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# Non-linear relationship between triglyceride glucose index and new-onset diabetes among individuals with non-alcoholic fatty liver disease: a cohort study

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## Abstract

**Background** The relationship between the triglyceride glucose (TyG) values and the development of diabetes in non-alcoholic fatty liver disease (NAFLD) patients is not yet well researched. This study aims to examine how the baseline TyG levels correlate with the incidence of new-onset diabetes in this specific cohort.

**Methods** This cohort included 2,506 normoglycemic Japanese adults with NAFLD who underwent routine health check-ups at Murakami Memorial Hospital between 2004 and 2015. Several statistical approaches, including restricted cubic splines and two-piecewise linear regression, were utilized to assess the relation between the TyG levels and diabetes risk.

**Results** Among the 2,506 participants (mean age: 44.78 ± 8.32 years; 81.09% male), 203 individuals (8.10%) developed diabetes over the course of the 11-year follow-up period. A U-shaped relationship was observed between the levels of TyG and the onset of diabetes, with an inflection point identified at a TyG value of 7.82 (95% CI: 7.72-8.00). Below this threshold, each one-unit elevation in TyG values reduced the probability of diabetes by 93% (HR = 0.07, 95% CI: 0.01–0.32, $P = 0.001$). Conversely, above this threshold, each one-unit elevation increased the probability of diabetes by 70% (HR = 1.70, 95% CI: 1.19–2.44, $P = 0.004$).

**Conclusions** The findings validate a U-shaped association between TyG levels and new-onset diabetes in adults with NAFLD. Both low and high TyG levels increase diabetes probability in such a group.

**Keywords** Triglyceride glucose, Cohort, Non-alcoholic fatty liver disease, Diabetes

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## Introduction

Diabetes, a condition of hyperglycemia, most commonly results from insulin resistance (IR) or an insufficiency of insulin secretion [1]. Global estimates predict that 629 million individuals will be affected by diabetes in 2045 [2]. Diabetic complications and their influence have a profound negative impact on individual health, impose a huge financial burden, and propel rising healthcare costs globally [3]. A vast amount of information is available on the etiology and risk factors of diabetes.

Non-alcoholic fatty liver disease (NAFLD) represents the most common worldwide chronic liver disease, with an estimated 25% of adults affected by it [4]. NAFLD is distinguished by excessive hepatic fat accumulation, which can range from simple steatosis to more virulent forms such as nonalcoholic steatohepatitis [5, 6]. The progression of NAFLD can lead to serious liver complications, including cirrhosis and even hepatocellular carcinoma [5, 6]. In addition to its hepatic symptoms, NAFLD is a strong relative factor for IR and a variety of types of metabolic disorder [7–10].

The triglyceride glucose (TyG) index, calculated using triglyceride (TG) levels and fasting plasma glucose (FPG) levels, is universally considered to be associated with IR [11]. The index is particularly valuable as it integrates both glucose and lipid metabolism, thereby providing a more holistic view of metabolic dysfunction [12, 13]. Previous studies have consistently demonstrated a strong positive relationship between levels of TyG and the development of diabetes in a range of populations [14–18]. In NAFLD, however, a direct relationship between the levels of TyG and the probability of diabetes is not well characterized, and whether a non-linear relationship between the TyG levels and NAFLD subjects' probability of diabetes exists is not yet established.

Therefore, the current study aimed to elucidate the relationship between baseline TyG index levels and new-onset diabetes probability in normoglycemic Japanese adults with NAFLD, with a specific intention to detect any threshold effects using nonlinear statistical analysis.

## Methods

### Study design and data source

This cohort analysis made use of the NAGALA database, which is accessible through the DRYAD repository and contains information collected at Murakami Memorial Hospital (2004–2015) [19]. The initial group consisted of 20,944 willing participants who underwent comprehensive medical exams. The original study was authorized by the Murakami Memorial Hospital Ethics Committee, and all subjects were required to provide written informed consent before recruitment.

### Study participants

A well-characterized study population was established by excluding individuals based on specific criteria from an original cohort of 20,944 Japanese participants. Inclusion in the study was not possible for the following reasons: a positive hepatitis B or C virus serology, a diagnosis of alcoholic fatty liver disease, diabetes, a FPG level of 6.1 mmol/L or above, prior drug use, and lack of covariate data. Additional criteria used to exclude individuals with NAFLD included excessive alcohol consumption [20, 21], the absence of ultrasonographic evidence of fatty liver, and an extreme TyG index. Certified sonographers used standardized ultrasonographic examinations to diagnose NAFLD [19]. The final analysis included 2,506 participants after all exclusion criteria were applied (Fig. 1).

### Definition of NAFLD

Fatty liver diagnosis was performed through abdominal ultrasonography by certified technicians using a calibrated ultrasound system [19]. Gastroenterologists systematically evaluated ultrasound images based on predefined diagnostic criteria, focusing on liver brightness, deep attenuation, vascular blurring, and hepatorenal echo contrast [19, 22]. Assessments were made without access to participants' additional clinical data to reduce interpretation bias [19].

