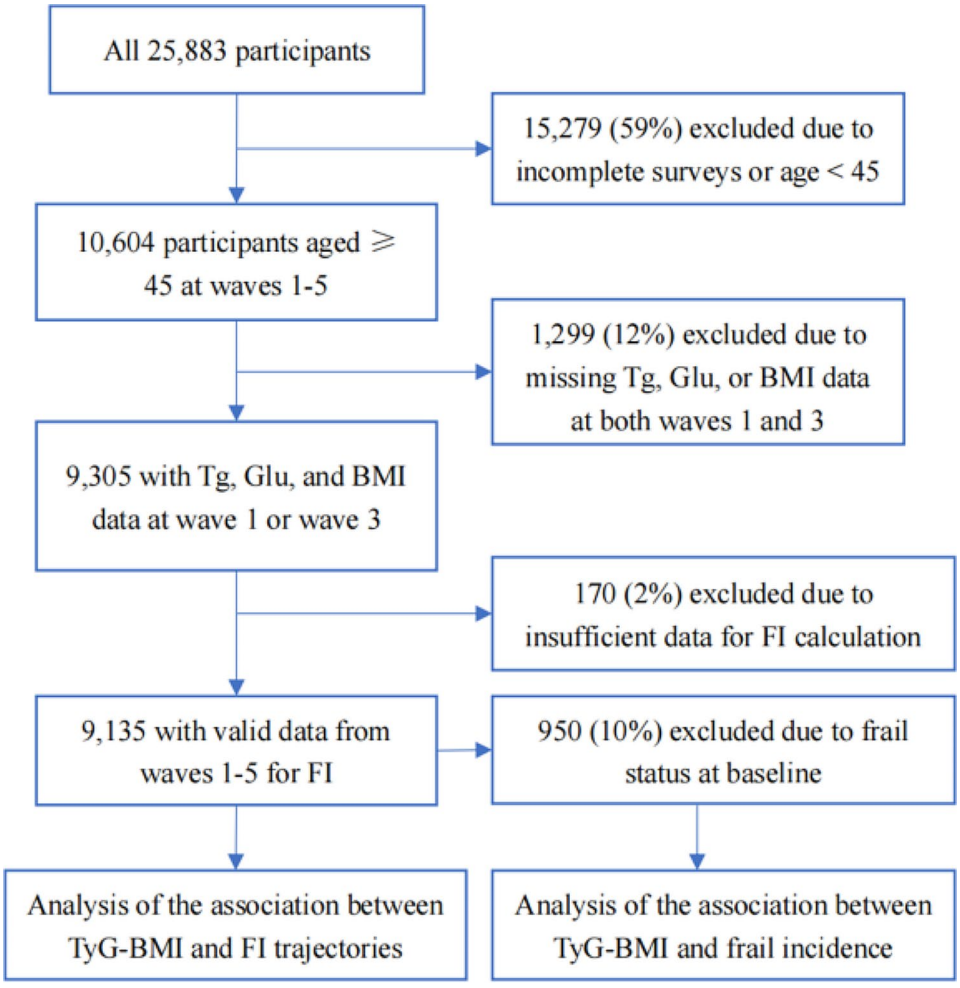

Fig. 1 Selection process of the study population; Tg Triglycerides; Glu Glucose; BMI Body mass index; FI frailty index; frail status FI ≥ 0.25

of clusters, determined using the elbow method, was found to be k=4 after 10 iterations (eFigure 11): Class 1 consistently had the lowest TyG-BMI, Class 2 consistently had the second-lowest TyG-BMI with a slight increase in 2015, Class 3 consistently had the second to highest with a slight increase. Class 4 consistently had the highest TyG-BMI, as detailed in Table 1; Fig. 2A B. The total silhouette coefficient for the K-means clustering was 0.550. Additionally, the percentage change in TyG-BMI from wave 1 to wave 3 was calculated using the following formula: percentage change in TyG-BMI = $(\text{TyG-BMI}_{r3}\text{- TyG-BMI}_{r1})/\text{TyG-BMI}_{r1}\times 100$.

Assessment of the frailty index (FI)

Frailty was assessed using the cumulative deficit approach based on age-related health deficits [22]. In this study, a standardized procedure was followed to construct the FI by selecting 30 items [23], including information on comorbidities, symptoms, disabilities, cognitive function, and depression; for details, see eTable 1 in the Supplements. Twenty-nine binary variables indicating the presence (1) or absence (0) of a health deficit and one continuous variable representing cognitive scores ranging from 0 to 1 were included. The FI was calculated by summing all health deficits and dividing by the number of included health items, resulting in a FI ranging from 0 to 1. A higher FI indicates a greater frailty level, with a FI≥0.25 indicating individuals as frail [2]. In our further analysis of the relationship between TyG-BMI and the frail incidence, we excluded study participants who were defined as frail at baseline.

To analyse the latent trajectory of the FI across the five surveys, a third-order group-based trajectory model (GBTM) was employed. Each study participant was assigned to the trajectory with the highest probability. Based on criteria such as the lowest Akaike information criterion (AIC) and Bayesian information criterion (BIC) values and an average posterior probability>70%, as well as a minimum sample size of ≥2% for each class, the study participants were classified into two distinct trajectories (eTable 13). In trajectory 1, participants had a relatively low FI at baseline and experienced a slow increase over time. In contrast, participants in trajectory 2 exhibited a higher FI at baseline and a rapid increase over time (Fig. 2F).

Covariates

Covariates included age, sex, marital status, smoking status, alcohol consumption, education level, physical activity level, C-reactive protein (CRP), and HbA1c. Marital status was categorized as married or other, smoking status as never smoked or former smoker, alcohol consumption as never drank or former drinker, education level as below primary school, primary school, middle school, high school or above. Participants' engagement in physical activity was assessed based on whether they engaged in light, moderate, or vigorous physical activity for at least 10 min once a week. For details, see eMethods in the Supplements.

Statistical analyses

Missing values were imputed using the random forest multiple imputation method in R, specifically using the "mice" package. The variables with missing values and their respective percentages were as follows: triglycerides (mg/dl): 19.1% in wave 1, 15.7% in wave 3; glucose (mg/dl): 19.1% in wave 1, 15.6% in wave 3; and items for calculating the FI in wave 1 to wave 5 (average percentages ranging from 1.3 to 2.1%, details in eTable 1 in the Supplements).

Descriptive analysis was conducted to examine the normality of continuous variables using histograms. Normally distributed variables are described using means±standard deviations (SDs), while skewed variables are described using medians (quartiles). Categorical data are presented as frequencies (proportions). Differences between groups for each variable were assessed using analysis of variance (ANOVA) or the Kruskal–Wallis H test for continuous variables and the χ^2 test for categorical variables.

