

# Triglyceride to high-density lipoprotein cholesterol ratio variability and incident diabetes: A 7-year prospective study in a Chinese population

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## Keywords

Diabetes, Triglyceride to high-density lipoprotein cholesterol ratio, Variability

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*J Diabetes Investig* 2021; 12:  
1864–1871

doi:10.1111/jdi.13536

## ABSTRACT

**Aims/Introduction:** The correlation between triglyceride to high-density lipoprotein cholesterol (TG/HDL-C) ratio variability and incident diabetes has not been fully elucidated. We aimed to characterize the relationship between TG/HDL-C ratio variability and new-onset diabetes in Chinese adults.

**Materials and Methods:** A total of 45,911 patients with three TG and HDL measurements between 2006 and 2011 were enrolled. Average real variability (ARV) were used to evaluate variability, and participants were grouped according to tertiles of TG/HDL-ARV.

**Results:** There were 3,724 cases of incident diabetes mellitus during the observation period ( $6.24 \pm 1.2$  years). The 7-year cumulative incidences of diabetes mellitus in tertiles 1, 2 and 3 were 6.13%, 8.09% and 11.77%, respectively. New-onset diabetes increased with the tertiles of TG/HDL-ARV. This association was further confirmed after adjustment for mean TG/HDL-C ratio, TG/HDL-C ratio change slope, fasting plasma glucose variability (ARV) and other traditional risk factors for diabetes, the hazard ratio value for incident diabetes was 1.38 (1.25–1.50) for the highest tertile, and risk of diabetes increases by 4% with a one standard deviation increase in TG/HDL-C ratio variability. Restricted cubic splines showed a dose–response relationship between TG/HDL-C ratio variability and incident diabetes. Similar results were obtained in various subgroup and sensitivity analyses.

**Conclusions:** High TG/HDL-C variability was associated with a higher risk of diabetes in Chinese adults, independent of the direction of TG/HDL-C variability.

## INTRODUCTION

The global prevalence of diabetes in adults has been increasing in recent decades. Over the past 30 years, the prevalence of diabetes in Chinese adults has risen rapidly, from 0.69% in 1980 to 10.9% in 2013<sup>1,2</sup>. Individuals that have been diagnosed with diabetes have significantly higher incidences of cardiovascular and cerebrovascular events, fundic disease, kidney injury, and peripheral vascular disease than individuals without diabetes<sup>3–5</sup>. Additionally, tight control of glucose cannot effectively lower the incidences of these complications, because diabetes is typically accompanied by hypertension and lipid metabolism disorders.

Dyslipidemia is an important link in the etiology and pathogenesis of diabetes, and often coexists with the disorder of glucose metabolism<sup>6–10</sup>. Hypertriglyceridemia was known to induce insulin resistance (IR) and to be part of a vicious circle, in which IR and compensatory hyperinsulinemia worsen the hypertriglyceridemia<sup>11</sup>. In contrast, Rützi *et al.*<sup>12</sup> showed that  $\beta$ -cells are protected by high-density lipoprotein cholesterol (HDL-C) and against glucose-induced apoptosis, thereby improving insulin sensitivity and glucose tolerance. Thus, triglycerides (TG) and HDL-C have negative and positive roles in the pathogenesis of diabetes, respectively. The ratio of these two parameters, TG/HDL-C, is a highly recommended predictor of IR<sup>13–15</sup> and significant in predicting diabetes<sup>16,17</sup>.

Received 10 March 2020; revised 2 February 2021; accepted 22 February 2021

However, the studies that led to the use of this ratio relied on a single time-point assessment of lipid concentrations, and did not determine the risk or protective effects of changes in the ratio over a period of time on incident diabetes.

Therefore, we aimed to explore the relationship between lipid profile and incident diabetes by determining the correlation between visit-to-visit TG/HDL ratio variability and incident diabetes using data from the Kailuan study, which is an ongoing prospective Chinese population-based cohort study.