Consistent with recent international diagnostic criteria, NAFLD was defined as an individual's alcohol consumption falling below the cutoff levels and the presence of fatty liver on ultrasonography [20, 21].

### Covariates

Demographic information (gender and age) and lifestyle characteristics (exercise frequency, alcohol consumption, smoking status) were collected using standardized questionnaires [19]. Anthropometric measurements (WC, diastolic blood pressure (DBP), systolic blood pressure (SBP), body mass index (BMI)), and laboratory assessments were performed by certified healthcare professionals following standardized protocols in consistent laboratory conditions. All biochemical parameters, including aspartate aminotransferase (AST), TG, high density lipoprotein cholesterol (HDL-c), FPG, glycosylated hemoglobin A1c (HbA1c), gamma-glutamyl transferase (GGT), total cholesterol (TC), and alanine aminotransferase (ALT), were analyzed using validated analytical methods in an accredited clinical laboratory [19]. Engaging in physical activity at least once a week was considered regular exercise [19]. The definition of visceral fat obesity was WC ≥ 80 cm for women and ≥ 90 cm for men [19].

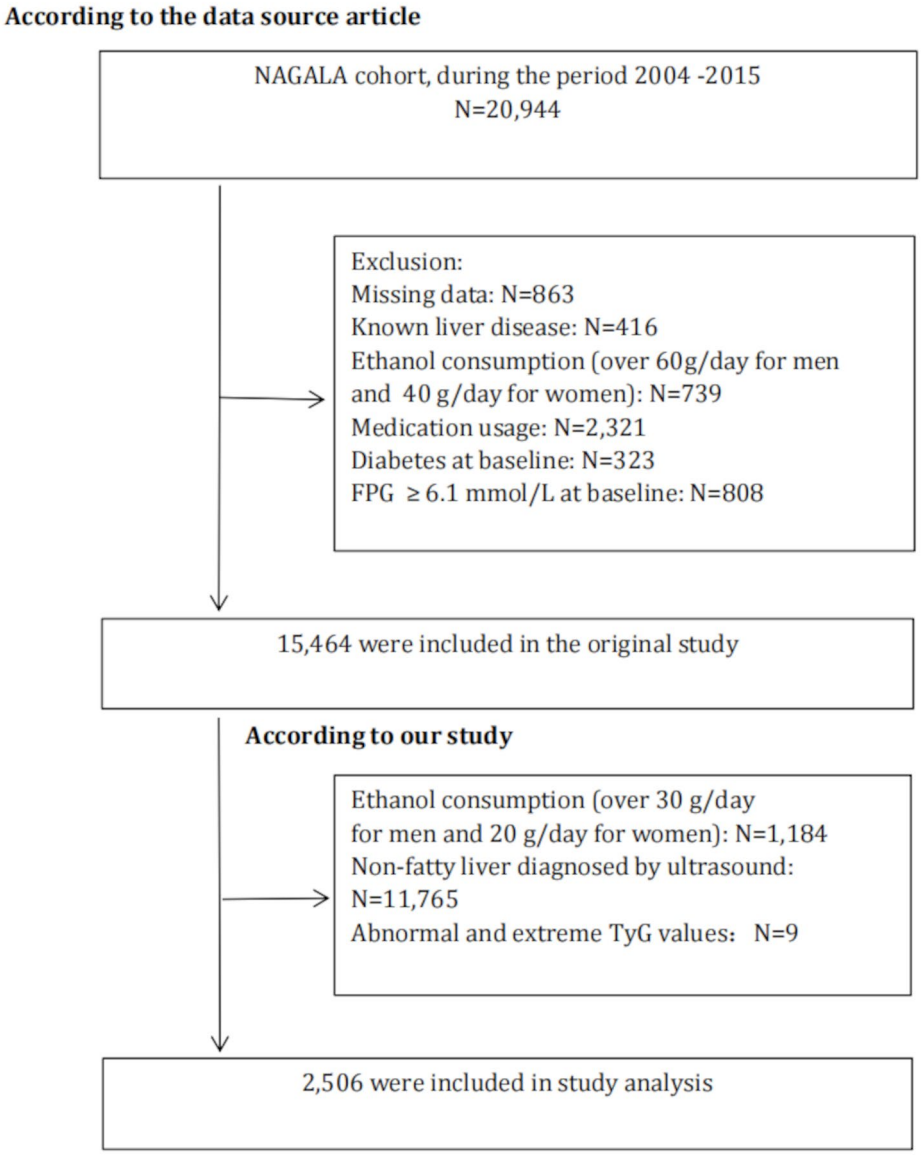


**Fig. 1** Study population

### Exposure and outcome

The exposure variable was the levels of TyG, calculated: $Ln\ [TG\ (mg/dL) \times FPG(mg/dL)/2]$ [23, 24]. The outcome was diabetes. Diabetes diagnosis was confirmed when meeting any of the following criteria during follow-up: self-reported physician diagnosis, HbA1c ≥ 6.5%, or FPG ≥ 7.0 mmol/L [1].

### Statistical analyses

Differences across TyG tertile levels were evaluated using one-way ANOVA for continuous variables and chi-square tests for categorical variables. Missing data for HDL-c were imputed using mean substitution [25].