Binary logistic regression analysis was used to assess the correlation between baseline TyG-BMI (quartiles), TyG-BMI change classes, cumulative TyG-BMI (quartiles), and the trajectory of FI development in 9135 participants. After excluding study participants who were already frail at baseline, Cox regression was employed to evaluate the relationships between the independent variables and the risk of frail incidence among the 8185 participants. In the analysis, the first quartile (low level) was used as the reference to calculate the odds ratio (OR), hazard ratio (HR) and 95% CI. The time variable was defined as the time elapsed for study participants to the first time when they became frail from the wave 2 to wave 5 surveys. Logistic regression and Cox regression were performed for the two models. Model 1 was the null model, while Model 2 was adjusted for age, sex, marital status, smoking status, alcohol consumption status, education level, physical activity level, CRP, and HbA1c. We used Logistic and Cox regression models to plot ROC (Receiver Operating Characteristic) curves and calculate AUC (Area Under the Curve) values, assessing predictive ability. The optimal cutoff value for the independent variable was determined using the maximum Youden index. A mixed-effects linear model was used to evaluate the relationships between independent variables and the progression of FI as a continuous dependent variable. Due to the right-skewed distribution of FI, the natural logarithm transformation (LN (FI+1)) * 100 was applied. TyG-BMI

Table 1 Baseline characteristics of 9135 participants according to the change in the TyG-BMI

Characteristic	Overall (*n* = 9135)	Class 1 (*n* = 2454)	Class 2 (*n* = 3276)	Class 3 (*n* = 2387)	Class 4 (*n* = 1018)	*P*
Age	58.18 ± 8.48	60.17 ± 9	57.99 ± 8.37	57.11 ± 7.93	56.52 ± 7.92	< 0.001
Sex						
Female	4968 (54.4)	1080 (44)	1769 (54)	1453 (60.9)	666 (65.4)	< 0.001
Male	4167 (45.6)	1374 (56)	1507 (46)	934 (39.1)	352 (34.6)	
Marital status						
Married	8225 (90)	2158 (87.9)	2937 (89.7)	2185 (91.5)	945 (92.8)	< 0.001
Other	910 (10)	296 (12.1)	339 (10.3)	202 (8.5)	73 (7.2)	
Ever smoke						
NO	5640 (61.7)	1230 (50.1)	2050 (62.6)	1632 (68.4)	728 (71.5)	< 0.001
YES	3495 (38.3)	1224 (49.9)	1226 (37.4)	755 (31.6)	290 (28.5)	
Ever drink						
NO	5603 (61.3)	1376 (56.1)	1984 (60.6)	1539 (64.5)	704 (69.2)	< 0.001
YES	3532 (38.7)	1078 (43.9)	1292 (39.4)	848 (35.5)	314 (30.8)	
Educational level						
Below primary school	4270 (46.7)	1273 (51.9)	1514 (46.2)	1024 (42.9)	459 (45.1)	< 0.001
Primary school	1996 (21.9)	558 (22.7)	728 (22.2)	505 (21.2)	205 (20.1)	
Middle school	1916 (21.0)	442 (18.0)	676 (20.6)	554 (23.2)	244 (24.0)	
High school or above	953 (10.4)	181 (7.4)	358 (10.9)	304 (12.7)	110 (10.8)	
Vigorous activity						
NO	5649 (61.8)	1316 (53.6)	1990 (60.7)	1604 (67.2)	739 (72.6)	< 0.001
YES	3486 (38.2)	1138 (46.4)	1286 (39.3)	783 (32.8)	279 (27.4)	
Moderate activity						
NO	3195 (35)	751 (30.6)	1120 (34.2)	898 (37.6)	426 (41.8)	< 0.001
YES	5940 (65)	1703 (69.4)	2156 (65.8)	1489 (62.4)	592 (58.2)	
Light activity						
NO	1230 (13.5)	308 (12.6)	425 (13)	337 (14.1)	160 (15.7)	0.053
YES	7905 (86.5)	2146 (87.4)	2851 (87)	2050 (85.9)	858 (84.3)	
CRP mg/L	2.42 ± 6.27	2.42 ± 8.07	2.22 ± 5.51	2.45 ± 5.28	3.06 ± 5.69	0.003
HbA1c g/dL	5.25 ± 0.79	5.11 ± 0.57	5.17 ± 0.63	5.36 ± 0.92	5.65 ± 1.12	< 0.001
r1BMI[a]	23.56 ± 3.73	19.69 ± 1.78	22.86 ± 1.89	25.95 ± 2.23	29.53 ± 2.7	< 0.001
r3BMI	23.86 ± 3.79	19.81 ± 1.75	23.28 ± 1.94	26.31 ± 2.18	29.79 ± 2.86	< 0.001
r1Triglycerides (mg/dl)	105.32 (75.23, 153.99)	77.88 (60.18, 104.43)	99.12 (74.34, 138.06)	131.87 (98.24, 187.62)	185.85 (129.87, 276.12)	< 0.001
r3Triglycerides (mg/dl)	115.04 (84.07, 169.91)	83.19 (66.37, 107.08)	110.62 (84.96, 153.1)	146.9 (107.96, 206.19)	205.31 (144.25, 292.92)	< 0.001
r1Glucose (mg/dl)	102.24 (94.50, 112.86)	98.64 (91.26, 107.46)	100.98 (93.96, 110.16)	104.94 (96.84, 115.92)	112.14 (100.62, 134.73)	< 0.001
r3Glucose (mg/dl)	95.50 (88.29, 106.31)	91.89 (84.68, 99.1)	95.5 (88.29, 104.50)	99.1 (91.89, 111.71)	106.31 (95.5, 131.53)	< 0.001
r1TyG-BMI[b]	205.03 ± 39.31	163.28 ± 15.63	195.53 ± 15.46	230.81 ± 18.11	275.77 ± 26.14	< 0.001
r3TyG-BMI[b]	208.76 ± 40.04	164.19 ± 15.7	200.82 ± 15.84	235.81 ± 18.47	278.34 ± 25.3	< 0.001
Cumulative TyG-BMI[c]	620.68 ± 112.54	491.2 ± 37.54	594.53 ± 30	699.93 ± 33.23	831.16 ± 55.9	< 0.001
r1FI[d]	0.12 (0.09, 0.18)	0.12 (0.08, 0.18)	0.12 (0.09, 0.18)	0.13 (0.09, 0.18)	0.15 (0.11, 0.21)	< 0.001
r2FI[d]	0.13 (0.09, 0.18)	0.12 (0.09, 0.18)	0.12 (0.09, 0.18)	0.15 (0.10, 0.19)	0.15 (0.11, 0.22)	< 0.001
r3FI[d]	0.16 (0.11, 0.22)	0.15 (0.11, 0.22)	0.15 (0.11, 0.21)	0.16 (0.12, 0.22)	0.19 (0.14, 0.26)	< 0.001
r4FI[d]	0.18 (0.13, 0.26)	0.18 (0.12, 0.25)	0.18 (0.12, 0.25)	0.20 (0.14, 0.27)	0.22 (0.16, 0.31)	< 0.001
r5FI[d]	0.21 (0.15, 0.29)	0.19 (0.13, 0.28)	0.19 (0.15, 0.28)	0.22 (0.15, 0.30)	0.25 (0.18, 0.36)	< 0.001
Trajectory 1[e]	5483 (60.0)	1548 (63.1)	2105 (64.3%)	1354 (56.7%)	476 (46.8%)	< 0.001
Trajectory 2[e]	3625 (40.0)	906 (36.9%)	1171 (35.7%)	1033 (43.3%)	542 (53.2%)	

r1 values from 2011; r2 values from 2013; r3 values from 2015; r4 values from 2018; r5 values from 2020; a BMI body mass index; b The TyG-BMI was calculated by the formula: Ln [Triglyceride (mg/dl) × Fasting blood glucose (mg/dl)/2] × BMI (kg/m^2); c Cumulative TyG-BMI was calculated by the formula (r1TyG-BMI + r3TyG-BMI)/2 × time(r3 − r1); d FI Frailty index; e Trajectory of FI; *P* value was based on analysis of variance, χ^2 or Kruskal-Wallis H test where appropriate

