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Normal Triglycerides Are Positively Associated with Plasma Glucose and Risk for Type 2 Diabetes in Chinese Adults

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Abstract: This study aimed to investigate the association of blood triglyceride levels with fasting blood glucose levels and type 2 diabetes (T2D) prevalence in Chinese adults with normal triglyceride levels (<1.7 mmol/L), using linear regression and binary logistic regression, respectively. This cross-sectional study included 16,706 Chinese adults, among which 1,067 had T2D. Triglycerides were positively associated with fasting plasma glucose after multivariate adjustment (β=0.034, P<0.001). One natural log unit increase in blood triglycerides was associated with a 61% higher multivariate-adjusted risk of T2D (odds ratio [OR], 1.61; 95% confidence interval [CI], 1.19-2.17; P=0.002). The positive associations remained when participants who were using lipid-lowering or anti-diabetic drugs were excluded. The optimal cut-off of triglycerides for T2D was 1.09 mmol/L (obtained using Receiver Operating Characteristic curve analysis). Participants with triglycerides of ≥1.09 mmol/L had a 28% higher risk of T2D (OR, 1.28; 95% CI, 1.07-1.53; P=0.006) compared to those with triglycerides below the cut-off. In conclusion, this study showed that, in people with normal triglyceride levels, higher triglycerides correlated with increased T2D diagnosis risk, with an optimal cut-off of 1.09 mmol/L. Therefore, adults with high "normal" triglyceride levels (1.09-1.69 mmol/L) may need to be closely monitored for the development of T2D.

Keywords: diabetes mellitus; triglyceride; glucose; association; risk factor

1. Introduction

Diabetes is one of the largest global public health concerns, imposing a heavy global burden on public health [1,2]. In 2021, approximately 529 million individuals were affected by type 2 diabetes (T2D) corresponding to 6.1% of the world's population [3,4]. Over 1 million deaths per year can be

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attributed to diabetes alone [5]. T2D accounts for ~90% of all diagnosed diabetes cases [6]. Therefore, it is important to identify modifiable factors for diabetes, particularly, T2D.

Epidemiological studies show that triglycerides are higher in patients with T2D [7,8]. Moreover, participants with higher than normal triglycerides (≥ 1.7 mmol/L or 150 mg/dL) [9] are associated with a higher risk of diabetes diagnosis [10,11], diabetes incidence [12–17], and diabetes mortality [11]. Higher than normal triglycerides are also associated with high cardiovascular mortality risk in people with diabetes [18].

To the best of our knowledge, only one study investigated the association between triglycerides and diabetes in people with normal triglycerides [19]. That study [19] found that higher normal triglycerides (from 1.13 to 1.69 mmol/L) were associated with an increased risk for new-onset T2D compared with those with triglycerides <1.13 mmol/L after a follow-up of 7.6 years. However, that study [19] has several limitations. First, only participants from Israel were studied. Second, the sample size was relatively small (N=3,722 participants with normal triglycerides). Third, whether normal triglycerides are associated with plasma glucose was not investigated. Fourth, whether normal triglycerides are associated with T2D prevalence was not investigated, as that study only enrolled participants without diabetes at baseline [19].

The current study aimed to investigate the associations between triglycerides and fasting plasma glucose and between triglycerides and T2D prevalence using a large group of Chinese adults (N=16,706) whose triglyceride levels were in the normal range (*i.e.*, < 1.7 mmol/L).

2. Materials and Methods

2.1. Participants

A total of 22,571 participants underwent a routine health examination between January and May 2019 at the Health Physical Examination Centre of the First Affiliated Hospital of Shandong First Medical University, Jinan, Shandong Province, China [20]. A total of 5,771 participants were excluded as their triglyceride levels were ≥ 1.7 mmol/L, i.e., not in the normal range recommended by the US National Lipid Association Expert Panel [9]. Thirteen participants were further excluded due to being younger than 18 years and another one was excluded due to missing blood pressure data. In addition, 80 participants who were taking insulin were excluded. The remaining 16,706 adult participants were included in this cross-sectional study (Figure 1).