Kaplan-Meier survival curves, accompanied by log-rank tests, were employed to compare diabetes-free survival rates across TyG index tertiles. Hazard ratios (HRs) with 95% confidence intervals (CIs) were generated using Cox proportional hazards models. Models were adjusted for potential confounders identified based on previous literature [14–18, 26, 27] and statistical criteria (change-in-estimate > 10% [28, 29] or $P < 0.05$ in univariate analysis): HDL-c, WC, AST, age, GGT, SBP [30, 31], ALT, sex [32, 33], TC, DBP [30, 31], regular exerciser, BMI, HbA1c [34], and smoking status [35–37].

Dose-response relationships were evaluated using restricted cubic splines (RCS). The optimal inflection point was identified through a recursive algorithm based on maximum likelihood estimation [38]. Model fitness was compared between linear and two-piece-wise

models using log-likelihood ratio tests [38]. Bootstrap resampling with 1000 replications generated 95% CI for the inflection point [38].

To test the robustness of the results, sensitivity analyses were conducted, including imputation of missing data and simplified covariate adjustments. E-values were computed to assess the potential influence of unmeasured confounders [39]. Subgroup analyses were also performed to investigate possible effect modifications.

All statistical analyses were carried out using EmpowerStats (version 4.2) and R software (version 4.2.0), with statistical significance set at $P < 0.05$.

**Table 1** Baseline characteristics of participants

| TyG tertile | T1(6.96–8.35) | T2(8.35–8.82) | T3(8.82–10.18) | *P* value |
|---|---|---|---|---|
| Participants | 835 | 835 | 836 | |
| Age, years | 44.70 ± 8.55 | 45.23 ± 8.46 | 44.43 ± 7.92 | 0.135 |
| BMI, kg/m$^2$ | 24.86 ± 2.99 | 25.63 ± 3.38 | 26.02 ± 2.87 | **< 0.001** |
| WC, cm | 84.15 ± 7.65 | 86.19 ± 8.11 | 87.66 ± 7.11 | **< 0.001** |
| FPG, mg/dL | 95.63 ± 6.73 | 97.03 ± 6.26 | 98.89 ± 6.19 | **< 0.001** |
| HbA1c, % | 5.28 ± 0.32 | 5.30 ± 0.34 | 5.32 ± 0.34 | **0.047** |
| GGT, U/L | 19.00 (14.00–26.00) | 22.00 (16.00–32.00) | 28.00 (20.00-39.25) | **< 0.001** |
| AST, U/L | 19.00 (16.00–24.00) | 20.00 (17.00–26.00) | 22.00 (18.00–27.00) | **< 0.001** |
| ALT, U/L | 24.00 (18.00–33.00) | 27.00 (20.00–38.00) | 30.00 (23.00–44.00) | **< 0.001** |
| TC, mg/dL | 198.22 ± 31.19 | 210.70 ± 31.96 | 222.59 ± 32.72 | **< 0.001** |
| TG, mg/dL | 64.56 ± 15.86 | 111.37 ± 16.45 | 203.10 ± 65.18 | **< 0.001** |
| SBP, mmHg | 120.85 ± 14.13 | 123.65 ± 15.00 | 125.79 ± 14.96 | **< 0.001** |
| DBP, mmHg | 75.80 ± 9.91 | 77.98 ± 10.15 | 79.72 ± 10.13 | **< 0.001** |
| HDL-c, mg/dL | 51.66 ± 11.81 | 45.49 ± 9.55 | 40.42 ± 8.50 | **< 0.001** |
| Sex | | | | **< 0.001** |
| Male | 599 (71.74%) | 683 (81.80%) | 750 (89.71%) | |
| Female | 236 (28.26%) | 152 (18.20%) | 86 (10.29%) | |
| Regular exerciser | | | | 0.087 |
| No | 707 (84.67%) | 694 (83.11%) | 727 (86.96%) | |
| Yes | 128 (15.33%) | 141 (16.89%) | 109 (13.04%) | |
| Smoking status | | | | **< 0.001** |
| Never | 465 (55.69%) | 385 (46.11%) | 330 (39.47%) | |
| Past | 193 (23.11%) | 236 (28.26%) | 212 (25.36%) | |
| Current | 177 (21.20%) | 214 (25.63%) | 294 (35.17%) | |
| New-onset diabetes | | | | **< 0.001** |
| No | 794 (95.09%) | 778 (93.17%) | 731 (87.44%) | |
| Yes | 41 (4.91%) | 57 (6.83%) | 105 (12.56%) | |

Categorical variables were displayed as N (%), and continuous variables were presented as median (interquartile range) or mean ± standard deviation. Missing values for HDL-c amounted to 4 (0.16%)

## Results

### Baseline characteristics

As shown in Table 1, of the 2,506 participants, men comprised 2,032 (81.09%), while women accounted for 474 (18.91%). The participants' average age was 44.78 ± 8.32. A significant increase was observed in DBP, FPG, SBP, HbA1c, TG, TC, GGT, AST, ALT, WC, BMI, the proportion of current smokers, and the male ratio as the levels of TyG increased. HDL-c showed a significant decrease with an increasing TyG index (Table 1). New-onset diabetes was identified in 203 participants (8.10%), with its prevalence increasing from T1 to T3 (4.91%, 6.83%, and 12.56%, respectively).