## MATERIALS AND METHODS

### Study participants

Between 2006 and 2007, clinical staff from Kailuan General Hospital, Tangshan, China, and 10 other affiliated hospitals of the Kailuan Group carried out physical examinations of employees, and collected relevant data. Subsequently, the clinical staff who participated in the first physical examination carried out two further physical examinations of the same population in the same location, in both 2008 to 2009 and 2010 to 2011. The components of the examination, anthropometric measurements and biochemical tests were the same as those carried out at the first physical examination.

The staff members of the Kailuan Group were included as participants in the study if they had participated in three physical examinations at approximately 2-year intervals in 2006–2007, 2008–2009 and 2010–2011, and without diagnosed diabetes. The exclusion criteria were missing TG, HDL-C or fasting plasma glucose (FPG) values; a history of diabetes; and lack of follow up or incomplete data.

Carried out according to the regulations of the Declaration of Helsinki, the present study was approved by the ethics committee of Kailuan General Hospital, and obtained written informed consent of all the participants.

### Data collection

The components of the investigation, anthropometric measurements and biochemical testing have been previously described in detail<sup>18</sup>.

Taken from the participants after an overnight fast, plasma samples were collected in ethylenediaminetetraacetic acid tubes between 07.00 and 09.00 hours the next morning. A Hitachi 7600 auto-analyzer (Hitachi; Tokyo, Japan) was used to determine plasma TG and HDL-C. The hexokinase/glucose-6-phosphate dehydrogenase method (BioSino Bio-Technology & Science Inc., Beijing, China) was used to measure FPG.

Height, body mass, blood pressure and other related measurements were made by trained medical staff in strict accordance with the appropriate standards. Personal lifestyle data, including birth date, sex, smoking status, alcohol use and past medical history (of hypertension, diabetes and ongoing use of medication, such as hypoglycemic, antihypertensive or lipid-lowering drugs) were self-reported in a questionnaire.

According to the standards of the American Diabetes Association in 2019, diabetes was defined as follows: FPG

$\geq 7.0$  mmol/L (126mg/dL) or FPG  $< 7.0$  mmol/L (126mg/dL), but with diagnosed diabetes or using hypoglycemic drugs in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis. Prediabetes was defined as an FPG concentration between 5.6 mmol/L (100 mg/dL) and 6.9 mmol/L (125 mg/dL), without self-reported history of diabetes or using hypoglycemic drugs. Ideal FPG was defined as an FPG concentration between 2.8 mmol/L (50 mg/dL) and 5.5 mmol/L (99 mg/dL), without self-reported history of diabetes or using hypoglycemic drugs<sup>19</sup>. Hypertension was defined as: (i) systolic blood pressure  $\geq 140$  mmHg or diastolic blood pressure  $\geq 90$  mmHg; or (ii) formerly diagnosed hypertension or using antihypertensive drugs<sup>20</sup>.

### End-point and follow up

The end-point of the study was a new diagnosis of diabetes mellitus. Participants who without incident diabetes during the follow-up period were considered to have completed the study when they died or at the end of the follow-up period, whichever came first. The study population was followed from baseline until death, a new diagnosis of diabetes or the date of the last physical examination, whichever came first. The diagnostic criteria used were based on the standards of the Chinese Diabetes Society.

### TG/HDL-C ratio variability

TG/HDL-C ratio variability was defined as the intraindividual variability in the ratio of the TG and HDL-C values obtained from three physical examinations. Four variability indexes were used:

- (1) the coefficient of variation =  $(SD/x \times 100\%)$ ,
- (2) standard deviation =  $\sqrt{\frac{1}{n-1} \sum_{i=1}^n (x_i - \bar{x})^2}$ ,
- (3) variation independent of the mean<sup>21,22</sup>, and
- (4) average real variability (ARV)<sup>23</sup>:

$$ARV = \frac{1}{N-1} \sum_{K=1}^{N-1} |\text{Value}_{K+1} - \text{Value}_K| \sum$$

TG/HDL-C ratio change slope: the concentrations of TG and HDL-C, measured at three physical examinations, constituted the TG and HDL-C dataset. The TG/HDL-C ratios in the year of physical examination were plotted to obtain the TG/HDL-C ratio regression line for that year. The regression lines were created using three sets of TG and HDL-C data, and the slope of this regression line represented the overall trend in TG/HDL-C ratio, and was used as an index of the long-term change in the TG/HDL-C ratio.