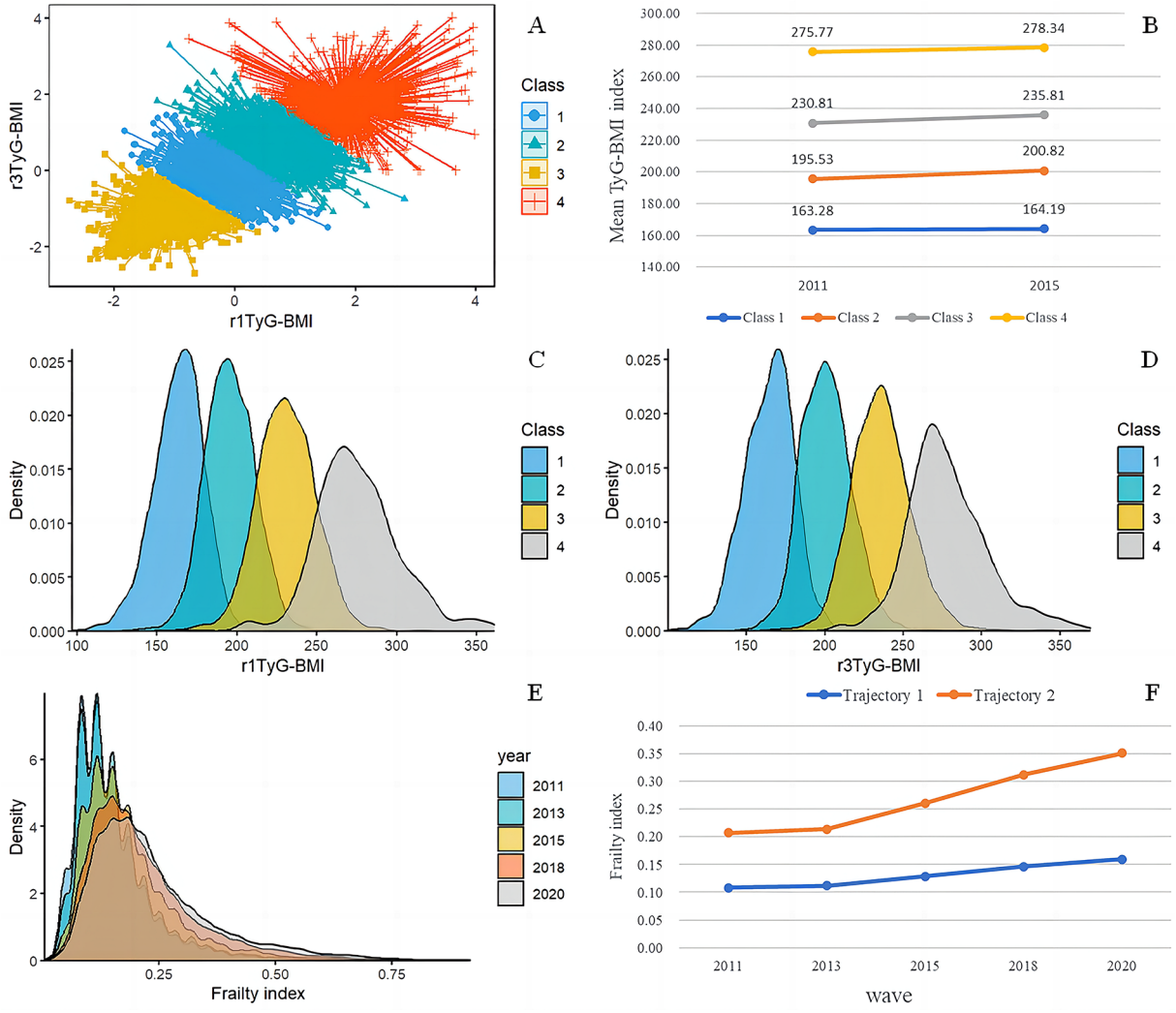

Fig. 2 **A** Four classes were found using the K-means method with Euclidean distance. **B** Data visualization for the classes of the change in the TyG-BMI. **C** Distribution for the TyG-BMI at 2011. D Distribution for the TyG-BMI at 2015. **E** Distribution for 5-surveys frailty index. **F** Five-surveys trajectories of FI for different categories

quartiles, TyG-BMI change classes, follow-up time, interactions between TyG-BMI levels, classes, and time, as well as covariates, were treated as fixed effects. Random intercepts and slopes were included for study participants, reflecting the differences in FI associated with different levels of TyG-BMI and its changes. The regression coefficients for different TyG-BMI levels and their changes reflected the differences in FI at those levels. The regression coefficient for time indicated the overall rate of change in FI over time (annual change in FI), while the regression coefficient for interaction terms reflected the additional rate of change in FI over time compared to the reference group, considering different TyG-BMI levels and its changes.

This study also utilized restricted cubic spline (RCS) functional regression models based on Model 2 logistic regression and Cox regression to explore the potential nonlinear relationships between baseline continuous TyG-BMI, cumulative TyG-BMI, and the percentage change in TyG-BMI with the trajectory of FI development and the frail incidence. The optimal number of inflection points was 5 based on a 10-fold cross-validation method. When examining the relationship between the percentage change in TyG-BMI and the dependent variable, baseline TyG-BMI was adjusted in addition to the covariates. Given that the TyG-BMI is derived from the combination of triglycerides, glucose, and BMI, we employed weighted quantile sum (WQS) regression in model 2. For this analysis, variables were categorized into quartiles, and a bootstrap sampling method was utilized, with 100 iterations. The sample was divided into a training set comprising 40% of the data and a validation set consisting of the remaining 60% to determine the weights for glucose, triglycerides, and BMI. These weights quantify

the individual contributions of each variable to the overall effect. A larger weight assignment to a variable indicates that this variable has a greater contribution to the overall effect predicted by the model.

To validate the robustness of the study results, some sensitivity analyses were conducted. (1) Study participants with missing blood test indicators in either the wave 1 or wave 3 surveys were excluded. Participants with more than 5 missing items out of the 30 items required to calculate the FI were also excluded, and the remaining participants' FI scores were recalculated based on the actual number of completed items. (2) Due to the controversy surrounding the cut-off value for defining frail status, an alternative cut-off value was used to redefine frail status (FI>0.21). (3) We compared the baseline characteristics between participants who were included in the study and those who were not. Stratified analyses based on sex, age (45–55, 56–65, 65~), marital, smoke, drink status, educational level, physical activity (with or no moderate to high physical activity), CRP (≤3 or >3 mg/L), HbA1c (<6 or ≥6 g/dL) were conducted to explore variations in effects among different subgroups. All analyses in this study were conducted with a two-tailed significance level of α=0.05 indicating statistical significance. The statistical software packages R version 4.3.3 and IBM SPSS version 25.0 (IBM Corp., Armonk, NY, USA) were utilized for the analyses.