Differences in diabetes-free probability across the TyG tertile levels were evident in Kaplan-Meier curves ($P < 0.001$). Higher TyG values were linked to lower diabetes-free probability over the 4,000-day follow-up period (Fig. 2).

### Univariate analyses

Table 2 demonstrated a significant relationship between the outcome and variables such as FPG, WC, HbA1c, TG, TC, GGT, AST, ALT, BMI, age, current smoking status, TyG, and HDL-c. Specifically, increases in these variables increased the probability of diabetes, with HDL-c being the exception.

### Multivariate analyses

As provided in Table 3, in Model II, each one-unit increase in TyG levels corresponded to a 43% higher probability of diabetes (HR = 1.43, 95% CI: 1.01–2.02, $P = 0.044$). In tertile analysis (T1: 6.96–8.35, T2: 8.35–8.82, T3: 8.82–10.18), participants in the T3 group showed significantly increased diabetes risk (HR = 1.46, 95% CI: 1.03–2.08, $P = 0.034$) compared to the T2 group, whereas no significant difference was observed in the T1 group (HR = 0.94, 95% CI: 0.62–1.44, $P = 0.791$).

### Nonlinear analyses

A nonlinear relationship between baseline TyG levels and diabetes incidence was observed (Fig. 3; Table 4). The inflection point occurred at a TyG value of 7.82 (95% CI: 7.72-8.00). For TyG values at or below 7.82, each one-unit elevation in TyG values decreased the probability of diabetes by 93% (HR = 0.07, 95% CI: 0.01–0.32, $P = 0.001$). In contrast, for TyG values above 7.82, each one-unit elevation increased the probability of diabetes by 70% (HR = 1.70, 95% CI: 1.19–2.44, $P = 0.004$) (Table 4).

### Subgroup analyses

Stratified analyses showed the TyG-diabetes relationship remained consistent across various subgroups, with no significant interactions (all $P$ for interaction > 0.05) (Table 5).

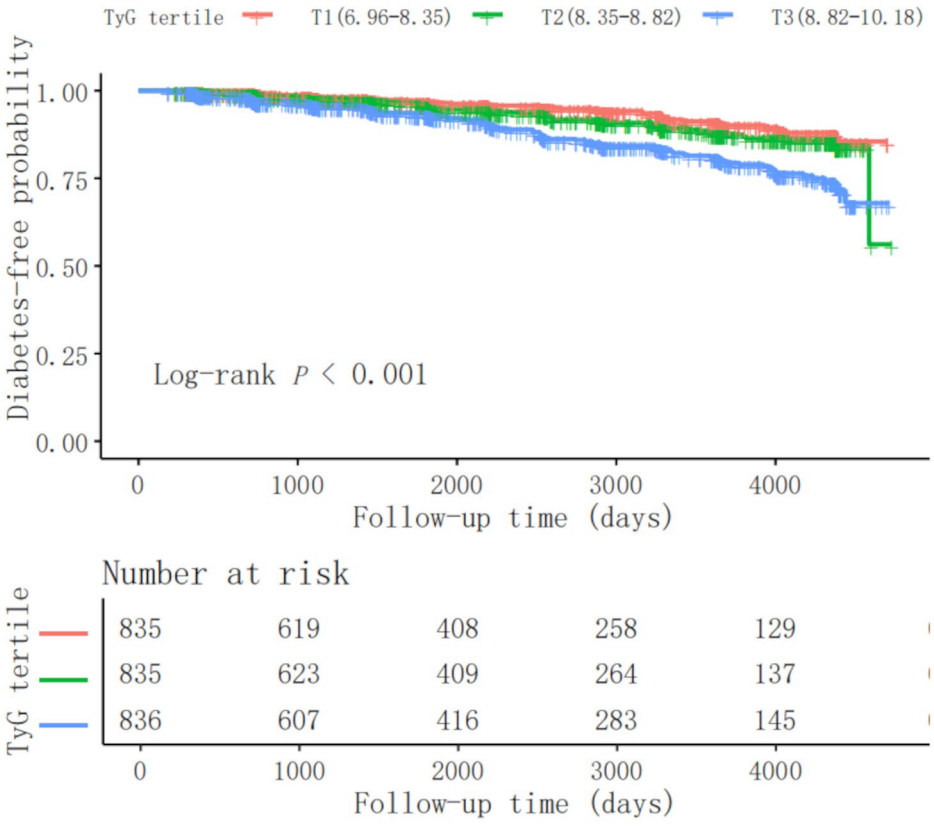


**Fig. 2** Kaplan–Meier diabetes-free survival curve across TyG tertile (log-rank, $P < 0.001$)

### Sensitivity analysis

The results remained consistent between analyses with missing data (Table 6) and after imputation (Table 4), with identical threshold effects at the TyG index of 7.82. Similarly, simplified adjusted models (Table S1), including only variables significant in univariate analysis, showed comparable threshold points and risk estimates to Table 4, supporting the reliability of the identified associations and threshold effect.

