U-Shaped Association Between the Triglycerides-Glucose index and the Risk of Incident Diabetes in Apparently Healthy Population: A Population-based Cohort Study

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Original investigation

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Abstract

Background

Although the triglycerides-glucose (TyG) index was thought to be a practical predictor of incident diabetes, the association between them has not been well characterized. The study aimed to further examine the association between the TyG index and incident diabetes in Japanese adults.

Methods

The cases were extracted of the individual participating in the NAGALA (NAfl in the Gifu Area, Longitudinal Analysis) study at Murakami Memorial Hospital from 2004 to 2015, and 14297 individuals apparently healthy at baseline were included in the study. Cox proportional hazards models were used to evaluate the associations between baseline TyG levels and incident of T2DM, and a two-piecewise linear regression model was used to examine the threshold effect of the baseline TyG on incident diabetes using a smoothing function. The threshold level (i.e., turning point) was determined using trial and error. A log likelihood ratio test was also conducted to compare the one-line linear regression model with a two-piecewise linear model.

Results

During a median follow-up period of 5.26 (women) and 5.88 (men) years, 47 women and 182 men developed Type 2 diabetes. The risk of diabetes was strongly associated with the baseline TyG index in the fully adjusted model in men but not in women, and no dose-dependent positive relationship between incident diabetes and TyG was observed across TyG tertiles. Intriguingly, two-piecewise linear regression analysis showed a U-shaped association between the TyG index and incident T2DM. The risk of incident diabetes decreased by around 90% in women with TyG < 7.27 (HR: 0.09; \( P = 0.0435 \)) and 80% in men with TyG < 7.97 (HR 0.21, \( P = 0.002 \)) with each increment of the TyG index after adjusting for confounders. In contrast, the risk of incident T2DM significantly elevated with the increase in TyG index in men with TyG > 7.97 (HR: 2.42, \( P < 0.001 \)) and women with TyG > 7.29 (HR 2.76, \( P = 0.0166 \)).

Conclusions

A U-shaped association was observed between the TyG index and incident T2DM among healthy individuals, with the TyG threshold of 7.97 in men and 7.27 in women. This information may be useful for reducing incident diabetes by maintaining the TyG index near these thresholds.

Background/introduction
The prevalence of diabetes has increased considerably worldwide over the past four decades [1], imposing a huge burden on mortality, morbidity, and health-care expenditure [1–6]. One of the effective interventions to prevent and overcome the burden of diabetes is identifying individuals at a high risk of developing diabetes [2, 7]. To this end, novel markers or risk factors need to be investigated to inform the application of preventive models on populations [2, 8, 9].

Among the traditional risk factors, levels of fasting plasma glucose (FPG) and triglycerides (TG) are associated with an increased risk of type 2 diabetes mellitus (T2DM)[2, 9–11]. As a derivative of FPG and TG[12–14], the triglycerides-glucose (TyG) index seems to help better predict the risk of T2DM than either component factor and has recently been suggested as a predictor of this risk in individuals without diabetes [2, 8, 15–17]. The TyG index was suggested to be considered as a screening tool for identifying people at a high risk of T2DM in clinical practice [18]. Although studies on the TyG index as a risk of T2DM have been conducted in Singapore, Korean, Thailand, and the white European population [17–20], no data on the Japanese population are currently available.

More importantly, previous cohort studies showed a positive relationship between high levels of the TyG index and the risk of incident diabetes [17–20], but the positive association disappeared at low levels of the TyG index [17, 18, 20]. This trend suggested a nonlinear association which had never been well characterized in previous studies. Additionally, previous studies did not exclude the individuals with impaired glucose tolerance or 5.7 ≤ HbA1c levels < 6.5%, thus, those result may not be well applied to the healthy population. This study, therefore, aimed to further investigate and characterize the relationship between the TyG index and incident diabetes in a large-scale Japanese cohort.

**Methods**

**Design and participants**

The data were derived from the population-based NAGALA (NAflld in the Gifu Area, Longitudinal Analysis) cohort study conducted at Murakami Memorial Hospital (Gifu, Japan), which was described in detail previously [21]. Briefly, The NAGALA was a cohort study of the individual who participated in the medical examination program at Murakami Memorial Hospital from May 1st, 1994 to Dec 31st, 2016 [21]. A large proportion of the participants received one to two exams per year. In this study, the cases were extracted of the individuals participating in the examination program at Murakami Memorial Hospital from 2004 to 2015[21]. The participants with alcoholic fatty liver, viral hepatitis, any medication usage, diagnosed with diabetes, fasting plasma glucose ≥ 6.1 mmol/L, or HbA1C ≥ 5.7% (considered to have pre-diabetes[22]) at baseline were excluded. Additionally, individuals with missing data of covariates, were also excluded. Moreover, the statistical method boxplot was used to remove 180 outliers (86 men and 94 women) of TyG index. Eventually, 7857 men and 6440 women were included in this study. As sex differences in the risk, pathophysiology and complications of diabetes existed [23], the male and female participants were analyzed separately in this study. This study was approved by the Ethics Committee of Murakami Memorial Hospital.
Exposure

The exposure in our study was the TyG index which was calculated based on the following formula: TyG = ln [fasting triglycerides (mg/dL) × fasting glucose (mg/dL)/ 2)] [24, 25].