Table 2 Associations of TyG-BMI (Q1-Q4) with FI trajectory and frail incidence

Variables	Events/*n*	Model 1[a]		Model 2[b]	
Baseline TyG-BMI[c] (*N*=9135)	Trajectory 2[e]	OR (95% CI)	*P*	OR (95% CI)	*P*
Q1 (97.18,176.18)	834/2284	Reference		Reference	
Q2 (176.18, 199.98)	812/2284	0.96 (0.85, 1.08)	0.498	1.04 (0.92, 1.19)	0.522
Q3 (200.00, 229.68)	900/2284	1.13 (1.00, 1.27)	**0.044**	1.25 (1.10, 1.42)	**0.001**
Q4 (229.69, 361.44)	1106/2283	1.63 (1.45, 1.84)	**<0.001**	1.83 (1.61, 2.09)	**<0.001**
	P for trend[f]		**<0.001**	*P* for trend[f]	**<0.001**
Baseline TyG-BMI[c] (*N*=8185)	Frail[d]	HR (95% CI)		HR (95% CI)	
Q1 (97.18,176.18)	708/2059	Reference		Reference	
Q2 (176.18, 199.98)	688/2077	0.95 (0.85, 1.05)	0.333	1.01 (0.91, 1.12)	0.907
Q3 (200.00, 229.68)	723/2045	1.03 (0.93, 1.14)	0.555	1.11 (1.00, 1.23)	0.055
Q4 (229.69, 361.44)	871/2004	1.32 (1.20, 1.46)	**<0.001**	1.42 (1.28, 1.58)	**<0.001**
	P for trend[f]		**<0.001**	*P* for trend[f]	**<0.001**

a Unadjusted for covariates; b Adjusted for Age, gender, marital status, smoke, drink, educational level, physical activity, CRP, HbA1c; Q1-4 Quartile 1–4; c The TyG-BMI was calculated by the formula ln [Triglyceride (mg/dl) × Fasting blood glucose (mg/dl)/2] × BMI (kg/m^2) and then it was split into quartiles; d Frailty index≥0.25; e Trajectory 2 of FI; f Tests for linear trends were performed by modelling the median value of each quantile to test ordered relations across quantiles of the TyG-BMI

Results

Baseline characteristics

The mean age was 58.18±8.48 years, with 4,968 females accounting for 54.4% of the sample. The average TyG-BMI levels at baseline and in 2015 were 205.03±39.31 and 208.76±40.04, respectively. Compared with participants in Class 1, those in Classes 2 to 4 showed a progressively increasing trend in average TyG-BMI in 2011 and 2015.

The average cumulative TyG-BMI was 620.68±112.54, and it also increased progressively from Classes 1 to 4. The median FI values from 2011 to 2020 increased annually and were as follows: 0.12 (0.09, 0.18), 0.13 (0.09, 0.18), 0.16 (0.11, 0.22), 0.18 (0.13, 0.26), and 0.21 (0.15, 0.29). The FI levels also increased progressively from Class 1 to 4. A total of 3,625 individuals were assigned to trajectory 2, accounting for 40.0% of the sample (see Table 1).

Association of baseline TyG-BMI with the trajectory of FI and the frail incidence

In Model 2, compared with research participants with the lowest baseline TyG-BMI, individuals in the third quartile of TyG-BMI had 25% greater odds of belonging to the high-speed FI growth trajectory (OR=1.25, 95% CI: 1.10, 1.42), while those with the highest TyG-BMI had 83% greater odds of belonging to the high-speed FI growth trajectory (OR=1.83, 95% CI: 1.61, 2.09). Regarding the relationship between baseline TyG-BMI and frail incidence, only individuals with the highest TyG-BMI had a greater frail risk compared with the reference group (HR=1.42, 95% CI: 1.28, 1.58; Table 2).

Baseline TyG-BMI can discriminate both FI trajectory and frail onset. With only TyG-BMI in the model, the AUC is 0.553 for FI trajectory and 0.542 for frail onset (eFigure 13 A, eFigure 14 A). TyG-BMI values above 222.19 and 220.35 significantly increase the likelihood of FI trajectory 2 and frailty onset, respectively (eTable 15). Including covariates improves the AUC to 0.690 for FI trajectory and 0.693 for frail onset, with optimal cutoffs at 222.19 and 151.74 (eTable 15). When fitting the RCS model with baseline TyG-BMI as a continuous variable, we discovered a nonlinear relationship between baseline TyG-BMI and trajectory 2 (overall $P<0.001$, nonlinear $P<0.001$), as well as between baseline TyG-BMI and the frail incidence rate (overall $P<0.001$, nonlinear $P<0.001$; Fig. 3).

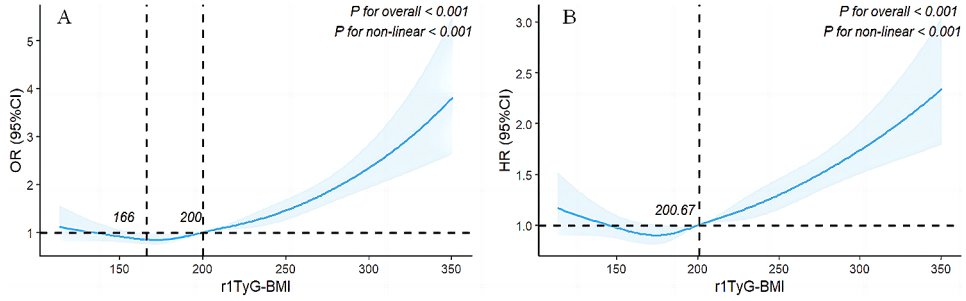

Fig. 3 A The nonlinear association between baseline TyG-BMI and trajectory of FI; B The nonlinear association between baseline TyG-BMI and frail incidence

Table 3 Associations of change in TyG-BMI with FI trajectory and frail incidence

Variables	Events/*n*	Model 1[a]		Model 2[b]	
Change in TyG-BMI[c] (*N* = 9135)	Trajectory 2[e]	OR (95% CI)	*P*	OR (95% CI)	*P*
Class 1	906/2454	Reference		Reference	
Class 2	1171/3276	0.95 (0.85, 1.06)	0.360	1.05 (0.94, 1.18)	0.374
Class 3	1033/2387	1.30 (1.16, 1.46)	**< 0.001**	1.49 (1.32, 1.70)	**< 0.001**
Class 4	542/1018	1.95 (1.68, 2.26)	**< 0.001**	2.17 (1.84, 2.56)	**< 0.001**
Change in TyG-BMI[c] (*N* = 8185)	Frail[d]	HR (95% CI)	*P*	HR (95% CI)	*P*
Class 1	746/2200	Reference		Reference	
Class 2	1004/2981	0.96 (0.89, 1.04)	0.348	1.04 (0.96, 1.13)	0.344
Class 3	840/2145	1.13 (1.04, 1.23)	**0.006**	1.23 (1.12, 1.34)	**< 0.001**
Class 4	400/859	1.49 (1.34, 1.65)	**< 0.001**	1.58 (1.42, 1.77)	**< 0.001**

a Unadjusted for covariates; b Adjusted for Age, gender, marital status, smoke, drink, educational level, physical activity, CRP, HbA1c; Q1-4 Quartile 1–4; c The TyG-BMI was calculated by the formula Ln [Triglyceride (mg/dl) × Fasting blood glucose (mg/dl)/2] × BMI (kg/m^2) and then it was split into quartiles; d Frailty index≥0.25; e Trajectory 2 of FI; f Tests for linear trends were performed by modelling the median value of each quantile to test ordered relations across quantiles of the TyG-BMI