### Statistical analysis

The participants were allocated to three groups based on the tertile of TG/HDL-C ratio variability (TG/HDL-ARV): tertile 1:  $TG/HDL-ARV \leq 0.23$ , tertile 2:  $0.23 < TG/HDL-ARV \leq 0.52$  and tertile 3:  $TG/HDL-ARV > 0.52$ . The baseline characteristics were compared among these tertile groups. Continuous

variables are described using the mean  $\pm$  standard deviation (normal distribution) and median (quartiles; abnormal distribution). Categorical variables are presented as number (percentage). Normally and abnormally distributed continuous datasets were compared by using Student's *t*-test and non-parametric test, respectively. The  $\chi^2$ -test was used to compare the categorical datasets.

The cumulative incidence of the primary outcome in each tertile group was calculated through the Kaplan–Meier method and compared through the log-rank test.

The correlation between TG/HDL-C ratio variability and incident diabetes mellitus was characterized by Cox proportional hazards models. *P*-values were calculated using two-tailed tests, and *P* < 0.05 was considered to represent statistical significance. The correlation between TG/HDL-ARV and diabetes was assessed using restricted cubic splines in accordance with Harrell's rule<sup>24</sup>. The receiver operating characteristic (ROC) curve and ROC area under the curve were obtained. SPSS version 13.0 (SPSS, Chicago, IL, USA) and SAS version 9.4 (SAS Institute, Cary, NC, USA) was used to carry out statistical analyses.

The accuracy of the results might have been affected by the use of lipid-lowering drugs, the inclusion of individuals with diabetes and end-points occurring within the first year of the follow-up period. Therefore, participants who had taken lipid-lowering drugs and those newly diagnosed diabetes within 1 year were excluded, respectively, in sensitivity analysis.

## RESULTS

### Baseline characteristics

A total of 57,927 participants underwent three physical examinations between 2006 and 2011. There were 1,069 participants with missing TG or HDL-C values and 658 with missing FPG values, who were excluded. In addition, 10,289 participants had a history of diabetes before their final physical examination. Data from the remaining 45,911 participants were analyzed.

Of these 45,911 participants, 34,739 (75.73%) were men and 11,172 (24.27%) were women, and they had a mean age of  $52.37 \pm 12.03$  years. The mean TG/HDL-ARV was  $1.15 \pm 1.03$ . According to tertiles of TG/HDL-ARV, the participants were allocated to three groups: tertile 1: TG/HDL-ARV  $\leq 0.23$ , tertile 2:  $0.23 < \text{TG/HDL-ARV} \leq 0.52$  and tertile 3: TG/HDL-ARV  $> 0.52$ . Compared with tertile 1, tertiles 2 and 3 had much higher body mass index (BMI), systolic blood pressure, diastolic blood pressure, FPG, TG, mean TG/HDL-C values, and contained higher percentages of current smokers, current drinkers and participants with a family history of diabetes, who were hypertensive or who were using lipid-lowering drugs. However, the age, plasma HDL-C and percentage of participants undertaking physical exercise in tertile 1 were higher than those in tertiles 2 and 3 (*P* < 0.05; Table 1).

### Cumulative incidence of diabetes mellitus

There were 3,724 cases of incident diabetes mellitus during the observation period ( $6.24 \pm 1.2$  years). The 7-year cumulative

incidences of diabetes mellitus in tertiles 1–3 were 6.13%, 8.09% and 11.77%, respectively. The cumulative incidence of diabetes mellitus among the tertile groups were statistical significance calculated using the log-rank test ( $\chi^2 = 331.00$ , *P* < 0.001; Figure 1).