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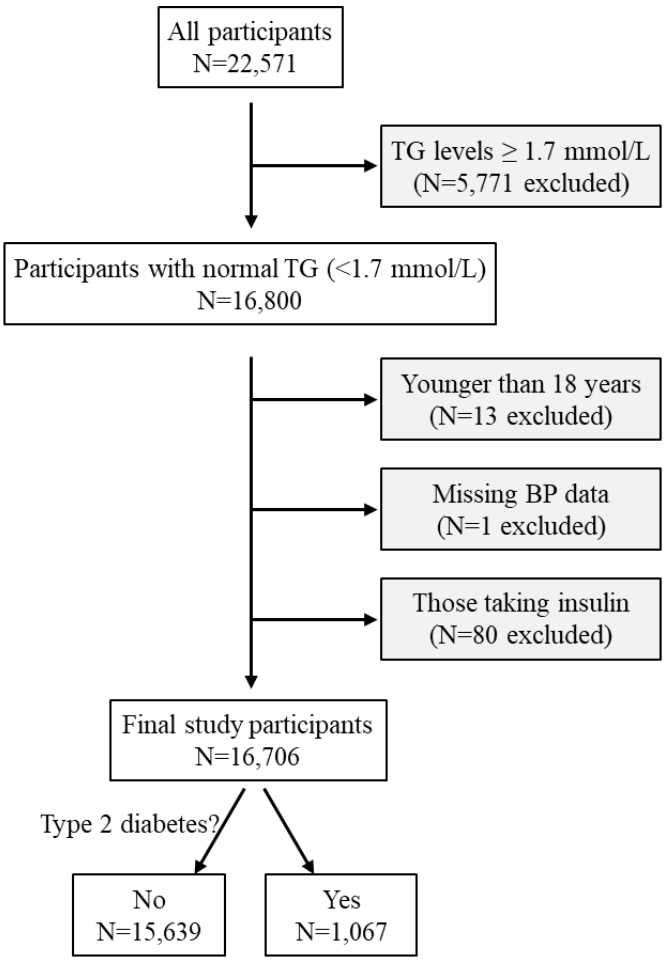

Figure 1. Flow diagram of the study participants. BP, blood pressure; TG, triglycerides.

2.2. Definition of diabetes and T2D

Diabetes was defined as fasting blood glucose ≥7 mmol/L or prior diagnosis or treatment of diabetes [20,21]. This study excluded those participants who were taking insulin (N=80, Figure 1). Therefore, diabetes in the current study was classified as T2D.

2.3. Covariates

Blood pressure was measured in all participants by trained professionals using Omron HBP-9020 Automated BP Monitors (Omron Healthcare Co. Ltd, Tokyo, Japan) in the seated position after the participant rested for 10 minutes. Blood pressure was measured 2 times at 2-min intervals and mean systolic and diastolic blood pressure were recorded [22]. BMI was calculated as weight in kilograms divided by height in meters squared. Venous blood samples were collected after an overnight fast. Fasting plasma glucose and serum concentrations of triglycerides, LDL cholesterol, and HDL cholesterol were measured using the Olympus AU2700 automatic biochemical analyzer. The use of lipid-lowering drugs was categorized as the number of lipid-lowering drugs prescribed (0, 1, or 2). The use of anti-diabetic drugs was categorized as the number of anti-diabetic drugs prescribed (0, 1, 2, 3, or 4).