Primary outcomes:

The outcome of incident Type 2 diabetes was defined as HbA1c ≥ 6.5% or fasting plasma glucose ≥ 7 mmol/L according to the diagnostic criteria of ADA or self-reported [21, 26].

Statistical analyses

Participants' characteristics were classified according to the level of baseline TyG index. Continuous variables are presented as mean ± S.D. or as median (Q1-Q3) for normally and abnormally distributed data separately. Categorical data are presented as frequencies (percentages). Statistical differences between the two groups were evaluated using the Mann-Whitney or Chi-square tests (Table 1). Stratified analyses were performed according to baseline age, BMI, waist circumference and fatty liver categories, and their interactions were tested (Fig. 1). Cox proportional hazards models were used to evaluate the associations between baseline TyG levels and incident of T2DM with or without adjustment for potential confounders, including baseline alcohol consumption, smoking status, systolic blood pressure, diastolic blood pressure, age, fatty liver, BMI, waist circumference, habit of exercise, family history of diabetes, HDL cholesterol and total cholesterol (Table 2). A two-piecewise linear regression model was used to examine the threshold effect of the baseline TyG on incident diabetes using a smoothing function (Fig. 2, Table 3). The threshold level (i.e., turning point) was determined using trial and error: firstly, the turning points were selected according to a pre-defined interval, and then the turning point was chosen which gave the maximum model likelihood. A log likelihood ratio test was also conducted to compare the one-line linear regression model with a two-piecewise linear model. Results were considered statistically significant when P < 0.05 (two-tailed). All statistical analyses were performed using the statistical packages R (The R Foundation; http://www.r-project.org; version 3.4.3) and EmpowerStats [27].
Table 1
Characteristics of the participants

| Baseline characteristic               | Women         | Men          | P value |
|---------------------------------------|---------------|--------------|---------|
| N                                     | 6440          | 7857         |         |
| Age, yr                               | 42.8 ± 8.6    | 43.9 ± 8.9   | < 0.001 |
| BMI, kg/m²                             | 20.9 ± 2.8    | 23.0 ± 2.9   | < 0.001 |
| Waist circumference (cm)              | 71.3 ± 7.8    | 80.3 ± 7.8   | < 0.001 |
| HDL cholesterol (mmol/L)              | 1.6 (1.4–1.9) | 1.3 (1.1–1.5)| < 0.001 |
| Total cholesterol (mmol/L)            | 5.0 ± 0.9     | 5.1 ± 0.8    | < 0.001 |
| Triglycerides (mmol/L)                | 0.6 (0.4–0.8) | 0.9 (0.6–1.4)| < 0.001 |
| Fasting plasma glucose (mmol/L)       | 5.0 ± 0.4     | 5.3 ± 0.4    | < 0.001 |
| TYG                                   | 7.7 ± 0.5     | 8.3 ± 0.6    | < 0.001 |
| Fatty liver                           |               |              | < 0.001 |
| No                                    | 6094 (94.6%)  | 5880 (74.8%) |         |
| Yes                                   | 346 (5.4%)    | 1977 (25.2%) |         |
| SBP (mmHg)                            | 108.8 ± 13.9  | 118.6 ± 14.1 | < 0.001 |
| DBP (mmHg)                            | 67.3 ± 9.6    | 74.7 ± 9.9   | < 0.001 |
| Regular exerciser                     |               |              | < 0.001 |
| No                                    | 5438 (84.4%)  | 6350 (80.8%) |         |
| Yes                                   | 1002 (15.6%)  | 1507 (19.2%) |         |
| Alcohol consumption, g/week           | 1.0 (0.0–8.4) | 25.0 (1.0–126.0) | < 0.001 |
| Smoking                               |               |              | < 0.001 |
| Never                                 | 5613 (87.2%)  | 2738 (34.8%) |         |
| Past                                  | 410 (6.4%)    | 2321 (29.5%) |         |
| Current                               | 417 (6.5%)    | 2798 (35.6%) |         |
| Incident diabetes                     |               |              | < 0.001 |
| No                                    | 6393 (99.3%)  | 7675 (97.7%) |         |
| Yes                                   | 47 (0.7%)     | 182 (2.3%)   |         |
| Father or mother with diabetes        |               |              | 0.562   |
| Baseline characteristic | Women        | Men          | P value |
|-------------------------|--------------|--------------|---------|
| No                      | 6229 (96.7%) | 7613 (96.9%) |         |
| Yes                     | 211 (3.3%)   | 244 (3.1%)   |         |
| ALT (IU/L)              | 13.0 (11.0–17.0) | 20.0 (15.0–27.0) | < 0.001 |
| AST (IU/L)              | 16.0 (13.0–19.0) | 18.0 (15.0–22.0) | < 0.001 |
| GGT (IU/L)              | 12.0 (10.0–14.0) | 19.0 (15.0–28.0) | < 0.001 |