### TG/HDL-C ratio variability and incident diabetes mellitus

Table 2 shows the correlation between TG/HDL-C ratio variability and diabetes mellitus, established using a Cox proportional hazards regression model. The risk of incident diabetes increased with the tertiles of TG/HDL-ARV (*P* for trend < 0.001). The association was confirmed after adjusted for age, sex, BMI, FPG, LDL-C, mean TG/HDL-C, TG/HDL-C change slope, physical exercise, smoking status, alcohol consumption, family history of diabetes, hypertension and the use of lipid-lowering drugs. Compared with tertile 1, the hazard ratio (HR) was 1.16 (95% confidence interval [CI] 1.06–1.27) and 1.38 (95% CI 1.26–1.51) for tertile 2 and 3. After further adjusted for FPG variability (ARV), which was in the causal pathway, the HR was 1.16 (95% CI 1.06–1.26) and 1.38 (95% CI 1.25–1.50) for tertile 2 and 3. In a multivariable-adjusted model (model 3), we found that risk of diabetes increases by 4% with a one standard deviation increase in TG/HDL-C ratio variability.

The correlation between TG/HDL-C ratio variability and diabetes was also verified by restricted cubic splines analysis in the current study, which showed a dose–response relationship (Figure 2). ROC analyses with four different biomarkers for incident diabetes were carried out (Figure S1).

Similar results were observed in all the subgroup analyses. The risk of incident diabetes increased with the tertiles of TG/HDL-ARV in all the subgroups, except the TG/HDL-change slope  $\leq 0$  group. There were higher adjusted HRs for diabetes in participants with a TG/HDL-change slope  $> 0$  and those with an ideal FPG. The adjusted HRs for diabetes in tertile 3 were 1.43 (95% CI 1.25–1.62) for the TG/HDL-change slope  $> 0$  group, 1.29 (95% CI 1.14–1.47) for the TG/HDL-change slope  $\leq 0$  group, 1.43 (95% CI 1.25–1.65) for the ideal FPG group and 1.31 (95% CI 1.17–1.48) for prediabetes group (Table 3).

With the decrease of the TG/HDL-C ratio among three TG/HDL-C ratio subgroups, a higher risk of diabetes was associated with high TG/HDL-C AVR. There were higher adjusted HRs for diabetes in participants with Q1 TG/HDL-C ratio. The adjusted HRs for diabetes in tertile 3 were 1.63 (95% CI 1.30–2.04) for the Q1 TG/HDL-C ratio group, 1.25 (95% CI 1.06–1.47) for the Q2 TG/HDL-C ratio group and 0.99 (95% CI 0.84–1.17) for the Q3 TG/HDL-C ratio group (Table S1).

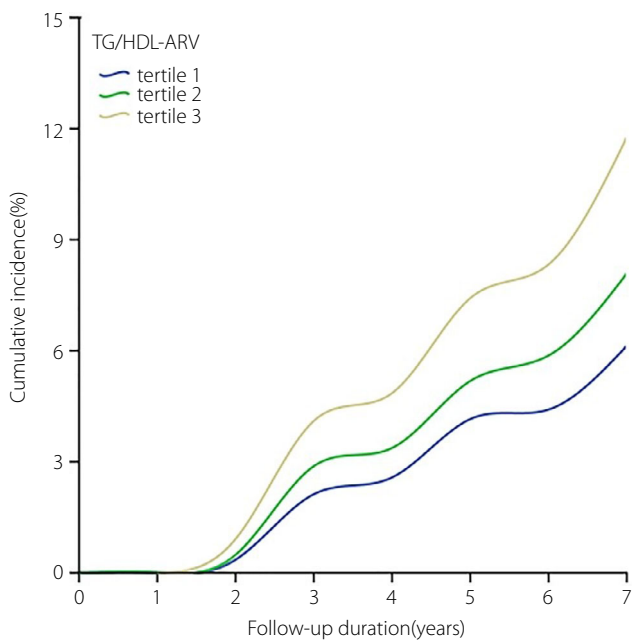
### TG variability, HDL-C variability and incident diabetes mellitus

The positive correlations between TG ARV, HDL-C ARV and incident diabetes are shown in Table S2. The risk of incident diabetes increased with tertiles of TG-ARV and HDL-ARV. In a multivariable-adjusted model (model 3), we found that the risk of diabetes increases by 33% with the highest tertiles of TG-ARV, and 8% with the highest tertiles of HDL-ARV.