2.4. Statistical analyses

All statistical analyses were performed using SPSS version 27.0 (IBM SPSS Statistics for Windows, Armonk, NY, International Business Machines Corporation). Data were expressed as mean and standard deviation (SD) for continuous variables or number and percentage for categorical

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variables [23]. Statistical comparisons of continuous data among groups were performed using one-way ANOVA (for LDL cholesterol) or Kruskal-Wallis one-way ANOVA (for age, triglycerides, glucose, BMI, systolic blood pressure, and HDL cholesterol) [18]. Statistical comparisons of categorical data among groups were performed using Pearson's Chi-square test [24]. The associations between triglycerides and glucose and between triglycerides and diabetes diagnosis were analyzed by linear regression and binary logistic regression, respectively, with or without adjustment for confounding factors including age, sex, BMI, systolic blood pressure, HDL cholesterol, LDL cholesterol, use of lipid-lowering drugs, and use of anti-diabetic drugs. Age, fasting plasma glucose, BMI, systolic blood pressure, triglycerides, and HDL cholesterol were natural log-transformed before putting into the regression models. Sensitivity analyses were conducted when those participants who were using lipid-lowering drugs or anti-diabetic drugs (N=414) were excluded. Receiver operating characteristic (ROC) curves were constructed and the area under the curve (AUC) was calculated to assess the association of triglycerides and diabetes diagnosis and to determine the optimal cutoff of triglycerides for increased risk of T2D according to the Youden index [25]. All tests were two-sided and a P value of < 0.05 was regarded as statistically significant.

3. Results

3.1. Clinical characteristics of the participants

The study included 16,706 participants aged 18–95 years with a mean (SD) age of 44.9 (14.3) years (Table 1). Among those participants, 1,067 had T2D. Participants with higher triglycerides had higher fasting plasma glucose, higher prevalence of T2D, and higher prevalence of use of anti-diabetic drugs. In addition, participants with higher triglycerides were older and had a higher percentage of males, higher body mass index (BMI), higher systolic blood pressure, higher low-density lipoprotein (LDL) cholesterol, and lower high-density lipoprotein (HDL) cholesterol (Table 1).

Table 1. Clinical characteristics of the 16,706 participants, stratified by quartiles of triglycerides.

	1st quartile	2rd quartile	3rd quartile	4th quartile	Overall	*P* for trend
TG, mean (SD), mmol/L	0.58 (0.10)	0.84 (0.07)	1.10 (0.08)	1.45 (0.13)	1.00 (0.34)	< 0.001
Sample size, N	4,152	4,179	4,083	4,292	16,706	NA
Age, mean (SD), y	39.9 (13.0)	44.6 (14.2)	46.7 (14.2)	48.3 (14.3)	44.9 (14.3)	< 0.001
Males, N (%)	1,538 (37.0)	2,091 (50.0)	2,451 (60.0)	2,802 (65.3)	8,882 (53.2)	< 0.001
FPG, mean (SD), mmol/L	4.97 (0.78)	5.17 (0.96)	5.32 (1.11)	5.49 (1.35)	5.24 (1.09)	< 0.001
BMI, mean (SD), kg/m^2	22.3 (3.0)	23.7 (3.3)	24.8 (3.3)	25.7 (3.2)	24.2 (3.5)	< 0.001
SBP, mean (SD), mm Hg	121 (17)	127 (18)	131 (19)	133 (19)	128 (19)	< 0.001
LDL-C, mean (SD), mmol/L	2.36 (0.58)	2.65 (0.65)	2.84 (0.69)	2.96 (0.70)	2.70 (0.69)	< 0.001
HDL-C, mean (SD), mmol/L	1.47 (0.29)	1.38 (0.27)	1.29 (0.25)	1.23 (0.24)	1.34 (0.28)	< 0.001

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Type 2 diabetes, N (%)	130 (3.1)	218 (5.2)	294 (7.2)	425 (9.9)	1,067 (6.4)	< 0.001
Number of people on anti-diabetic drugs, N (%)	63 (1.5)	84 (2.0)	109 (2.7)	137 (3.2)	393 (2.4)	< 0.001
Number of people on lipid-lowering drugs, N (%)	27 (0.7)	35 (0.8)	46 (1.1)	46 (1.1)	154 (0.9)	0.085

Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; N, number; NA, not applicable; SBP, systolic blood pressure; SD, standard deviation; TG, triglycerides.