Continuous variables are presented as mean ± S.D. or as median (Q1-Q3) for normally and abnormally distributed data separately. Categorical data are presented as frequencies (percentages).
### Table 2
Associations of baseline TyG with incident diabetes

| Incident diabetes | Crude model | Multivariate-Adjusted Model I | Multivariate-Adjusted Model II |
|-------------------|-------------|-------------------------------|-------------------------------|
|                   | HR(95% CI)  | $P$ value                     | HR(95% CI)  | $P$ value | HR(95% CI)  | $P$ value |
| **Women**         |             |                               |                               |
| TYG (continuous)  | 6.1 (3.4, 11.2) | $< 0.001$                     | 2.7 (1.4, 5.1) | 0.004     | 1.9 (0.9, 4.0) | 0.109     |
| TYG Tertile       |             |                               |                               |
| T1 (< 7.46)       | 1           |                               | 1                             | 1         |
| T2 (7.46–7.92)    | 1.3 (0.4, 3.9) | 0.703                         | 1.0 (0.3, 3.2) | 0.989     | 0.9 (0.3, 3.0) | 0.91      |
| T3 (> 7.92)       | 6.3 (2.5, 16.0) | $< 0.001$                     | 3.0 (1.1, 8.3) | 0.03      | 2.3 (0.8, 6.7) | 0.131     |
| **Men**           |             |                               |                               |
| TYG (continuous)  | 3.5 (2.7, 4.6) | $< 0.001$                     | 2.0 (1.5, 2.7) | $< 0.001$ | 1.7 (1.2, 2.5) | 0.002     |
| TYG Tertile       |             |                               |                               |
| T1 (< 8.01)       | 1           |                               | 1                             | 1         |
| T2 (8.01–8.5)     | 1.4 (0.9, 2.4) | 0.145                         | 1.0 (0.6, 1.6) | 0.879     | 0.8 (0.5, 1.4) | 0.524     |
| T3 (> 8.5)        | 3.9 (2.5, 6.0) | $< 0.001$                     | 1.7 (1.1, 2.7) | 0.028     | 1.3 (0.8, 2.1) | 0.351     |

Crude model adjust for None.

Adjust I model adjust for Age, Fatty liver, BMI and Waist circumference.

Adjust II model adjust for model 1 plus ethanol consumption, habit of exercise, HDL cholesterol, total cholesterol, smoking status, systolic blood pressure, diastolic blood pressure and family history of diabetes.
## Table 3
Threshold effect analysis of baseline TyG on incident diabetes using piece-wise linear regression

| Incident diabetes | Crude model | Multivariate-Adjusted Model I | Multivariate-Adjusted Model II |
|-------------------|-------------|-------------------------------|-------------------------------|
|                   | HR(95%CI)   | P value                       | HR(95%CI)                     | P value                       | HR(95%CI)                     | P value                       |
| Women             |             |                               |                               |                               |                               |                               |
| TYG < 7.27        | 0.09 (0.01, 0.81) | 0.0321                       | 0.10 (0.01, 0.97)             | 0.0469                       | 0.09 (0.01, 0.93)             | 0.0435                       |
| TYG > 7.27        | 9.27 (4.84, 17.75) | < 0.0001                      | 3.85 (1.87, 7.93)             | 0.0002                       | 2.76 (1.20, 6.34)             | 0.0166                       |
| Men               |             |                               |                               |                               |                               |                               |
| TYG < 7.97        | 0.47 (0.18, 1.24) | 0.1253                       | 0.23 (0.09, 0.61)             | 0.0032                       | 0.21 (0.08, 0.57)             | 0.0021                       |
| TYG > 7.97        | 4.83 (3.55, 6.57) | < 0.0001                      | 2.82 (2.03, 3.93)             | < 0.0001                      | 2.42 (1.66, 3.53)             | < 0.0001                      |

Crude model adjust for None.

Adjust I model adjust for Age, Fatty liver, BMI and Waist circumference.

Adjust II model adjust for model 1 plus ethanol consumption, habit of exercise, HDL cholesterol, total cholesterol, smoking status, systolic blood pressure, diastolic blood pressure and family history of diabetes.