**Table 1** | Baseline characteristics of the participants in 2010–2011

Variable	Total	Tertile 1	Tertile 2	Tertile 3	P
n	n = 45,911	n = 15,321	n = 15,311	n = 15,279	–
Age (years)	52.37 ± 12.03	53.17 ± 12.42	52.50 ± 12.15	51.43 ± 11.42	<0.001
Male (%)	34776 (75.75)	10854 (70.84)	11519 (75.23)	12403 (81.18)	<0.001
BMI (kg/m <sup>2</sup> )	24.82 ± 3.11	24.06 ± 3.06	24.78 ± 3.06	25.63 ± 3.00	<0.001
SBP (mmHg)	128.35 ± 16.68	126.45 ± 17.00	128.13 ± 16.64	130.49 ± 16.15	<0.001
DBP (mmHg)	83.20 ± 9.19	81.69 ± 9.12	83.04 ± 9.10	84.88 ± 9.06	<0.001
FBG (mmol/L)	5.15 ± 0.47	5.10 ± 0.46	5.15 ± 0.46	5.20 ± 0.47	<0.001
Triglyceride (mmol/L)	1.30 (0.96–1.87)	0.95 (0.74–1.24)	1.24 (1.00–1.57)	2.04 (1.51–2.78)	<0.001
LDL-C (mmol/L)	2.49 ± 0.63	2.44 ± 0.63	2.52 ± 0.61	2.50 ± 0.64	<0.001
HDL-C (mmol/L)	1.54 ± 0.32	1.64 ± 0.31	1.54 ± 0.30	1.44 ± 0.31	<0.001
TG/HDL-C in 2006	0.82 (0.55–1.30)	0.61 (0.43–0.83)	0.81 (0.58–1.15)	1.34 (0.81–2.22)	<0.001
TG/HDL-C in 2008	0.88 (0.56–1.30)	0.60 (0.43–0.85)	0.89 (0.62–1.13)	1.41 (0.91–2.22)	<0.001
TG/HDL-C in 2010	0.84 (0.55–1.33)	0.60 (0.41–0.83)	0.85 (0.58–1.20)	1.39 (0.84–2.28)	<0.001
Mean TG/HDL-C	0.89 (0.62–1.35)	0.59 (0.44–0.82)	0.84 (0.66–1.09)	1.51 (1.11–2.12)	<0.001
TG/HDL-change slope	0.00 (–0.14–0.17)	–0.01 (–0.09–0.08)	0.01 (–0.18–0.21)	0.04 (–0.38–0.50)	<0.001
FBG-ARV	0.47 (0.29–0.72)	0.46 (0.28–0.70)	0.47 (0.29–0.72)	0.49 (0.30–0.75)	<0.001
Physical exercise, n (%)	6,540 (14.25)	2,259 (14.74)	2,213 (14.46)	2,068 (13.54)	0.007
Current smoker, n (%)	15,645 (34.08)	4,613 (30.11)	5,132 (33.52)	5,900 (38.62)	<0.001
Current drinker, n (%)	16,246 (35.39)	4,838 (31.58)	5,223 (34.12)	6,185 (40.49)	<0.001
Family history of diabetes, n (%)	1,462 (3.18)	443 (2.89)	447 (3.12)	542 (3.55)	0.004
Hypertension, n (%)	19,704 (42.94)	5,803 (37.90)	6,420 (41.95)	7,481 (48.94)	<0.001
Lipid-lowering drugs therapy, n (%)	375 (0.82)	60 (0.39)	104 (0.68)	211 (1.38)	<0.001

Continuous variables are described by mean ± standard deviation (normal distribution)/median (quartile) (abnormal distribution); categorical variables are presented by number (percentage). Tertile 1: triglyceride to high-density lipoprotein cholesterol ratio average real variability (TG/HDL-ARV) ≤0.23, tertile 2: 0.23 < TG/HDL-ARV ≤ 0.52, tertile 3: TG/HDL-ARV >0.52. BMI, body mass index; DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; SBP, systolic blood pressure.



**Figure 1** | Cumulative incidence of diabetes mellitus in the triglyceride to high-density lipoprotein cholesterol ratio average real variability (TG/HDL-ARV) tertile groups.