To examine the potential impact of unmeasured confounding variables, an E-value was calculated. The results remained robust, unless an unobserved confounder had an HR exceeding 2.79.

## Discussion

This cohort study, which involved 2,506 normoglycemic NAFLD patients, sought to investigate the TyG-diabetes relationship over an 11-year follow-up period. A U-shaped relationship was identified, with a threshold effect at a TyG index of 7.82 (95% CI: 7.72-8.00). Below this threshold, the risk of diabetes decreased (HR = 0.07, 95% CI: 0.01–0.32), but above it, the risk increased substantially (HR = 1.70, 95% CI: 1.19–2.44).

This study bears methodological similarities to prior cohort studies, yet reveals unique findings. All studies utilized cohort designs to explore the TyG index-diabetes relationships in diverse populations. Zhang et al. [14] studied 5,706 normal-weight participants from rural China, finding a significantly increased diabetes risk in the highest quartile levels compared to the lowest of the TyG (HR = 3.91, 95% CI: 2.22–6.87). Similarly, Li et al. [15] observed that TyG level elevation increased diabetes risk (HR = 3.34, 95% CI: 3.11–3.60) with a significant nonlinear relationship. In Japanese populations, Xuan et al. [16] detected a threshold effect at 7.97, with a decreased risk below (HR = 0.21, 95% CI: 0.08–0.57) and increased risk above (HR = 2.42, 95% CI: 1.66–3.53). The current study, focusing on 2,506 NAFLD patients, revealed a comparable threshold effect at 7.82, with decreased risk below (HR = 0.07, 95% CI: 0.01–0.32) and increased risk above (HR = 1.70, 95% CI: 1.19–2.44). These variations in risk patterns and magnitudes highlight the distinct metabolic characteristics of NAFLD patients, especially concerning IR and glucose homeostasis. These findings highlight the complex, nonlinear relationship between the baseline levels of TyG and the probability of diabetes in NAFLD individuals.

In the stratified analyses, the TyG-diabetes relationship remained consistent across different subgroups, including sex, smoking status, exercise habits, WC, BMI, and

**Table 2** Univariate Cox proportional hazards regression

| Exposure | Statistics | HR (95% CI) | *P* value |
|---|---|---|---|
| Sex | | | |
| Male | 2032 (81.09%) | Reference | |
| Female | 474 (18.91%) | 1.37 (0.97, 1.93) | 0.075 |
| Age, years | 44.78 ± 8.32 | 1.03 (1.01, 1.05) | **0.004** |
| TG, mg/dL | 110.00 (77.00-158.75) | 1.01 (1.00, 1.01) | **< 0.001** |
| TC, mg/dL | 210.51 ± 33.46 | 1.01 (1.00, 1.01) | **0.004** |
| GGT, U/L | 23.00 (16.00–33.00) | 1.01 (1.00, 1.01) | **0.012** |
| AST, U/L | 22.34 ± 9.79 | 1.02 (1.01, 1.03) | **< 0.001** |
| WC, cm | 86.00 ± 7.77 | 1.06 (1.05, 1.08) | **< 0.001** |
| BMI, kg/m$^2$ | 25.50 ± 3.12 | 1.14 (1.10, 1.18) | **< 0.001** |
| ALT, U/L | 27.00 (20.00–39.00) | 1.01 (1.01, 1.02) | **< 0.001** |
| Regular exerciser | | | |
| No | 2128 (84.92%) | Reference | |
| Yes | 378 (15.08%) | 0.72 (0.46, 1.13) | 0.155 |
| HbA1c, % | 5.30 ± 0.33 | 22.40 (14.25, 35.19) | **< 0.001** |
| Smoking status | | | |
| Never | 1180 (47.09%) | Reference | |
| Past/ Current | 1326 (52.91%) | 1.34 (1.01, 1.78) | **0.041** |
| FPG, mg/dL | 97.18 ± 6.54 | 1.15 (1.12, 1.18) | **< 0.001** |
| SBP, mmHg | 123.43 ± 14.84 | 1.01 (1.00, 1.02) | 0.111 |
| DBP, mmHg | 77.83 ± 10.19 | 1.01 (1.00, 1.02) | 0.108 |
| TyG | 8.58 ± 0.54 | 1.99 (1.54, 2.59) | **< 0.001** |
| HDL-c, mg/dL | 45.86 ± 11.04 | 0.98 (0.96, 0.99) | **0.004** |

Categorical variables were displayed as N (%), and continuous variables were presented as median (interquartile range) or mean ± standard deviation