### Supplemental Table 1. Crude association of incident diabetes with participants' characteristics

| Variable              | Women                  | Men                     |
|-----------------------|------------------------|-------------------------|
|                       | HR(95%CI)  | P value | HR(95%CI) | P value |
| Age                   | 1.05 (1.02, 1.09)     | 0.005                   | 1.04 (1.02, 1.06) | < 0.001 |
| BMI                   | 1.28 (1.20, 1.37)     | < 0.001                 | 1.23 (1.19, 1.27) | < 0.001 |
| Waist circumference   | 1.11 (1.08, 1.14)     | < 0.001                 | 1.09 (1.07, 1.11) | < 0.001 |
| HDL cholesterol       | 0.13 (0.05, 0.34)     | < 0.001                 | 0.18 (0.11, 0.30) | < 0.001 |
| Total cholesterol     | 1.64 (1.22, 2.21)     | 0.001                   | 1.31 (1.12, 1.54) | 0.001 |
| Incident diabetes       | Crude model | Multivariate-Adjusted Model I | Multivariate-Adjusted Model II |
|------------------------|-------------|-------------------------------|-------------------------------|
|                        | HR(95%CI)   | P value                       | HR(95%CI)                     | P value                       |
| **Triglycerides**      | 6.38 (3.45, 11.78) | < 0.001                       | 2.14 (1.83, 2.50)             | < 0.001                       |
| **Fasting plasma glucose** | 20.08 (9.73, 41.43) | < 0.001                       | 18.60 (11.63, 29.74)          | < 0.001                       |
| **TYG**                | 6.12 (3.36, 11.156) | < 0.001                       | 3.53 (2.71, 4.61)             | < 0.001                       |
| **Fatty liver**        |             |                               |                               |                               |
| No                     | 1           |                               |                               |                               |
| Yes                    | 11.14 (6.14, 20.22) | < 0.001                       | 4.86 (3.61, 6.56)             | < 0.001                       |
| **SBP**                | 1.04 (1.02, 1.05) | < 0.001                       | 1.03 (1.02, 1.04)             | < 0.001                       |
| **DBP**                | 1.06 (1.03, 1.08) | < 0.001                       | 1.05 (1.03, 1.06)             | < 0.001                       |
| **Regular exerciser**  |             |                               |                               |                               |
| No                     | 1           |                               |                               |                               |
| Yes                    | 0.77 (0.33, 1.82) | 0.551                         | 0.71 (0.47, 1.09)             | 0.115                         |
| **Alcohol consumption**| 0.99 (0.98, 1.00) | 0.146                         | 1.00 (1.00, 1.001)            | 0.994                         |
| **Smoking status**     |             |                               |                               |                               |
| Never                  | 1           |                               |                               |                               |
| Past                   | 1.06 (0.25, 4.38) | 0.94                          | 1.00 (0.67, 1.51)             | 0.987                         |
| Current                | 3.79 (1.76, 8.16) | < 0.001                       | 1.60 (1.13, 2.25)             | 0.008                         |
| **Father or mother with diabetes** |             |                               |                               |                               |
| No                     | 1           |                               |                               |                               |
| Yes                    | 1.63 (0.39, 6.72) | 0.503                         | 2.28 (1.24, 4.19)             | 0.008                         |
Results

Participants’ characteristics

The current study enrolled 7857 men and 6440 women. Table 1 presents the clinical and biochemical characteristics of the population studied. The average age, BMI, waist circumference, total cholesterol, triglycerides, fasting plasma glucose, the TyG index, blood pressure, alcohol consumption, the percentage of fatty liver, as well as the proportions of smokers and regular exercisers were significantly higher in men than those in women. In contrast, the average HDL cholesterol was lower in men than in women. Besides, 47 women and 182 men developed T2DM over a median follow-up period of 5.26 years and 5.88 years, respectively.

Univariate analysis of the association between incident diabetes and baseline characteristics

The univariate analysis of the association between incident diabetes and baseline characteristics indicated that age, BMI, waist circumference, total cholesterol, fasting plasma glucose, triglycerides, the TyG index, fatty liver, blood pressure, and current smoking were all possible risk factors of incident diabetes. Meanwhile, the HDL cholesterol presented a protective effect in both women and men (Supplemental Table 1). Unlike women, men having a parent with diabetes may have a significantly higher risk for incident diabetes.

Stratified analysis

Age, BMI, waist circumference, and fatty liver were identified risk factors for diabetes[28–31]. To evaluate and control for confounding factors, we measured the effect of the baseline TyG index on the risk of incident diabetes within each of the strata categorized according to the above-mentioned factors. In the analysis stratified by age, BMI, waist circumference, and fatty liver, a positive association between the TyG index and the risk of incident diabetes was found in men, while no significant association was observed in females after adjusting for potential confounding factors (Fig. 1). These confounders included ethanol consumption, habit of exercise, HDL cholesterol, total cholesterol, smoking status, systolic blood pressure, diastolic blood pressure, and family history of diabetes, as well as age, BMI, waist circumference and fatty liver, except for the stratification factor itself (Fig. 1). Moreover, the interaction analysis showed that age, BMI, waist circumference, and fatty liver did not play an interactive role in the association between incident diabetes and the TyG index in both genders (all P-values for interaction > 0.05) (Fig. 1).