**Sensitivity analysis**

To minimize the effect of drug therapy and reverse causation, participants who had taken lipid-lowering drugs and those with newly diagnosed diabetes within 1 year were excluded, respectively, in sensitivity analysis. Similar results were observed in sensitivity analysis. In the multivariable-adjusted model, the HRs in tertile 2 were 1.38 (95% CI 1.26–1.51) and 1.37 (95% CI 1.25–1.50) for sensitivity analysis group a and b (Table S3).

**DISCUSSION**

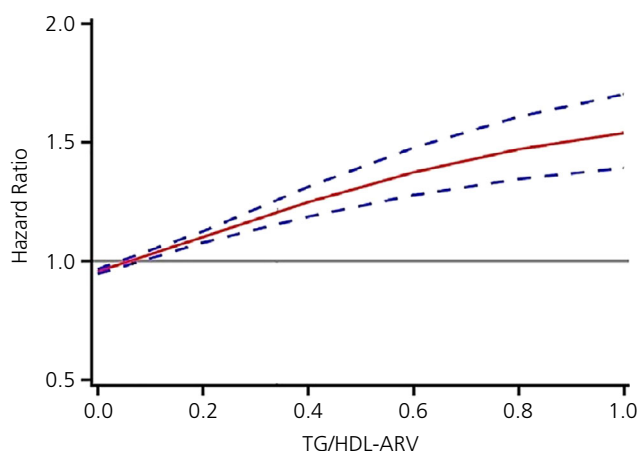
To the best of our knowledge, this was the first study to determine a positive correlation between TG/HDL-C ratio variability and new-onset diabetes in a large cohort. Furthermore, restricted cubic splines showed a dose–response relationship between TG/HDL-C ratio variability and incident diabetes, and ROC curves also showed its potential in detecting diabetes. These findings were confirmed in sensitivity and subgroup analyses, suggesting that this relationship was fairly universal.

The role of dyslipidemia in the pathogenesis of diabetes is well known<sup>6–10</sup>. The TG/HDL-C ratio was recommended for the prediction of IR and the reflection of β-cell function<sup>13–14,25–27</sup>. It was also a highly sensitive and specific predictor for new-onset diabetes<sup>16</sup>. However, previous studies used single measurements of lipids, and did not evaluate the association between changes

**Table 2** | Risk of incident diabetes according to triglyceride to high-density lipoprotein cholesterol ratio average real variability

	No. events	Per 1,000 person-years	Model 1	Model 2	Model 3
Tertile 1	859	8.91	1	1	1
Tertile 2	1,144	11.96	1.37 (1.26–1.50)	1.16 (1.06–1.27)	1.16 (1.06–1.26)
Tertile 3	1,721	18.20	2.11 (1.94–2.29)	1.38 (1.26–1.51)	1.37 (1.25–1.50)
1-SD increase (1.33)			1.06 (1.05–1.07)	1.04 (1.03–1.06)	1.04 (1.03–1.06)
<i>P</i> for trend			<0.001	<0.001	<0.001

Model 1 was adjusted for age and sex. Model 2 was further adjusted for body mass index, glucose, low-density lipoprotein-cholesterol, mean triglyceride to high-density lipoprotein cholesterol ratio, triglyceride to high-density lipoprotein cholesterol ratio change slope, physical exercise, smoking status, alcohol consumption, family history of diabetes, hypertension, and the use of lipid-lowering drugs. Model 3 was further adjusted for glucose variability. SD, standard deviation.

**Figure 2** | Spline graphical representation of the correlation between triglyceride to high-density lipoprotein cholesterol ratio variability and incident diabetes in the multivariable-adjusted model (model 3). TG/HDL-ARV, triglyceride to high-density lipoprotein cholesterol ratio average real variability.

in these parameters and the risk of diabetes. A cohort study carried out in Iran showed that a higher risk of diabetes was associated with an increase in the TG/HDL-C ratio<sup>28</sup>. However, just two physical examinations were carried out in that study, which was insufficient to accurately characterize any changes in the TG/HDL-C ratio. A positive correlation between high variability in TC and HDL-C with diabetes has been described in several studies, whereas TG/HDL-C variability has not been mentioned<sup>29,30</sup>. The present study adds to current knowledge regarding the association between lipid fluctuations and incident diabetes. After adjustment for traditional risk factors for diabetes, including mean FPG, BMI, hypertension and even further adjustment for FPG variability (ARV), incident diabetes significantly increased with higher TG/HDL-C variability, independent of baseline FPG levels and the direction of TG/HDL-C variation.