**Table 3** Influence of TyG on new-onset diabetes under various models

| Exposure | Crude model HR (95%CI) *P* value | Model I HR (95%CI) *P* value | Model II HR (95%CI) *P* value |
|---|---|---|---|
| TyG | 1.99 (1.54, 2.59) **< 0.001** | 1.51 (1.14, 2.00) **0.004** | 1.43 (1.01, 2.02) **0.044** |
| TyG tertile | | | |
| T1(6.96–8.35) | 0.74 (0.49, 1.10) 0.138 | 0.91 (0.60, 1.36) 0.636 | 0.94 (0.62, 1.44) 0.791 |
| T2(8.35–8.82) | Reference | Reference | Reference |
| T3(8.82–10.18) | 1.80 (1.30, 2.48) **< 0.001** | 1.50 (1.08, 2.09) **0.016** | 1.46 (1.03, 2.08) **0.034** |

Crude model: Non-adjusted. Model I adjust for: age, sex, WC, SBP, DBP, regular exerciser, BMI, HbA1c, and smoking status. Model II adjust for: HDL-c, WC, AST, age, GGT, SBP, ALT, sex, TC, DBP, regular exerciser, BMI, HbA1c, and smoking status

age, with no significant interaction effects (all *P* for interaction > 0.05). Notably, never smokers showed a significantly stronger association between the baseline levels of TyG and the probability of diabetes (HR = 1.80, 95%CI: 1.00-3.23) compared with past or current smokers (HR = 1.26, 95%CI: 0.81–1.94), consistent with previous findings that smoking status influences IR and glucose metabolism [35–37]. Furthermore, the TyG-diabetes relationship was more pronounced in women (HR = 1.74, 95%CI: 0.70–4.35) versus men (HR = 1.38, 95%CI: 0.94–2.02), supporting evidence of sex-specific differences in the TyG-diabetes relationship [32, 33].

Multivariate analyses indicated a positive linear association between the baseline levels of TyG, treated as a continuous variable, and the probability of diabetes. However, tertile analysis revealed a more complex pattern: the highest tertile showed an increased risk, while the lowest tertile showed a reduced risk when compared to the middle tertile. This divergent pattern suggested the presence of a nonlinear relationship, prompting further analyses that confirmed a U-shaped association with a threshold at a baseline TyG value of 7.82. The robustness of these findings was validated through extensive sensitivity analyses. Consistent results were obtained when comparing analyses with missing data ($N = 2{,}502$) and after imputation ($N = 2{,}506$), revealing identical threshold effects at a TyG index of 7.82. Both simplified and fully adjusted models demonstrated comparable inflection points and risk estimates, substantiating the reliability of the identified U-shaped association and threshold effect.

In adults with NAFLD, TyG-diabetes relationship demonstrates a distinctive U-shaped pattern, where both elevated and reduced TyG levels contribute to diabetes pathogenesis through different mechanisms. In NAFLD patients with elevated TyG, excessive hepatic lipid accumulation triggers lipotoxicity through overwhelming free fatty acid levels [40, 41]. This lipotoxicity promotes diabetes development through multiple pathways: IR induced by saturated fatty acid-induced inflammation and GP130-STAT3 signaling [42, 43]; β-cell dysfunction through reactive oxygen species generation [44–47]; and disrupted glucose homeostasis via altered hepatokine secretion and PPARγ-mediated impairment of insulin signaling [48–50]. Hepatic steatosis in NAFLD exacerbates systemic IR, consequently increasing TyG levels [42, 43]. NAFLD progression is further promoted with elevated TyG via lipotoxicity and oxidative stress, forming a vicious cycle [40, 41]. These processes are all interconnected and constitute a vicious cycle promoting diabetes progression.

In contrast, profoundly low TyG levels signify a critical metabolic anomaly precipitating diabetes development [51]. The underlying pathophysiology includes impaired glucose utilization and metabolic rigidity, disrupting cellular energy balance via defective fuel substrate transition [52]. Such disruptions initiate compensatory mechanisms: diminished glucose absorption enhances IR [12], and metabolic rigidity compromises cellular energy efficiency [52]. Moreover, malnutrition-related pancreatic impairments and modified glucose-TG interactions [53, 54] establish a continuous cycle of metabolic decline culminating in diabetes [55].

Current findings demonstrate a clear U-shaped correlation between the baseline levels of TyG and probability of