Multivariable analysis

Multivariate regression analysis was conducted to assess the independent effects of the baseline TyG index on incident diabetes, (Table 2). The risk of diabetes was strongly associated with the baseline TyG index (as a continuous variable) in the crude model in women (HR = 6.1, 95% CI 3.4 to 11.2; P < 0.001) and men (HR = 3.5, 95% CI 2.7 to 4.6; P < 0.001). The relationship remained statistically significant in women
(HR = 2.7, 95% CI 1.4 to 5.1; \( P = 0.004 \)) and men (HR = 2.0, 95% CI 1.5 to 2.6; \( P < 0.001 \)) after adjusting for age, fatty liver, BMI, and waist circumference (multivariate-adjusted model 1, Table 2). Moreover, further adjustment for ethanol consumption, habit of exercise, HDL cholesterol, total cholesterol, smoking status, systolic blood pressure, diastolic blood pressure, and family history of diabetes did not alter the significant association in men (HR = 1.7, 95% CI 1.2 to 2.5; \( P = 0.002 \)) (multivariate-adjusted model 2, Table 2). However, the risk between the TyG index and the risk of incident diabetes was not significant in women after further adjustment in multivariate-adjusted model 2 (Table 2). We then divided the participants into tertiles according to the levels of TyG index. In both genders, the crude model, Model I or Model II did not show any typical dose-dependent positive relationship between the TyG index and the risk of incident T2DM, suggesting the existence of a nonlinear association.

**Two-piecewise linear regression model analysis using a smoothing function**

Since the previous multivariable analysis suggested the nonlinear correlation between the TyG index and the risk of incident T2DM, a two-piecewise linear regression model was used to further elucidate their association using a smoothing function. Excitingly, adjusted smoothed plots showed a U-shaped association between the risk of incident diabetes and the TyG index in both genders (Fig. 2). According to the two-piecewise linear regression model, the TyG magnitude was significantly negatively correlated with the log Relative Risk (\( \log \text{RR} \)) for incident diabetes with a TyG index of < 7.27 in women and < 7.97 in men after adjusting for confounding variables (Table 3 and Fig. 2). With the per-unit increase in the TyG index, the risk of T2DM decreased nearly 90% (HR = 0.09, 95% CI 0.01 to 0.93) in women and 80% (HR = 0.21, 95% CI 0.08 to 0.57) in men after adjusting for age, fatty liver, waist circumference, BMI, ethanol consumption, habit of exercise, HDL cholesterol, total cholesterol, smoking status, systolic blood pressure, diastolic blood pressure, and family history of diabetes. Furthermore, the risk of incident diabetes decreased to the lowest level as the TyG index increased up to the thresholds (TyG = 7.27 in women vs. TyG = 7.97 in men) (Table 3 and Fig. 2). In contrast, the TyG magnitude was significantly positively associated with the risk of incident diabetes when higher than 7.27 (HR = 2.76, 95% CI 1.20 to 6.34) in women and 7.97 (HR = 2.42, 95% CI 1.66 to 3.53) in men (Table 3).

**Discussion**

To the best of our knowledge, this is the first study to describe a U-shaped association between the TyG index and the risk of incident T2DM. Moreover, we revealed a turning point (TyG = 7.27 in women vs. TyG = 7.97 in men) using threshold effect analysis (Table 3 and Fig. 2). Besides, as far as we know, in Japan area, the is the first study conducted to investigate the association between TyG and incident diabetes.

The association between the TyG index and the development of diabetes has been examined in previous studies in other areas [17, 18, 20, 32–34]. Ming Zhang et al. found that the risk of incident T2DM was increased with elevated TyG quartiles among 8003 Chinese participants[33]. Similarly, the Chungju Metabolic Disease Cohort (CMC) study revealed an increased risk of incident diabetes in participants with
TyG index in Quartiles 2, 3 and 4, compared to those in Quarter 1[32]. Consistently, different studies on a white European population, middle-aged Koreans, residents of the northern region of Singapore reported a significantly higher risk of incident diabetes among participants in the highest TyG quartile relative to the lowest quartile[17, 18, 20]. However, all of these studies did not exclude the individuals with prediabetes (impaired glucose tolerance or 5.7 ≤ HbA1c levels < 6.5% [35]).

In the present study, all the participants with impaired fasting glucose tolerance or HbA1c ≥ 5.7 were excluded, and some new insights were demonstrated. Overall, there was a U-shaped association between the TyG index and the risk of developing T2DM. Besides, the thresholds (TyG = 7.27 in women vs. TyG = 7.97 in men) were identified on which the risk of incident diabetes was the lowest in this population (Table 3 and Fig. 2). Well in line with certain previous studies [17, 18, 20, 32–34], the risk of developing T2DM significantly increased with the elevated TyG index in men with TyG > 7.97 and women with TyG > 7.29 (Table 3 and Fig. 2). However, a lower level of TyG index (< 7.27 in women and < 7.97 in men) substantially changed the association between the TyG index and incident diabetes. In participants with TyG levels lower than the thresholds, the risk of incident diabetes among women and men decreased nearly by 90% and 80%, respectively, with each increment in the TyG index after fully adjusting for confounders (Table 3 and Fig. 2). This has not been reported in the existing literatures.