Association of changes in TyG-BMI with the trajectory of FI and the frail incidence

Compared with research participants with consistently lowest TyG-BMI levels (Class 1), in Model 2, the odds of belonging to the high-growth trajectory were greater for the groups with consistently second to highest TyG-BMI levels (Class 3) and with consistently the highest TyG-BMI levels (Class 4), with an OR of 1.49 (95% CI: 1.32, 1.70) and 2.17 (95% CI: 1.84, 2.56), respectively. Similarly, individuals with Class 3 and the Class 4 in Model 2 had a progressively increasing frail risk, with HR of 1.23 (1.12, 1.34) and 1.58 (1.42, 1.77), respectively (Table 3).

When fitting the RCS curve to the percentage change in TyG-BMI as a continuous variable, there was a linear relationship (*P* for overall = 0.002; *P* for overall = 0.078) between the percentage change in TyG-BMI and the FI trajectory as well as the frail incidence rate (*P* for overall = 0.002; *P* for overall = 0.257). However, it is worth noting that even though the differences were not statistically significant, there were increasing odds for individuals to belong to trajectory 2 and an increased risk of frail incidence with an excessive decrease in TyG-BMI (Fig. 4).

Association of cumulative TyG-BMI with the trajectory of FI and the frail incidence

Compared with individuals with low cumulative TyG-BMI levels, individuals in the third percentile in Model 2 had 20% greater odds of belonging to the high-speed

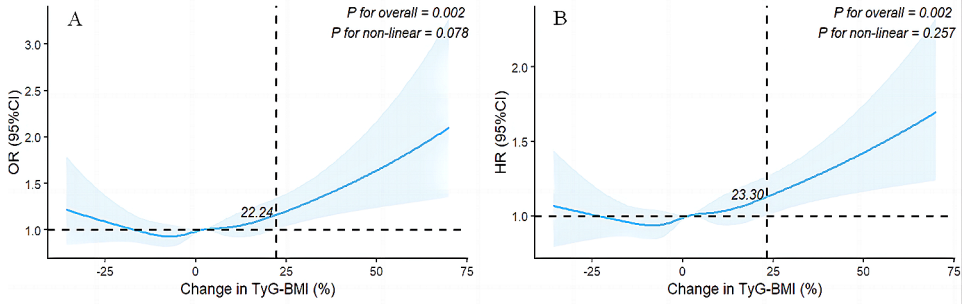

Fig. 4 A The nonlinear association between percentage change in TyG-BMI and the trajectory of FI; B The nonlinear association between percentage change in TyG-BMI and the frail incidence

Table 4 Associations of cumulative TyG-BMI (Q1-Q4) with FI trajectory and frail incidence

Variables	Events/*n*	Model 1[a]		Model 2[b]	
Cumulative TyG-BMI[c] (*N* = 9135)	Trajectory 2[e]	OR (95% CI)	*P*	OR (95% CI)	*P*
Q1 (339.22, 536.62)	926/2284	Reference		Reference	
Q2 (536.65, 609.20)	906/2283	0.95 (0.84, 1.07)	0.361	1.04 (0.92, 1.19)	0.506
Q3 (609.25, 694.32)	944/2285	1.07 (0.95, 1.2)	0.304	1.20 (1.05, 1.36)	**0.007**
Q4 (694.40, 1079.53)	1164/2283	1.67 (1.48, 1.88)	**< 0.001**	1.94 (1.70, 2.22)	**< 0.001**
	P for trend[f]		**< 0.001**	*P* for trend[f]	**< 0.001**
Cumulative TyG-BMI[c] (*N* = 8185)	Frail[d]	HR (95% CI)		HR (95% CI)	
Q1 (339.22, 536.62)	690/2048	Reference		Reference	
Q2 (536.65, 609.20)	695/2072	0.97 (0.88, 1.06)	0.450	1.04 (0.95, 1.14)	0.383
Q3 (609.25, 694.32)	727/2068	1.02 (0.93, 1.11)	0.711	1.10 (1.00, 1.21)	**0.043**
Q4 (694.40, 1079.53)	878/1997	1.33 (1.22, 1.45)	**< 0.001**	1.46 (1.33, 1.60)	**< 0.001**
	P for trend[f]		**< 0.001**	*P* for trend[f]	**< 0.001**

a Unadjusted for covariates; b Adjusted for Age, gender, marital status, smoke, drink, educational level, physical activity, CRP, HbA1c; Q1-4 Quartile 1–4; c The cumulative TyG-BMI was calculated by the formula (r1TyG-BMI + r3TyG-BMI)/2× time(r3 − r1) and then it was split into quartiles; c Frailty index ≥ 0.25; e Trajectory 2 of FI; f Tests for linear trends were performed by modelling the median value of each quantile to test ordered relations across quantiles of the TyG-BMI

FI growth trajectory (OR = 1.20, 95% CI: 1.05, 1.36), while those in the fourth percentile had 94% greater odds (OR = 1.94, 95% CI: 1.70, 2.22). Regarding the frail incidence, individuals in the third (HR = 1.10, 95% CI: 1.00, 1.21) and fourth (HR = 1.46, 95% CI: 1.33, 1.60) percentile of the cumulative TyG-BMI had a greater risk of frail incidence compared with those in the lowest percentile (Table 4).

Cumulative TyG-BMI can discriminate both the FI trajectory and the risk of frailty onset. With only cumulative TyG-BMI in the model, the AUC is 0.554 for FI trajectory and 0.543 for frail onset (eFigure 13B, eFigure 14B). When cumulative TyG-BMI exceeds 685.17 and 743.27, the likelihood of belonging to FI trajectory 2 and the risk of frail onset significantly increase (eTable 15). Including covariates improves the model's discriminative ability, with AUCs of 0.691 for FI trajectory and 0.694 for frail onset (eFigure 13B, eFigure 14B). The optimal cutoff values are 347.68 and 457.17, respectively (eTable 15). When the RCS curve was fitted to the cumulative TyG-BMI as a continuous variable, a nonlinear relationship was found between the cumulative TyG-BMI and FI trajectory 2 (*P* for overall < 0.001, *P* for nonlinear < 0.001) and the frail incidence (*P* for overall < 0.001, *P* for nonlinear < 0.001) (Fig. 5).