3.2. Triglycerides were positively associated with fasting plasma glucose in participants with normal triglycerides

The increase in triglycerides was accompanied by an increase in fasting plasma glucose (Figure 2). Linear regression analyses confirmed that triglycerides were positively associated with fasting plasma glucose after adjustment for all the tested confounders ($\beta = 0.034$, $P < 0.001$, Table 2).

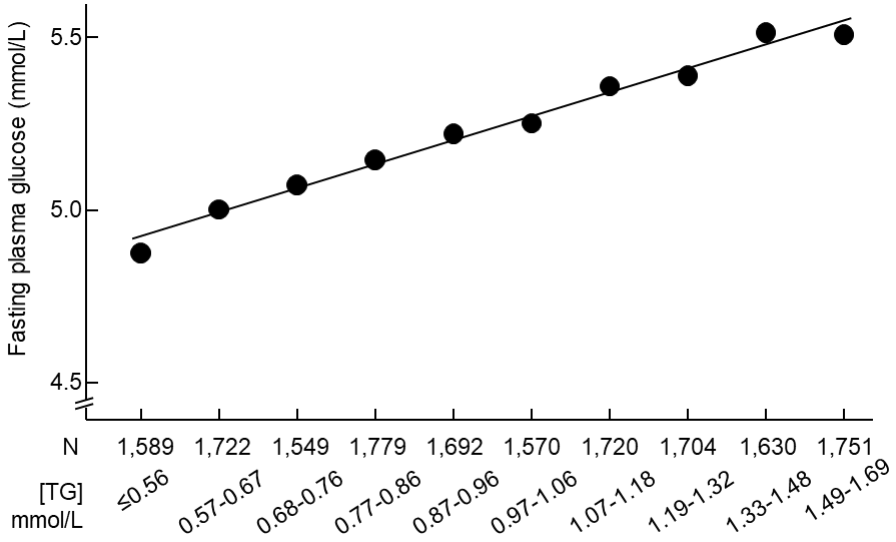

Figure 2. Mean fasting plasma glucose and serum triglyceride concentrations in 16,706 participants with normal triglycerides. Triglycerides were stratified according to the observed deciles. TG, triglycerides.

Table 2. Association between fasting plasma glucose [1] (dependent) and triglycerides [1] (independent) in 16,706 participants with normal triglycerides.

Models	β	P value
Model 1	0.211	< 0.001
Model 2	0.098	< 0.001
Model 3	0.036	< 0.001
Model 4	0.034	< 0.001

[1] Natural log-transformed. Model 1: Not adjusted; Model 2: Adjusted for age and sex; Model 3: Adjusted for factors in Model 2 plus body mass index, systolic blood pressure, LDL cholesterol, and HDL cholesterol; Model 4: Adjusted for factors in Model 3 plus use of lipid-lowering drugs and use of anti-diabetic drugs.

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3.3. Higher triglycerides were a risk factor for T2D in participants with normal triglycerides

Logistic regression analyses showed that higher triglycerides (continuous variable) were associated with higher risks of T2D, and a 1-natural-log-unit increase in triglycerides (*e.g.*, from 0.50 to 1.36 mmol/L or from 44 to 120 mg/dL) was associated with a 61% higher multivariate-adjusted risk of diabetes diagnosis (odds ratio [OR], 1.61; 95% confidence interval [CI], 1.19-2.17; P=0.002; Table 3).

Table 3. Natural log-transformed triglycerides and risk for type 2 diabetes in 16,706 participants with normal triglycerides.

Models	Odds ratio	95% CI	P value
Model 1	3.85	3.17-4.68	< 0.001
Model 2	2.21	1.79-2.73	< 0.001
Model 3	1.45	1.14-1.83	0.002
Model 4	1.61	1.19-2.17	0.002

Abbreviations: CI, confidence interval. Model 1: Not adjusted; Model 2: Adjusted for age and sex; Model 3: Adjusted for factors in Model 2 plus body mass index, systolic blood pressure, LDL cholesterol, and HDL cholesterol; Model 4: Adjusted for factors in Model 3 plus use of lipid-lowering drugs and use of anti-diabetic drugs.