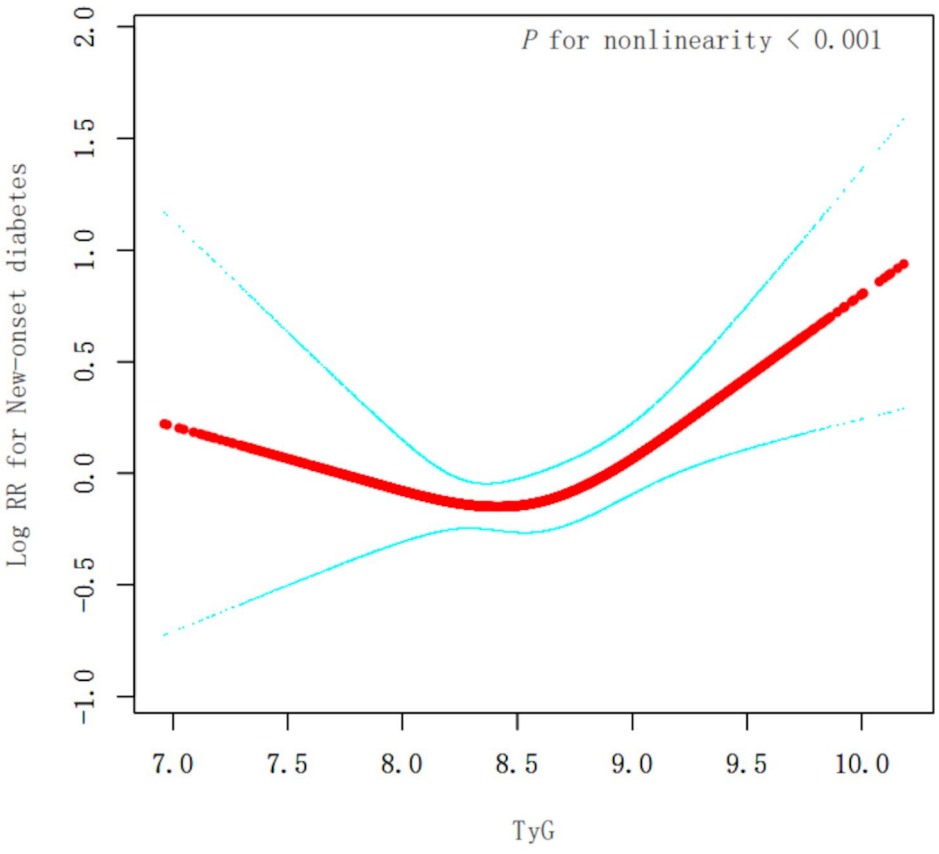


**Fig. 3** Nonlinear association between TyG index and new-onset diabetes. RCS analysis revealed a threshold, nonlinear relationship. The red solid line represents the adjusted log relative risk, while the blue dashed curves indicate the 95% CI. Models adjusted for HDL-c, WC, AST, age, GGT, SBP, ALT, sex, TC, DBP, regular exerciser, BMI, HbA1c, and smoking status

**Table 4** Threshold effect analysis of TyG and diabetes using two-piece-wise regression (*N* = 2,506)

| New-onset diabetes | HR, 95%CI | *P* value |
|---|---|---|
| One-line linear regression | 1.43 (1.01, 2.02) | **0.044** |
| Two-piece-wise regression | | |
| Inflection points of TyG | 7.82 | |
| ≤ 7.82 | 0.07 (0.01, 0.32) | **0.001** |
| > 7.82 | 1.70 (1.19, 2.44) | **0.004** |
| *P* for log-likelihood ratio test | | **0.001** |
| 95% CI for inflection points | 7.72, 8.00 | |

Adjust for: HDL-c, WC, AST, age, GGT, SBP, ALT, sex, TC, DBP, regular exerciser, BMI, HbA1c, and smoking status

diabetes in NAFLD populations. The analysis pinpointed a critical value around 7.82, providing potential clinical implications for varying groups based on their TyG levels. For individuals with TyG values above 7.82, evidence suggests that each incremental increase correlates with a heightened risk of diabetes (HR = 1.70), underscoring the importance of vigilant metabolic surveillance, lifestyle adjustments, or therapeutic interventions. Conversely, for those with TyG values below this threshold, the risk appears reduced; however, very low TyG levels might signal essential malnutrition and metabolic issues that warrant careful consideration. Thus, it is advisable to avoid excessive dietary limitations that may lead to further reductions in TyG and subsequent metabolic issues. A moderate approach to maintaining metabolic equilibrium is advisable for this demographic. Expanding this research to multicenter studies could further authenticate the inflection point's applicability across varied demographics.

### Study strengths and limitations

This investigation is distinguished by several strengths. Primarily, it serves as an inaugural study linking the TyG index with the incidence of diabetes in NAFLD cohorts, unveiling a novel U-shaped association (inflection point: 7.82, 95% CI: 7.72-8.00). Secondly, it employs standardized diagnostic protocols for NAFLD through ultrasound assessments conducted by accredited technicians and evaluated by unbiased gastroenterologists. Thirdly, it includes exhaustive statistical evaluations adjusted for multiple confounders, including

**Table 5** Stratified analyses of the association between TyG levels and diabetes risk across different subgroups

| Characteristic | Participants | HR (95%CI) *P* value | *P* for interaction |
|---|---|---|---|
| Sex | | | 0.456 |
| Male | 2032 | 1.38 (0.94, 2.02) 0.098 | |
| Female | 474 | 1.74 (0.70, 4.35) 0.233 | |
| Age, years | | | 0.572 |
| 19–43 | 1230 | 1.39 (0.85, 2.27) 0.195 | |
| 44–72 | 1276 | 1.39 (0.84, 2.28) 0.199 | |
| BMI, kg/m$^2$ | | | 0.611 |
| < 25 | 1223 | 1.56 (0.85, 2.86) 0.153 | |
| ≥ 25 | 1283 | 1.31 (0.87, 1.99) 0.201 | |
| Visceral fat obesity | | | 0.817 |
| No | 1605 | 1.55 (0.93, 2.59) 0.090 | |
| Yes | 901 | 1.43 (0.89, 2.30) 0.142 | |
| Regular exerciser | | | 0.783 |
| No | 2128 | 1.42 (0.98, 2.06) 0.062 | |
| Yes | 378 | 1.40 (0.49, 3.99) 0.532 | |
| Smoking status | | | 0.617 |
| Never | 1180 | 1.80 (1.00, 3.23) **0.049** | |
| Past/Current | 1326 | 1.26 (0.81, 1.94) 0.307 | |