Association of change in TyG-BMI and cumulative TyG-BMI (Q1-Q4) with FI progression

Compared with research participants in Class 1 in Model 2, individuals in Class 4 exhibited a significantly higher FI (β = 1.08, 95% CI: 1.14, 1.34) and the fastest rate of FI development progression (β = 0.76, 95% CI: 0.58, 0.93). Individuals in Class 2 and Class 3 showed significantly faster FI progression, with β values of 0.38 (95% CI: 0.25, 0.52) and 0.76 (95% CI: 0.58, 0.93), respectively. Individuals in the highest cumulative TyG-BMI percentile demonstrated a significantly higher FI (β = 1.24, 95% CI: 1.14, 1.34) and the fastest rate of FI progression (β = 0.56, 95% CI: 0.42, 0.70). There was no statistically significant difference in FI between individuals in the third percentile and those in the first percentile, but FI progressed at a faster rate (β = 0.25, 95% CI: 0.11, 0.38) (Table 5).

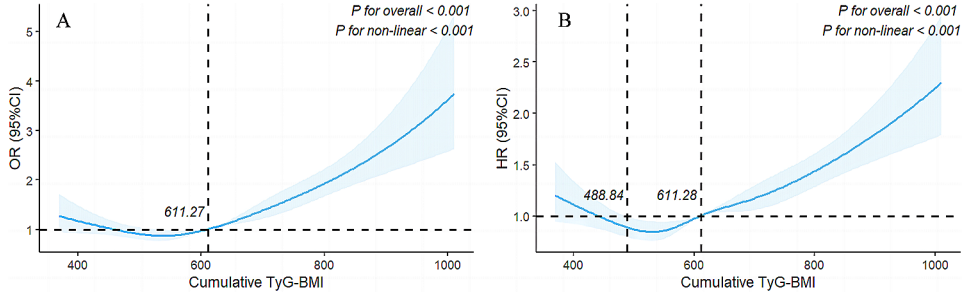

Fig. 5 A The nonlinear association between percentage cumulative TyG-BMI and the trajectory of FI; B The nonlinear association between percentage cumulative TyG-BMI and the frail incidence

Table 5 Associations of the change in TyG-BMI and cumulative TyG-BMI with FI progression

Variable (*N* = 9135)	Model 1[a]		Model 2[b]	
	β (95% CI)	*P*	β (95% CI)	*P*
Change in TyG-BMI				
Class 1	Reference		Reference	
Class 2	-0.28 (-0.65,0.08)	0.131	-0.05 (-0.43, 0.33)	0.781
Class 3	-0.28 (-0.35,0.44)	0.838	0.19 (-0.22, 0.61)	0.358
Class 4	0.04 (0.65,1.68)	**< 0.001**	1.08 (0.54, 1.62)	**< 0.001**
Year	1.16 (1.63,1.79)	**< 0.001**	1.24 (1.14, 1.34)	**< 0.001**
Class 1*year				
Class 2*year	0.12 (0.01,0.23)	**0.028**	0.15 (0.02, 0.27)	**0.022**
Class 3*year	0.33 (0.21,0.44)	**< 0.001**	0.38 (0.25, 0.52)	**< 0.001**
Class 4*year	0.69 (0.54,0.84)	**< 0.001**	0.76 (0.58, 0.93)	**< 0.001**
Cumulative TyG-BMI[c]				
Q1 (339.22, 536.62)	Reference		Reference	
Q2 (536.65, 609.20)	-0.40 (-0.81, 0.01)	0.054	-0.16 (-0.58, 0.26)	0.447
Q3 (609.25, 694.32)	-0.11 (-0.52, 0.29)	0.587	-0.02 (-0.45, 0.40)	0.912
Q4 (694.40, 1079.53)	0.54 (0.13, 0.95)	**0.009**	0.72 (0.29, 1.15)	**< 0.001**
Year	1.71 (1.63, 1.80)	**< 0.001**	1.24 (1.14, 1.34)	**< 0.001**
Q1*year				
Q2*year	0.12 (0.00, 0.24)	**0.044**	0.13 (0.00, 0.27)	0.058
Q3*year	0.16 (0.04, 0.28)	**0.010**	0.25 (0.11, 0.38)	**< 0.001**
Q4*year	0.54 (0.42, 0.66)	**< 0.001**	0.56 (0.42, 0.70)	**< 0.001**

a Unadjusted for covariates; b Adjusted for Age, gender, marital status, smoke, drink, educational level, physical activity, CRP, HbA1c; Q1-4 Quartile 1–4; c The Cumulative TyG-BMI was calculated by the formula (r1TyG-BMI + r3TyG-BMI)/2× time(r3 − r1) and then it was split into quartiles

WQS analyses

After adjusting for covariates in Model 2, we found that BMI had the greatest contribution to the rapid development of the FI trajectory, with a contribution weight of 0.49 in 2011 and 0.66 in 2015. Triglycerides ranked second in terms of contributing to the rapid development of frailty during these two surveys, with weights of 0.38 and 0.27, respectively. Similarly, for the frail incidence, BMI was the primary influencing factor, with weights of 0.39 in 2011 and 0.66 in 2015. The weights of triglycerides and glucose were consistent across the two surveys (Fig. 6).

Sensitivity and subgroup analyses

According to the sensitivity analyses, we did not observe a significant difference in the baseline characteristics between participants and non-participants. And all the results remained largely consistent with the initial findings, except for the disappearance of the nonlinear relationship between the percentage change in TyG-BMI and the frail incidence. These findings are detailed in eTable 2–8 and eFigure 1–5 in supplements. Subgroup analysis showed that in Model 2, the association between TyG-BMI and frail incidence risk disappeared in participants over 65 years old (eTable 16–19) and those who were unmarried (eTable 20–23). Conversely, smokers (eTable 24–27), individuals with higher education (eTable 32–35), and those with elevated CRP (eTable 40–43) and HbA1c (eTable 44–47) levels had a higher risk of frail onset and were more likely to belong to FI trajectory 2. The WQS and fitted RCS curve results showed no significant changes compared to the original findings (Supplements 2).

Discussion

Our findings indicate that individuals with a high baseline TyG-BMI, a persistently second to highest and highest TyG-BMI, and the higher cumulative TyG-BMI are more likely to experience a high-speed FI growth trajectory and are at a greater frail risk. In terms of the development speed of FI, those in class 2–4 TyG-BMI levels experienced progressively faster development of FI. Additionally, participants with high cumulative TyG-BMI levels also experienced a progressively faster development of FI. The RCS curve demonstrated a U-shaped association between baseline TyG-BMI, percentage change in TyG-BMI, cumulative TyG-BMI, and the rapid development trajectory of FI as well as the risk of frail incidence among the study participants. BMI was the most significant contributor to the rapid FI trajectory and the frail incidence in baseline and wave 3. In those over 65 years old and unmarried, increased TyG-BMI was not linked to frail incidence. And TyG-BMI interacted with education, smoking, CRP, and HbA1c.