Current evidence shows that glucose homeostasis is directly and indirectly affected by TG and HDL-C. High TG, low

HDL-C and high TG/HDL-C ratio promote the onset or progression of diabetes<sup>6–10,16,17</sup>. Although the causal relationships described by this correlation are complex, the mechanisms of TG/HDL-C variability affecting glucose metabolism are being determined. The severity of  $\beta$ -cell dysfunction increased with pancreatic lipid content in individuals without diabetes<sup>25,26</sup>. Another study showed that  $\beta$ -cell function returns after a reduction in pancreatic lipid<sup>27</sup>, which emphasizes the effect of changes in lipid profiles on the development of diabetes. Dyslipidemia facilitates the development of pancreatic  $\beta$ -cell apoptosis, reduced insulin biosynthesis, defective insulin secretion and abnormal glucose metabolism. Aberrant fatty acid metabolism, including lipid accumulation, endoplasmic reticulum stress, oxidative stress, inflammation and defects in insulin signaling, eventually result in  $\beta$ -cell damage and apoptosis<sup>31–33</sup>. In contrast, HDL-C has been suggested to play an antidiabetic role by improving insulin sensitivity and protecting  $\beta$ -cells<sup>12</sup>. Regulation of lipoprotein lipase, function of cholesterol ester transfer protein and a defect in apolipoprotein production, associated with excessive insulin secretion in diabetes patients with IR or hyperinsulinemia, are the key of diabetic dyslipidemia<sup>34</sup>. Furthermore, the vicious circle involving TG, HDL-C and IR markedly increases the risk of developing and the progression of diabetes.

The correlation between TG/HDL-C ratio variability within different TG/HDL-C ratio subgroups and diabetes might suggest new diabetes prevention strategies. The TG/HDL-C ratio and its variability could be used to predict the incidence of diabetes more sensitively as a new biomarker panel. Recent studies have shown that the variability of several biomarkers, such as BP, BMI, TG, HDL-C, LDL-C and glucose, are independently associated with cardiovascular events, stroke, heart failure, diabetes, mortality and other diseases<sup>35–38</sup>. The fluctuation of biomarkers reflects the internal physiological regulation and metabolic changes, as well as the cumulative effects of lifestyle, nutrition and other external environmental stimuli, which is closely related to vascular endothelial cell injury, adipose tissue inflammation, cellular inflammatory cytokines production, oxidative stress, insulin resistance, neurohumoral dysfunction (e.g., abnormal function of renin-angiotensin system or

**Table 3** | Risk of incident diabetes according to triglyceride to high-density lipoprotein cholesterol ratio average real variability

Subgroup	Model 1	Model 2	Model 3
TG/HDL-change slope >0 (n = 23,361)			
Tertile 1	1	1	1
Tertile 2	1.41 (1.24–1.61)	1.23 (1.08–1.40)	1.23 (1.09–1.40)
Tertile 3	2.10 (1.87–2.37)	1.42 (1.25–1.62)	1.43 (1.25–1.62)
P for trend	<0.001	<0.001	<0.001
TG/HDL-change slope ≤0 (n = 22,550)			
Tertile 1	1	1	1
Tertile 2	1.34 (1.18–1.52)	1.09 (0.96–1.24)	1.08 (0.96–1.23)
Tertile 3	2.12 (1.89–2.38)	1.32 (1.16–1.49)	1.29 (1.14–1.47)
P for trend	<0.001	<0.001	<0.001
Ideal FBG (n = 33,430)			
Tertile 1	1	1	1
Tertile 2	1.40 (1.22–1.60)	1.18 (1.03–1.35)	1.17 (1.02–1.34)
Tertile 3	2.17 (1.92–2.47)	1.46 (1.27–1.67)	1.43 (1.25–1.65)
P for trend	<0.001	<0.001	<0.001
Prediabetes (n = 12,481)			
Tertile 1	1	1	1
Tertile 2	1.27 (1.13–1.43)	1.13 (1.01–1.27)	1.14 (1.01–1.28)
Tertile 3	1.77 (1.59–1.98)	1.31 (1.16–1.47)	1.31 (1.17–1.48)
P for trend	<0.001	<0.001	<0.001