The Receiver Operating Characteristic (ROC) curve analysis confirmed that higher triglycerides were significantly associated with higher risks of T2D (area under the curve, 0.63; 95% CI, 0.61-0.64; P<0.001; Figure 3). The prevalence of T2D was 4.5% and 9.3% in those with triglycerides <1.09 mmol/L and ≥1.09 mmol/L, respectively (Table 4). The optimal cutoff value, assessed by the Youden Index, was 1.09 mmol/L. When triglycerides were treated as a dichotomous variable using this optimal cutoff (*i.e.*, ≥1.09 mmol/L or <1.09 mmol/L), participants with triglycerides at or above the cutoff had a 28% higher risk of diabetes diagnosis (OR, 1.28; 95% CI, 1.07-1.53; P=0.006; Table 5) compared with those with triglycerides below the cutoff.

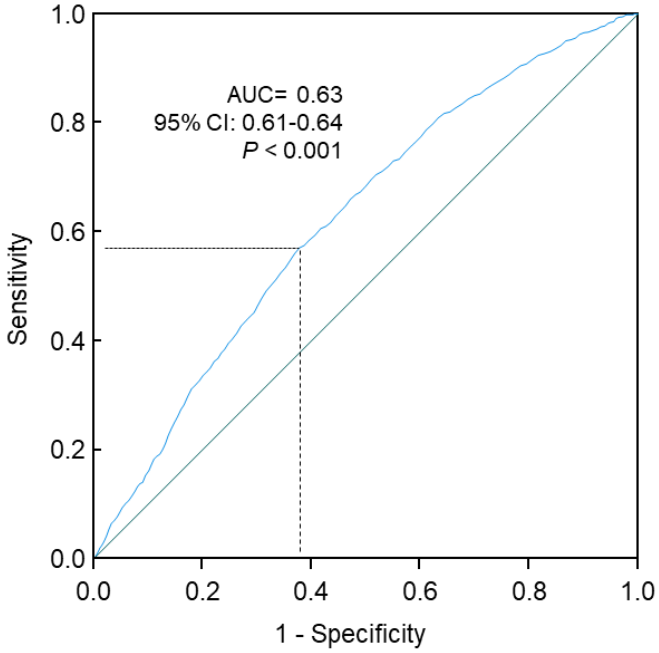

Figure 3. ROC curve analysis of the association of triglycerides with risks of type 2 diabetes. Sensitivity represents true-positive results and 1-specificity represents false-positive results. The optimal cutoff of triglycerides for increased risk of type 2 diabetes was 1.09 mmol/L, with a sensitivity of 0.57 and specificity of 0.62. 95% CI, 95% confidence interval; AUC, area under the curve; ROC, receiver operating characteristic.

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Table 4. Prevalence of type 2 diabetes, stratified by the triglyceride cutoff of 1.09 mmol/L.

	Triglycerides, <1.09 mmol/L	Triglycerides, ≥1.09 mmol/L	Overall
Sample size	10,189	6,517	16,706
Type 2 diabetes, N	458	609	1,067
Type 2 diabetes, %	4.5%	9.3%	6.4%

Table 5. OR (95% CI) for type 2 diabetes associated with higher triglycerides using the optimal cutoff (≥1.09 vs <1.09 mmol/L).

Models	Odds ratio	95% CI	P value
Model 1	2.19	1.93-2.48	< 0.001
Model 2	1.59	1.40-1.81	< 0.001
Model 3	1.26	1.09-1.45	0.002
Model 4	1.28	1.07-1.53	0.006

Abbreviations: CI, confidence interval. Model 1: Not adjusted; Model 2: Adjusted for age and sex; Model 3: Adjusted for factors in Model 2 plus body mass index, systolic blood pressure, LDL cholesterol, and HDL cholesterol; Model 4: Adjusted for factors in Model 3 plus use of lipid-lowering drugs and use of anti-diabetic drugs.