Actually, consistent with our study findings, previous cohort studies showed that after adjusting for confounders, the risk of incident diabetes increased significantly only in the third and fourth TyG quartiles[17, 18, 20, 34], but not in the second quartile, when compared with that in the first quartile[17, 18, 20]. This indicates a nonlinear association between the TyG index and incident diabetes. Furthermore, in the Vascular-Metabolic CUN cohort, the nonlinear relation became more obvious in the subgroup with the normal fasting glucose level in the stratified analyses[17]. Interestingly, some previous studies suggested that the risk of incident Type 2 diabetes was elevated across all TyG quartiles [32, 33]. However, most of these studies performed the analyses in all participants with fasting glucose level < 7 mmol/L and did not exclude those with impaired fasting glucose or with 5.7 ≤ HbA1c levels < 6.5% (prediabetes)[12, 21, 24]. Besides, the previous studies had a relatively small population scale. Hence, the nonlinear association between the TyG index and the risk of incident diabetes might have been neglected.

Although the U shape association between TyG and incident diabetes in apparent healthy individuals was firstly revealed in this study, there were several limitations that must be noted. Firstly, the current study was carried out only in a Japanese population, making the generalizability of its findings to non-Japanese populations uncertain. This implies the need to verify our results by conducting future studies on other ethnicities. Secondly, the oral glucose tolerance test was not performed in this study, and the prevalence of incident diabetes might have been underestimated. Lastly, the effects of the TyG index on the risk of incident diabetes require further investigation.

Despite the limitations mentioned above, this study had several strengths. Firstly, the data set extracted from the NAGALA database was relatively large and complete, covering wide range of TyG levels. Secondly, this study was performed in an apparently healthy population because we excluded all
individuals with HbA1c levels ≥ 5.7% or impaired fasting glucose. These two strengths allowed us to evaluate the association across an extensive TyG range in healthy individuals and establish the U-shaped association between the TyG index and incident diabetes. Thirdly, our analysis of the relationship between the TyG index and incident diabetes was adjusted for more potential confounding factors, when compared to previous studies, probably making the result more robust and reliable.

Conclusions

For the first time, the current study reported that there was a U-shaped association between the TyG index and the risk of incident diabetes among healthy individuals, with a TyG threshold of 7.97 in men and 7.27 in women, raising a possibility of the TyG index as an intervention target for preventing incident diabetes. This study is expected to encourage future clinical and mechanistic studies to confirm our current findings and to better understand what roles the TyG index plays in the development of T2DM.

Abbreviations

TyG index
triglycerides-glucose index
NAGALA
NAfld in the Gifu Area, Longitudinal Analysis
T2DM
type 2 diabetes mellitus
FPG
fasting plasma glucose
TG
triglycerides
logRR
log Relative Risk

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Murakami Memorial Hospital.

Consent for publication

Not applicable
Availability of data and materials

Data are available upon reasonable request, and the deidentified participant data are available from Masahide Hamaguchi.

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Competing interests

The authors declare that they have no competing interests

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Author contributions:

XuanX helped to design the study and contributed to the data analyses and wrote the manuscript. HM had full access to all the data in the study and helped to provide the details, as well as revised the article. CQ analyzed the data and revised the manuscript. TO, HY, OA, KT and FM contributed to the data collection and revised the article. YG, GZ, LZ and LX contributed to reviewed and revised the manuscript. QY helped to design the study and reviseed the manuscript. Xie X originated and designed the study, took responsibility of the accuracy of the data analysis, revised the manuscript critically, and was the guarantor of this work. All authors were involved in the writing of the manuscript and approved the manuscript's final version.

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References

1. Wang T, Lu J, Shi L, Chen G, Xu M, Xu Y, Su Q, Mu Y, Chen L, Hu R, et al. Association of insulin resistance and beta-cell dysfunction with incident diabetes among adults in China: a nationwide, population-based, prospective cohort study. The lancet Diabetes endocrinology. 2020;8(2):115–24.

2. Chamroonkiadtikun P, Ananchaisarp T, Wanichanon W: The triglyceride-glucose index, a predictor of type 2 diabetes development: A retrospective cohort study. Primary care diabetes 2019.

3. members NRFC. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. Lancet. 2016;387(10027):1513–30.

4. Fernandez-Twinn DS, Hjort L, Novakovic B, Ozanne SE, Saffery R. Intrauterine programming of obesity and type 2 diabetes. Diabetologia. 2019;62(10):1789–801.

5. Bommer C, Heesemann E, Sagalova V, Manne-Goehler J, Atun R, Bärnighausen T, Vollmer S. The global economic burden of diabetes in adults aged 20–79 years: a cost-of-illness study. The lancet Diabetes endocrinology. 2017;5(6):423–30.

6. Economic Costs of Diabetes in the U.S. in 2017. Diabetes care 2018, 41(5):917–928.

7. Schwarz PE. [Screening and prevention of diabetes]. Der Internist. 2015;56(10):1124–33.

8. Simental-Mendia LE, Gamboa-Gomez CI, Aradillas-Garcia C, Rodriguez-Moran M, Guerrero-Romero F. The triglyceride and glucose index is a useful biomarker to recognize glucose disorders in apparently healthy children and adolescents. European journal of pediatrics 2020.

9. Moradi-Lakeh M, Forouzanfar MH, El Bcheraoui C, Daoud F, Afshin A, Hanson SW, Vos T, Naghavi M, Murray CJ, Mokdad AH. High Fasting Plasma Glucose, Diabetes, and Its Risk Factors in the Eastern Mediterranean Region, 1990–2013: Findings From the Global Burden of Disease Study 2013. Diabetes Care. 2017;40(1):22–9.