Currently, there is no direct evidence for a relationship between the TyG-BMI and frailty. However, a decrease in insulin sensitivity leads to alterations in the oxidative-antioxidative balance and accelerated inflammatory responses, particularly due to increased adipose tissue and decreased muscle mass density, resulting in sustained inflammation. Additionally, with ageing, the immune system may exhibit low-level chronic inflammation [24], which can increase the production of reactive oxygen species and potentially impair the overall antioxidant capacity of the body, leading to the development of various diseases [25, 26]. Furthermore, functional impairment of the inflammatory response can disrupt the oxidative-antioxidative balance in the body and lead to significant pathological dysfunction, such as metabolic and frail syndromes [9]. For instance, glucose dysregulation in a prediabetic state can lead to chronic inflammation and metabolic disorders, which in turn contribute to the onset and progression of frailty, with IR is one of the primary mechanisms increasing the risk of developing a prediabetic state [27]. Additionally, Prediabetic conditions are often accompanied by comorbidities such as hypertension, which increase renal vascular pressure

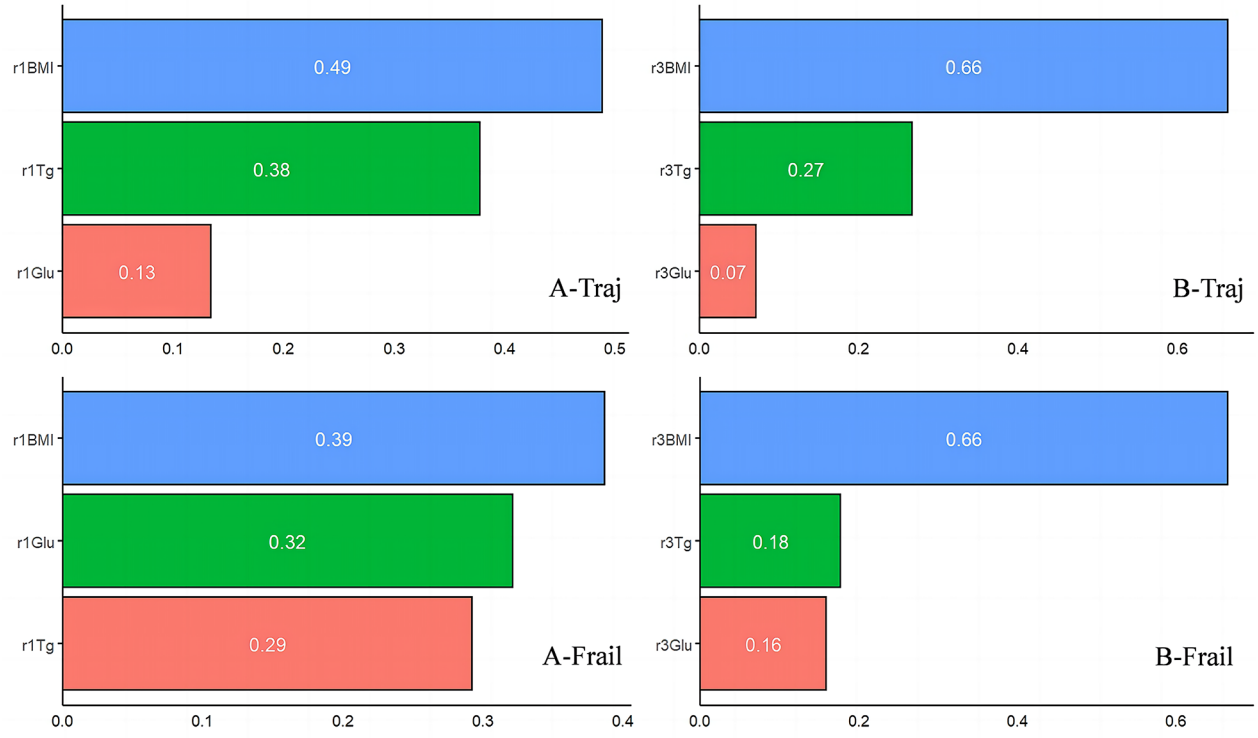

Fig. 6 Estimated weights assigned to TyG-BMI with the WQS model; Model adjusted for Age, gender, marital status, smoke, drink, educational level, physical activity, CRP, HbA1c; A, B-Traj Contribution weight of FI trajectory 2; C, D Contribution weight of frail incidence; r1 values from 2011; r3 values from 2015. Glu Glucose; Tg Triglycerides; BMI body mass index

and cause arteriosclerosis, further leading to metabolic dysfunctions such as IR and elevated proteinuria levels. Previous studies have shown that IR, measured by the HOMA-IR, and high proteinuria levels are associated with cognitive decline in frail elderly individuals with prediabetes, thereby accelerating the progression of frailty in the elderly [27, 28]. Raúl F Pérez-Tasigchana et al. evaluated IR using the HOMA-IR and reported a significant association between IR and an increased risk of frailty [29]. Similarly, Po-Sen Peng et al. reported a correlation between high IR levels and frailty among older adults in the United States [8], which supports our research findings. In a cross-sectional study conducted by Faysal Şaylık et al. in Turkey involving 430 nondiabetic patients aged 65 years and older who had experienced myocardial infarction, a modified FI was used to assess comorbidities and the TyG as a convenient measure of IR. They found a positive correlation between the TyG and the FI [19]; although the sample size was relatively small and an in-depth analysis of frailty was not conducted, the results suggest that the TyG index can predict the frail incidence. Subsequently, Yin Yuan et al. conducted a prospective cohort study in Fujian Province, China, involving 1,866 elderly individuals to further explore the relationship between changes in the TyG index and frailty. They also used a FI based on health deficits to assess the frailty status of the study participants and found a significantly increased risk of frailty in individuals with high baseline TyG levels and a stable high TyG trajectory. Their study also revealed a correlation between a stable high TyG trajectory and frailty only among participants with a BMI≥24 kg/m² [20], indicating that BMI plays an important role in the relationship between IR and frailty. Therefore, in this study, we used the TyG-BMI, which combines the TyG index and BMI, to comprehensively investigate the relationship between metabolic health risks and frailty. We found that individuals with higher baseline TyG-BMI index levels had a greater frail incidence risk and experienced a faster progression of FI.

The TyG-BMI is not only associated with cardiovascular diseases and other indicators of frailty, but it is also correlated with a series of health indicators related to frailty. For instance, a cross-sectional study conducted in Japan revealed a strong correlation between the TyG-BMI and hypertension [16], and Guotai Sheng and colleagues in China reported that the TyG-BMI can predict the incidence of non-alcoholic fatty liver disease [30]. Xiaotong Li and coauthors reported that individuals with a high TyG-BMI are at a greater risk of developing diabetes [31]. Shuping Yang and collaborators further observed that diabetes patients with a high TyG-BMI are at increased risk of heart failure [32]. However, there is a lack of research on the relationships between changes in the TyG-BMI and adverse health outcomes over time.