Note 1: Above stratification adjusted for HDL-c, WC, AST, age, GGT, SBP, ALT, sex, TC, DBP, regular exerciser, BMI, HbA1c, and smoking status

Note 2: The stratification variable is unadjusted in each instance

**Table 6** Threshold effect analysis of TyG and diabetes with missing data (*N* = 2,502)

| New-onset diabetes | HR, 95%CI | *P* value |
|---|---|---|
| One-line linear regression | 1.42 (1.01, 2.01) | **0.045** |
| Two-piece-wise regression | | |
| Inflection points of TyG | 7.82 | |
| ≤ 7.82 | 0.07 (0.02, 0.32) | **0.001** |
| > 7.82 | 1.70 (1.19, 2.43) | **0.004** |
| *P* for log-likelihood ratio test | | **0.001** |
| 95% CI for inflection points | 7.71, 8.00 | |

Adjust for: HDL-c, WC, AST, age, GGT, SBP, ALT, sex, TC, DBP, regular exerciser, BMI, HbA1c, and smoking status. Missing values for HDL-c amounted to 4 (0.16%)

metabolic, anthropometric, and lifestyle variables. Fourthly, advanced statistical methods utilizing RCS and two-piece-wise regression models facilitate a detailed exploration of non-linear associations. Additionally, the integrity of the results is reinforced by multiple sensitivity tests and E-value computations.

It is important to acknowledge certain limitations. Primarily, the diagnosis of NAFLD depends solely on ultrasound outcomes without comprehensive hepatic steatosis grading, which could impact the accuracy of results since the severity of steatosis may affect the TyG index and diabetes risk [20, 21, 56]. The absence of liver biopsy data restricts the quantitative analysis of hepatic lipid content. Secondly, the NAGALA database (2004–2015) does not include Fibroscan data, which could have offered a more precise evaluation of liver fibrosis [20, 21, 57]. Prospective studies incorporating Fibroscan and detailed assessments of liver steatosis are recommended to further investigate the interactions between liver fibrosis, steatosis, baseline TyG levels, and diabetes probability. Thirdly, the absence of random glucose measurements and oral glucose tolerance tests in the criteria for diabetes diagnosis likely led to an underestimation of diabetes prevalence in this cohort. Furthermore, given that the study exclusively involved Japanese adults, additional research is necessary to confirm the applicability of these findings to other ethnic groups. Additionally, whereas the study was based on NAFLD criteria, a recent consensus (2023) has proposed MASLD (metabolic dysfunction-associated steatotic liver disease) to emphasize metabolic dysfunction [58]. Future research might consider incorporating MASLD diagnostic parameters.

## Conclusion

In a cohort of 2,506 Japanese adults diagnosed with NAFLD, using data from the NAGALA database, this study delineated a U-shaped correlation between the baseline levels of TyG and the probability of diabetes onset, identifying a critical inflection point at a TyG index of 7.82 (95% CI: 7.72-8.00). Clinically, stabilizing the TyG index near this value could prove advantageous, given that deviations either above or below this point are linked to an elevated risk of diabetes. Distinct approaches are advisable depending on the TyG values: those with elevated indices may benefit from lifestyle modifications, pharmacological treatment, and rigorous metabolic surveillance, whereas for individuals with lower indices, it is crucial to monitor for signs of malnutrition and metabolic imbalances without further reducing the TyG levels. Additional multicenter research might help further enhance the robustness of these findings and assess the applicability of this inflection point across varied demographic groups.

**Abbreviations**

| | |
|---|---|
| TyG | Triglyceride glucose index |
| WC | Waist circumference |
| BMI | Body mass index |
| DBP | Diastolic blood pressure |
| SBP | Systolic blood pressure |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |

| | |
|---|---|
| GGT | Gamma-glutamyl transferase |
| HDL-c | High-density lipoprotein cholesterol |
| TC | Total cholesterol |
| TG | Triglycerides |
| FPG | Fasting plasma glucose |
| HbA1c | Hemoglobin A1c |
| HR | Hazard ratios |
| CI | Confidence intervals |
| IR | Insulin resistance |
| NAFLD | Non-alcoholic fatty liver disease |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12944-025-02518-5.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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**Author contributions**
X.M.L: Research design, data analysis and manuscript drafting. K.L and X.H.L: Data collection and cleansing. Y.L, Z.M.X, and S.Q. G: Research designs and manuscript revisions. All authors collaborated on article and cleared final version.

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**Data availability**
Data can be accessed at: https://doi.org/10.5061/dryad.8q0p192.

## Declarations

**Ethics approval and consent to participate**
The study was authorized by the Murakami Memorial Hospital Ethics Committee, and all subjects were required to provide written informed consent before recruitment.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

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