10. Moazzafary A, Asgari S, Tohidi M, Kazempour-Ardebili S, Azizi F, Hadaegh F. Change in fasting plasma glucose and incident type 2 diabetes mellitus: results from a prospective cohort study. BMJ open. 2016;6(5):e010889.

11. Riediger ND, Clark K, Lukianchuk V, Roulette J, Bruce S. Fasting triglycerides as a predictor of incident diabetes, insulin resistance and β-cell function in a Canadian First Nation. Int J Circumpolar Health. 2017;76(1):1310444.

12. Richter J, Focke D, Ebert T, Kovacs P, Bachmann A, Lössner U, Kralisch S, Kratzsch J, Beige J, Anders M, et al. Serum levels of the adipokine progranulin depend on renal function. Diabetes Care. 2013;36(2):410–4.

13. Wang L, Cong HL, Zhang JX, Hu YC, Wei A, Zhang YY, Yang H, Ren LB, Qi W, Li WY, et al. Triglyceride-glucose index predicts adverse cardiovascular events in patients with diabetes and acute coronary syndrome. Cardiovascular diabetology. 2020;19(1):80.
14. Nam KW, Kwon HM, Jeong HY, Park JH, Kwon H, Jeong SM. High triglyceride-glucose index is associated with subclinical cerebral small vessel disease in a healthy population: a cross-sectional study. Cardiovascular diabetology. 2020;19(1):53.

15. Park GM, Cho YR, Won KB, Yang YJ, Park S, Ann SH, Kim YG, Park EJ, Kim SJ, Lee SG, et al. Triglyceride glucose index is a useful marker for predicting subclinical coronary artery disease in the absence of traditional risk factors. Lipids Health Dis. 2020;19(1):7.

16. Alizargar J, Bai CH, Hsieh NC, Wu SV. Use of the triglyceride-glucose index (TyG) in cardiovascular disease patients. Cardiovascular diabetology. 2020;19(1):8.

17. Navarro-Gonzalez D, Sanchez-Inigo L, Pastrana-Delgado J, Fernandez-Montero A, Martinez JA. Triglyceride-glucose index (TyG index) in comparison with fasting plasma glucose improved diabetes prediction in patients with normal fasting glucose: The Vascular-Metabolic CUN cohort. Preventive medicine. 2016;86:99–105.

18. Low S, Khoo KCJ, Irwan B, Sum CF, Subramaniam T, Lim SC, Wong TKM: The role of triglyceride glucose index in development of Type 2 diabetes mellitus. Diabetes research and clinical practice 2018, 143:43–49.

19. Ramirez-Velez R, Perez-Sousa MA, Gonzalez-Ruiz K, Cano-Gutierrez CA, Schmidt-RioValle J, Correa-Rodriguez M, Izquierdo M, Romero-Garcia JA, Campos-Rodriguez AY, Triana-Reina HR, et al: Obesity- and Lipid-Related Parameters in the Identification of Older Adults with a High Risk of Prediabetes According to the American Diabetes Association: An Analysis of the 2015 Health, Well-Being, and Aging Study. Nutrients 2019, 11(11).

20. Lee JW, Lim NK, Park HY. The product of fasting plasma glucose and triglycerides improves risk prediction of type 2 diabetes in middle-aged Koreans. BMC endocrine disorders. 2018;18(1):33.

21. Okamura T, Hashimoto Y, Hamaguchi M, Obora A, Kojima T, Fukui M. Ectopic fat obesity presents the greatest risk for incident type 2 diabetes: a population-based longitudinal study. Int J Obes. 2019;43(1):139–48.

22. Akerblom A, Wojdyla D, Steg PG, Wallentíí L, James SK, Budaj A, Katus HA, Himmelmann A, Huber K, Siegbahn A, et al. Prevalence and relevance of abnormal glucose metabolism in acute coronary syndromes: insights from the PLATElet inhibition and patient Outcomes (PLATO) trial. J Thromb Thrombolysis. 2019;48(4):563–9.

23. Kautzky-Willer A, Harreiter J, Pacini G: Sex and Gender Differences in Risk, Pathophysiology and Complications of Type 2 Diabetes Mellitus. Endocrine reviews 2016, 37(3):278–316.

24. Yassin A, Haider A, Haider KS, Caliber M, Doros G, Saad F, Garvey WT. Testosterone Therapy in Men With Hypogonadism Prevents Progression From Prediabetes to Type 2 Diabetes: Eight-Year Data From a Registry Study. Diabetes Care. 2019;42(6):1104–11.

25. Park K, Ahn CW, Lee SB, Kang S, Nam JS, Lee BK, Kim JH, Park JS. Elevated TyG Index Predicts Progression of Coronary Artery Calcification. Diabetes Care. 2019;42(8):1569–73.