Further analyses were conducted when triglycerides were treated as quartiles. Results showed that higher triglycerides (top versus bottom quartile) were associated with a 54% higher multivariate-adjusted risk of T2D diagnosis (OR, 1.54; 95% CI, 1.14-2.09; Table 6).

Table 6. OR (95% CI) of triglycerides in quartiles for type 2 diabetes diagnosis in 16,706 participants with normal triglycerides.

Models	Q1	Q2	Q3	Q4	P for trend
Model 1	1	1.70 (1.36-2.13)	2.40 (1.94-2.97)	3.40 (2.78-4.16)	< 0.001
Model 2	1	1.20 (0.96-1.51)	1.48 (1.19-1.84)	1.94 (1.57-2.39)	< 0.001
Model 3	1	1.03 (0.81-1.30)	1.10 (0.87-1.39)	1.32 (1.05-1.66)	0.020
Model 4	1	1.15 (0.84-1.58)	1.22 (0.90-1.66)	1.54 (1.14-2.09)	0.009

Abbreviations: CI, confidence interval; OR, odds ratio; Q, quartile. Model 1: Not adjusted; Model 2: Adjusted for age and sex; Model 3: Adjusted for factors in Model 2 plus body mass index, systolic blood pressure, LDL cholesterol, and HDL cholesterol; Model 4: Adjusted for factors in Model 3 plus use of lipid-lowering drugs and use of anti-diabetic drugs.

3.4. Sensitivity analyses

Sensitivity analyses showed that the positive associations of triglycerides with fasting plasma glucose and T2D prevalence remained when those 414 participants who were using lipid-lowering drugs or anti-diabetic drugs were excluded (Tables 7 and 8).

Table 7. Sensitivity analysis of the association between fasting plasma glucose[1] (dependent) and triglycerides[1] (independent) when those 414 participants who were using lipid-lowering drugs or anti-diabetic drugs were excluded.

Models	β	P value
Model 1	0.261	< 0.001
Model 2	0.183	< 0.001

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Model 3	0.145	0.005

[1] Natural log-transformed. Model 1: Not adjusted; Model 2: Adjusted for age and sex; Model 3: Adjusted for factors in Model 2 plus body mass index, systolic blood pressure, LDL cholesterol, and HDL cholesterol.

Table 8. Sensitivity analysis of the association of triglycerides (natural log-transformed) with type 2 diabetes diagnosis when those 414 participants who were using lipid-lowering drugs or anti-diabetic drugs were excluded.

Models	Odds ratio	95% confidence interval	P value
Model 1	4.83	3.76-6.21	< 0.001
Model 2	2.77	2.12-3.64	< 0.001
Model 3	1.62	1.20-2.18	0.002

Model 1: Not adjusted; Model 2: Adjusted for age and sex; Model 3: Adjusted for factors in Model 2 plus body mass index, systolic blood pressure, LDL cholesterol, and HDL cholesterol.

4. Discussion

This study found, for the first time, that triglycerides were positively associated with fasting plasma glucose in a large group of Chinese participants who had normal triglycerides. In addition, triglycerides in the normal range were positively associated with T2D prevalence, and those with high normal triglycerides (1.09-1.69 mmol/L) had a 28% higher multivariate-adjusted risk of T2D compared with those with low normal triglycerides (<1.09 mmol/L).

The positive association between hypertriglyceridemia and diabetes is well-known [10–18]. Most evidence supports a causal role of abnormally high triglycerides in diabetes pathogenesis. For example, in people without diabetes at baseline, higher fasting triglycerides predicted impaired glucose tolerance [26], impaired fasting glucose, new-onset diabetes [14–17,19], and diabetes-caused mortality [11]. In addition, some triglyceride-lowering drugs are frequently reported to be associated with better glycemic control; examples of these drugs include the peroxisome proliferator-activated receptors (PPAR) alpha agonist fenofibrate [27], the PPAR alpha/delta agonist GFT505 [28], and the diacylglycerol acyltransferase 1 inhibitor pradigastat [29].