Only Rong-Rui Huo and colleagues analysed the association between changes in the TyG-BMI and the risk of stroke in middle-aged and elderly Chinese individuals. They discovered that individuals with consistently high TyG-BMI and a high cumulative TyG-BMI over four years had a greater risk of stroke [18]. Subsequently, Rui Liu and coauthors reported a positive correlation between an increase in the TyG-BMI over four years and the risk of hypertension in Chinese adults aged 45 years and older [33]. Building upon these findings, our study further investigated the relationships between changes in the TyG-BMI and cumulative TyG-BMI and between the incidence and development of frailty, a comprehensive indicator of health status. We found that individuals with consistently high TyG-BMI and a high cumulative TyG-BMI had a greater risk of frailty, consistent with the previously observed association between TyG-BMI levels and adverse health outcomes. This finding may be attributed to a common pathogenic mechanism, namely, IR, underlying the incidence of these adverse health outcomes. Additionally, we observed a rapid growth trend in the progression of FI among individuals with consistently high TyG-BMI levels and a high cumulative TyG-BMI. Moreover, the rate of FI progression increased with increasing TyG-BMI. Therefore, reducing and altering the persistence status and levels of the TyG-BMI may help prevent the frail incidence and slow the rate of progression towards frailty. Our study found no correlation between TyG-BMI and frail incidence in unmarried participants or those over 65 years old. Unmarried elderly individuals often face lower social support and worse physical conditions due to factors like widowhood or disability, which have a greater impact on frailty [34], In our study, 50% of frail participants were unmarried, suggesting that being unmarried has a stronger influence on frail incidence than TyG-BMI. Frailty is primarily age-related, with systemic physiological decline being a major cause [6]. Thus, higher age effect overshadows TyG-BMI's impact in older adults, emphasizing the importance of early prevention. Additionally, the older age of unmarried participants (65 vs. 58) further explains the lack of association between TyG-BMI and frailty in this group. Smokers and those with high CRP and HbA1c levels had a higher risk of frailty and were more likely to follow a rapid frailty index trajectory, indicating these groups should be prioritized in prevention efforts. Surprisingly, higher education levels were associated with increased frailty risk, likely due to higher mental stress and sedentary lifestyles [35, 36], Further research is needed to fully understand these mechanisms.

In contrast to previous studies, the present research revealed that the RCS curves showed a U-shaped correlation between the TyG-BMI and the risk of frailty. Additionally, the percentage change in TyG-BMI during follow-up also showed a U-shaped correlation with the onset and rapid progression of frailty. Similarly, the 3-year cumulative TyG-BMI demonstrated a similar nonlinear relationship with the onset and rapid development of FI. One possible reason for the inconsistency this study and previous findings is the introduction of the BMI index, as both excessively high and low body weights are detrimental to health [37]. For instance, Linli Yuan, in their meta-analysis, concluded that being underweight or overweight increases the risk of frailty in individuals [38]. Similarly, previous research by Keke Dang et al., based on the NHANES cohort, indirectly supported our findings; they observed a U-shaped correlation between the TyG-BMI and the risk of cardiovascular disease mortality in Americans [15], with cardiovascular diseases playing a significant role in the development and progression of frailty [39]. Moreover, study participants with a baseline TyG-BMI between 160 and 200 exhibited lower odds of rapid frailty progression, and those with cumulative TyG-BMI levels between 488.84 and 611.28 had a reduced frail risk, suggesting an optimal TyG-BMI range. Both excessively high and low TyG-BMI are detrimental to health maintenance, and further research is needed to determine the precise values of this optimal range. It is also important to avoid overcorrection when attempting to reduce the TyG-BMI, as excessively low values may also promote the development of frailty. Additionally, the results from the quantile regression analysis differed from those found by Rong-Rui Huo and colleagues, who identified triglycerides as having the greatest contribution to stroke incidence at baseline and at the third follow-up [18], given that high triglyceride levels are a common trigger for stroke [40]. In our study, baseline BMI contributed most significantly to the onset of frailty and the trajectory of high-speed FI growth, followed by triglyceride levels, indirectly confirming the independent and prominent role of BMI in the relationship between IR and the development progression of frailty. Notably, by the third follow-up, BMI was a greater contributing factor to frail onset than was baseline BMI. This shift might be due to the decrease in physical activity and the increase in body fat content associated with ageing, leading to persistent systemic low-grade inflammation and the multifaceted deterioration of the participants' physical condition [29]. Additionally, participants might have controlled their blood glucose and triglyceride levels through medication, but weight change is more difficult for older people. Therefore, when intervening in the frail status of participants, maintaining a healthy weight is crucial. Furthermore, in the prevention and treatment of frailty, recent studies have found that SGLT2 (sodium-glucose cotransporter 2) inhibitors, such as canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin, are considered an effective and safe potential approach due to

their positive effects on controlling blood glucose levels and reducing mitochondrial oxidative stress in endothelial cells [41]. Future research should focus on developing strategies that combine weight loss with the use of SGLT2 inhibitors to reduce TyG-BMI, thereby preventing the onset and progression of frailty in elderly individuals.

The main strengths of this study include the following: (1) This is the first investigation of the relationship between TyG-BMI and the onset and progression of frailty; (2) We utilized various statistical methods, such as GBTM analysis and linear mixed-effects models, to comprehensively explore the development of frailty among participants, allowing for a detailed understanding of frailty progression at different TyG-BMI levels; and (3) The large sample size and extended follow-up period enabled a thorough investigation of the relationship between TyG-BMI and frail progression. The main limitations of this study are as follows: (1) The disease information involved in the study was self-reported by patients, which could lead to misclassification bias, although previous research has found high consistency between self-reported diseases and medical records [42]; (2) We were only able to obtain blood test data at two time points, which limited a more in-depth analysis of the relationship between TyG-BMI trajectories and frail progression; (3) Despite adjusting for various potential confounders, we were unable to access some potential confounding information, such as dietary and genetic which plays a significant role in the development of IR and frailty [43, 44]; (4) Although we excluded participants with baseline frailty in our Cox regression analysis, thereby somewhat reducing the issue of reverse causation, this study is observational and cannot establish definitive causal relationships; (5) We did not obtain accurate indices of IR (HOMA-IR) to analyse the relationship between IR and frailty, which limited our ability to interpret the association between IR and frailty, although the TyG-BMI is considered a good surrogate for the HOMA-IR index and can more comprehensively assess metabolic health, making it more suitable for large-scale epidemiological cohort studies; (6) We only included participants who completed all five surveys, which could have introduced selection bias, as participants lost to follow-up due to reasons such as death might have experienced significant changes in frail status in a short period, potentially leading to an underestimation of the association between TyG-BMI and frailty; (7) And all participants in this study were Chinese, and thus the results may not be directly generalizable to other countries.

Conclusion

A sustained high TyG-BMI and an increase in the TyG-BMI are associated with rapid development of the FI and a greater frail risk. However, excessively low TyG-BMI levels also appear to contribute to frail development. Maintaining a healthy BMI may have the greatest impact on preventing the onset and progression of frailty. Future research should further investigate the relationship between excessively low TyG-BMI levels and frailty, identify the optimal TyG-BMI range, and develop effective strategies to maintain a healthy TyG-BMI.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-024-02373-1 .

Supplementary Material 1

Supplementary Material 2

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Author contributions
Concept: KG. Data curation: KG, QW, ZXS, XWW, JMZ, SYL, YFY and JLMH. Methodology: KG, JLMH, LZ, RQ, LPJ, YJH. Project administration and resources: ZRL, JLMH. Manuscript Writing: KG, QW. Review and editing: JLMH, LZ, RQ, LPJ, YJH, ZRL, ZXS, XWW, JMZ, SYL, YFY. Supervision: KG, QW, JLMH, ZRL. Funding: ZRL. All authors read and approved the final manuscript.

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Data availability
The data can be accessed from the China Health and Retirement Longitudinal Study (CHARLS) (http://charls.pku.edu.cn/) with application.

Declarations

Ethics approval and consent to participate
The Ethics Committee of Peking University approved the CHARLS (IRB00001052-11015). All participants provided informed consent at the baseline assessment.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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