26. Standards of medical care in diabetes–2011. Diabetes care 2011, 34 Suppl 1(Suppl 1):S11-61.

27. EmpowerStats. http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA.
28. Lallukka S, Yki-Järvinen H. Non-alcoholic fatty liver disease and risk of type 2 diabetes. Best practice research Clinical endocrinology metabolism. 2016;30(3):385–95.

29. Jeon J, Jung KJ, Jee SH. Waist circumference trajectories and risk of type 2 diabetes mellitus in Korean population: the Korean genome and epidemiology study (KoGES). BMC Public Health. 2019;19(1):741.

30. Narayan KM, Boyle JP, Thompson TJ, Gregg EW, Williamson DF. Effect of BMI on lifetime risk for diabetes in the U. S. Diabetes Care. 2007;30(6):1562–6.

31. Kalyani RR, Golden SH, Cefalu WT. Diabetes and Aging: Unique Considerations and Goals of Care. Diabetes Care. 2017;40(4):440–3.

32. Lee SH, Kwon HS, Park YM, Ha HS, Jeong SH, Yang HK, Lee JH, Yim HW, Kang MI, Lee WC, et al. Predicting the development of diabetes using the product of triglycerides and glucose: the Chungju Metabolic Disease Cohort (CMC) study. PloS one. 2014;9(2):e90430.

33. Zhang M, Wang B, Liu Y, Sun X, Luo X, Wang C, Li L, Zhang L, Ren Y, Zhao Y, et al. Cumulative increased risk of incident type 2 diabetes mellitus with increasing triglyceride glucose index in normal-weight people: The Rural Chinese Cohort Study. Cardiovascular diabetology. 2017;16(1):30.

34. Lee DY, Lee ES, Kim JH, Park SE, Park CY, Oh KW, Park SW, Rhee EJ, Lee WY. Predictive Value of Triglyceride Glucose Index for the Risk of Incident Diabetes: A 4-Year Retrospective Longitudinal Study. PloS one. 2016;11(9):e0163465.

35. Diagnosis and classification of diabetes mellitus. Diabetes care 2012, 35 Suppl 1(Suppl 1):S64-71.

Figures
| Sub-group                          | No. of participants | HR   | (95%CI)    | P interaction |
|-----------------------------------|---------------------|------|------------|---------------|
| **Women**                         |                     |      |            |               |
| Age Tertile(years)                |                     |      |            |               |
| >=46                              | 2309                | 1.9  | (0.6, 5.8) | 0.0529        |
| >=39, <46                         | 1991                | 4.5  | (0.9, 22.0)|               |
| <39                               | 2140                | 0.4  | (0.1, 1.8) |               |
| **Fatty liver**                   |                     |      |            | 0.7451        |
| No                                | 6094                | 1.6  | (0.6, 4.1) |               |
| Yes                               | 346                 | 1.3  | (0.3, 5.3) |               |
| **Waist circumference (cm)**      |                     |      |            | 0.8527        |
| <80                               | 5575                | 1.6  | (0.6, 4.4) |               |
| =80                               | 865                 | 1.9  | (0.6, 6.6) |               |
| **BMI (kg/m2)**                   |                     |      |            | 0.9677        |
| <25                               | 5951                | 1.8  | (0.8, 4.2) |               |
| =25                               | 489                 | 1.4  | (0.2, 8.5) |               |
| **Men**                           |                     |      |            |               |
| Age Tertile(years)                |                     |      |            | 0.1562        |
| >=47                              | 2772                | 1.5  | (0.9, 2.6) |               |
| >=39, <47                         | 2579                | 1.9  | (1.1, 3.4) |               |
| <39                               | 2506                | 2.8  | (1.2, 6.8) |               |
| **Fatty liver**                   |                     |      |            | 0.3107        |
| No                                | 5880                | 1.5  | (0.9, 2.7) |               |
| Yes                               | 1977                | 2.2  | (1.4, 3.4) |               |
| **Waist circumference (cm)**      |                     |      |            | 0.9757        |
| <90                               | 7011                | 1.7  | (1.1, 2.7) |               |
| =90                               | 846                 | 2    | (1.1, 3.6) |               |
| **BMI (kg/m2)**                   |                     |      |            | 0.9533        |
| <25                               | 6176                | 1.8  | (1.1, 2.9) |               |
| =25                               | 1681                | 1.9  | (1.1, 3.2) |               |

Figure 1
The association between the TyG index and incident diabetes stratified by age, fatty liver, waist circumference and BMI at baseline. Each stratification was adjusted for ethanol consumption, habit of exercise, HDL cholesterol, total cholesterol, smoking status, systolic blood pressure, diastolic blood pressure and family history of diabetes as well as all other presented subgroups except the stratification factor itself.

Figure 2

U shape relationship of the TyG index incident diabetes: women (A) and men (B). The solid black line represented the smooth curve fit between the TyG index and incident diabetes. The dotted curves were the 95% CI of the fit. The association was adjusted for age, fatty liver, waist circumference, BMI, ethanol consumption, habit of exercise, HDL cholesterol, total cholesterol, smoking status, systolic blood pressure, diastolic blood pressure and family history of diabetes.