Some potential mechanisms have been proposed to explain the possible diabetes-causing role of hypertriglyceridemia. High concentrations of triglycerides and their metabolites could inhibit glucose transporter activity by reducing phosphoinositide 3-kinase [30]. In addition, high triglycerides could decrease glucose utilization by inhibiting glucose oxidation [31]. Moreover, high triglycerides decrease glycogen synthesis rate as well as glycogen content in the muscle [32].

However, some genetic studies provide conflicting information. For example, triglyceride-enhancing alleles have been reported to be either positively associated with [33], inversely associated with [16,34,35], or not associated with diabetes [36]. One of the genetic studies [16] revealed inconsistency between genetic and non-genetic results from the same cohort of participants: baseline circulating triglyceride levels were positively associated with new-onset diabetes; whereas triglycerides-enhancing alleles were negatively associated with new onset of the disease. The reasons underlying the observed inconsistencies [16] are unknown; some of the selected genetic alleles might have other functions beyond regulating circulating triglycerides.

So far, only one study investigated the association between triglycerides and T2D in people with normal triglycerides [19] and found that higher normal triglycerides (from 1.13 to 1.69 mmol/L) were associated with an increased risk for new-onset T2D compared with those with triglycerides <1.13 mmol/L after a follow-up of 7.6 years in 3,722 Israeli participants who did not have diabetes at baseline. However, it is unknown whether normal triglycerides are associated with plasma glucose or T2D prevalence. Therefore, more studies are needed to address these questions, and it would also be of value to use participants from another ethnic background, as ethnicity often affects health status and disease outcomes [37–40].

This study found that, in a large group of Chinese adults with normal triglycerides, triglycerides were positively associated with fasting plasma glucose. The mechanism underlying this novel finding is unclear. It is unknown whether the above-mentioned mechanisms, which explain the effect of hypertriglyceridemia on blood glucose, work under normal triglyceride conditions. It is also worth noting that one cannot rule out the possibility that higher blood glucose could lead to higher circulating triglycerides due to the cross-sectional design of the current study.

The current study also revealed that triglycerides were positively associated with diabetes prevalence in people with normal triglycerides. Thus, this study expanded the positive association between abnormally high triglycerides and diabetes prevalence [10,11] to people with "normal" triglycerides (< 1.7 mmol/L) and found that people with a triglycerides level between 1.09 and 1.69 mmol/L had a 28% higher risk of T2D compared with those with triglycerides <1.09 mmol/L.

This study had several strengths. First, the associations between triglycerides and plasma glucose and between triglycerides and T2D were adjusted for both HDL cholesterol and LDL cholesterol, as these two types of cholesterol are common confounding factors for triglycerides [28,41,42]. Second, this study had a large sample size (N = 16,706). This study also had several limitations. First, the cross-sectional nature of the study could not establish a causal relationship between triglycerides and plasma glucose and between triglycerides and T2D. Second, this study only adjusted for a limited number of confounders.

5. Conclusions

This study found that higher triglycerides were positively associated with fasting plasma glucose and T2D prevalence in Chinese adult participants with normal triglycerides. Adults with high "normal" triglyceride levels (1.09-1.69 mmol/L) may need to be closely monitored for the development of T2D.

Author Contributions: Conceptualization: Y.W., G.Y.; Methodology: H.L., S.M., T.Q., H.S., Q.X., Resources: X.H., W.H., G. Z.; Formal analysis and investigation: Y.W.; Writing - original draft preparation: Y.W., M.J., D.S., A.J.R.H.; Writing - review and editing: all authors.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Research Ethics Committee of the First Affiliated Hospital of Shandong First Medical University (approval code: S545).

Informed Consent Statement: Patient consent was waived on the basis that this study was to analyze a deidentified dataset.

Data Availability Statement: Datasets are available from corresponding authors on reasonable request.

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Conflicts of Interest: The authors declare no conflicts of interest.

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