Model 1 was adjusted for age and sex. Model 2 was further adjusted for body mass index, glucose, low-density lipoprotein-cholesterol, mean triglyceride to high-density lipoprotein cholesterol ratio (TG/HDL), TG/HDL-change slope, physical exercise, smoking status, alcohol consumption, family history of diabetes, hypertension and the use of lipid-lowering drugs. Model 3 was further adjusted for glucose variability (ARV). \**P* for the interaction of TG/HDL-ARV and TG/HDL-change slope was 0.011.

sympathetic nerve activity) and arteriosclerosis<sup>39–42</sup>. High variability of biomarkers might also be a manifestation of underlying diseases. Maintaining the internal environmental homeostasis is particularly important for basic life activities.

The main strengths of the present study were its large scale and the nearly 7 years of follow up. However, there were several limitations. First, it was an observational study that was not capable of identifying cause–effect relationships. For this reason, we carried out a sensitivity analysis, after excluding participants who developed incident diabetes within 1 year, and found consistent results. Second, just three TG and HDL-C measurements were made per participant, which was a considerable limitation. Although an analysis based on more assessments would more accurately evaluate the fluctuation of the TG/HDL-C ratio, measuring the TG/HDL-C ratio multiple times in a short period of time in such a large cohort study seems to be infeasible. Third, the incidence of diabetes might have been underestimated, due to the lack of glycated hemoglobin (HbA1c) and oral glucose tolerance test data. However, a national survey in China reported that the prevalence of diabetes and prediabetes measured by FPG was 24.3% and 22.8%, respectively, whereas the prevalence of diabetes and prediabetes diagnosed by 2-h plasma glucose and HbA1c was just 6.1% and 4.0%<sup>43</sup>. Thus, the proportion of individuals who were misdiagnosed as diabetes and prediabetes was low, which hardly

affects the present results. As HbA1c has not been sufficiently characterized to support routine adoption, the current Chinese guidelines do not recommend the use of HbA1c for diagnosis of diabetes. Meanwhile, considering that in a large cohort, such as that in the present study, each additional test would inevitably cost a quantity of manpower, material resources and physical examination time. For this reason, China's guidelines indicate that FPG or oral glucose tolerance test 2-h plasma glucose might be used alone for epidemiological or population screening purposes<sup>43</sup>. Therefore, the Kailuan study did not carry out the HbA1c and oral glucose tolerance tests. However, we will gradually carry out these tests in the follow-up for a more accurate analysis. Finally, the specific lifestyle of the participants, such as their dietary patterns, were not included in the analyses. However, we measured fasting TG and HDL-C concentrations, to reduce the confounding effect of diet on blood lipids as much as possible. Despite these limitations, the present study has identified a highly novel correlation between TG/HDL-C variability and incident diabetes in a large cohort.

In conclusion, TG/HDL-C ratio variability was found to be an independent predictor of new-onset diabetes in the present study. This finding implies that the stabilization of the TG/HDL-C ratio was effective in reducing the risk of diabetes. Further epidemiological experimental research should be carried out to confirm this finding and to gain a fuller understanding

of the mechanisms linking visit-to-visit TG/HDL-C ratio variability and diabetes.

## ACKNOWLEDGMENTS

This work has been supported by the National Natural Science Foundation of China (No. 81870312).

## DISCLOSURE

The authors declare no conflict of interest.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Figure S1** | Receiver operating characteristic curves of four different biomarkers for incident diabetes.

**Table S1** | Risk of incident diabetes according to triglyceride to high-density lipoprotein cholesterol average real variability within tertiles of the triglyceride to high-density lipoprotein cholesterol ratio.

**Table S2** | Risk of incident diabetes according to triglyceride average real variability and high-density lipoprotein average real variability.

**Table S3** | Risk of incident diabetes according to triglyceride to high-density lipoprotein cholesterol average real variability.