

Higher triglyceride to high-density lipoprotein cholesterol ratio increases cardiovascular risk: 10-year prospective study in a cohort of Chinese adults

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Keywords

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ABSTRACT

Aims/Introduction: A higher ratio of triglyceride to high-density lipoprotein cholesterol (TG/HDL-C) is considered as the independent risk index of cardiovascular (CV) events. However, cohort studies regarding this correlation are rarely reported, especially in the Chinese population. The aim of present study was to explore the relationship of the TG/HDL-C ratio with CV risks among Chinese adults during 10-year follow-up period.

Materials and Methods: We carried out a prospective study using data obtained from 96,542 individuals in Kailuan, who were grouped through the median value (0.8533) of the TG/HDL-C ratio. Adverse outcomes mainly referred to major CV events. We used the person-years incidence and cumulative incidence to predict the morbidity. The risk of CV events was estimated through Cox proportional hazard models.

Results: The mean age of the cohort was 51.5 ± 12.6 years, and 79.6% of participants were men. During a median follow-up period of 9.75 years, 5,422 major CV events occurred, including 1,312 myocardial infarction cases and 4,228 stroke cases. The cumulative incidence of myocardial infarction, stroke and total CV events was 1.36% (range 1.29–1.43%), 4.38% (range 4.25–4.51%) and 5.62% (range 5.47–5.76%), respectively. Compared with low the TG/HDL-C ratio (≤ 0.8533) group, the high TG/HDL-C ratio (>0.8533) group had higher morbidity of CV events. The hazard ratio of total CV events, stroke and myocardial infarction was 1.19 (95% CI 1.12–1.26), 1.11 (95% CI 1.03–1.18) and 1.50 (95% CI 1.33–1.70), respectively. Furthermore, the TG/HDL-C ratio and major CV events had a line-shaped relationship with each other.

Conclusions: Among the Chinese population, a higher TG/HDL-C ratio is correlated with an increased risk of major CV events.

INTRODUCTION

Despite the advanced diagnosis and treatment strategies, cardiovascular (CV) events are still the main causes of death worldwide. Dyslipidemia is seen as a well-documented risk indicator for CV disease (CVD)¹, which can be reflected by decreased high-density lipoprotein cholesterol (HDL-C) content, increased triglycerides (TG) and the predominance of small dense low-density lipoprotein (sd-LDL) particles^{2,3}. Recently, a well-

defined atherogenic dyslipidemia parameter, namely, the TG/HDL-C ratio, has been thought to be correlated with CV events^{4–6}. Compared with other individual lipid profiles, the TG/HDL-C ratio can be a better predictive indicator for insulin resistance (IR)^{7–9}, obesity¹⁰ and coronary heart disease¹¹ by reflecting the complex interactions of lipoprotein metabolism¹². Although some studies have shown the relationship between the TG/HDL-C ratio and CV events, cohort studies regarding this correlation have been rarely reported, especially in the Chinese population.

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In the present study, the correlation of the TG/HDL-C ratio with major CV event risks, including stroke and myocardial infarction (MI), was prospectively examined in a cohort of Chinese adults from the Kailuan population during a 10-year follow-up period.

METHODS

Population studied

The prospective cohort study was carried out in the Kailuan community, and the comprehensive and functional community was governed through Kailuan Corporation in Tangshan City (Hebei, China). From 2006.6 to 2007.10, Kailuan Corporation organized the physical examination for 101,510 working and retired employees in Kailuan General Hospital and its 10 affiliated hospitals. The detailed information about the characteristics and study design of the Kailuan study population has been described in the previous study¹³. The medical data were recorded by trained medical personnel and stored in the research database (Oracle 10.2g) that was hosted in the servers at Kailuan General Hospital.

The inclusion criteria for participants were as follows: (i) aged ≥ 18 years; and (ii) willing to join in the research and sign an informed consent. Among these participants, we excluded those who had incomplete medical data ($n = 1,281$), who had a history of any malignant cancer ($n = 377$) or who had a history of stroke and MI ($n = 3,310$). Finally, a total of 96,542 participants (76,854 men, 79.6%) were covered in the research. The research adhered to the Declaration of Helsinki and was approved by the ethics committee of Kailuan General Hospital. All of the participants agreed to sign written informed consent.

Data acquisition

The detailed data of the epidemiological survey and anthropometric measurements were previously published¹⁴. The researchers would deliver the questionnaires to collect the participants' sociodemographic data (e.g., sex, education and age), personal and family medical history (e.g., diabetes, hypertension, CVs) and living habits (e.g., physical activity, smoking status and alcohol status). Smoking status was defined as: daily, occasionally, former and never. Alcohol consumption was defined as a daily consumption of at least 100 mL of moderate pure alcohol ($\geq 50\%$) per day in recent years. Physical activity was defined as: very active (≥ 80 min/week), moderately active (1–79 min/week) and inactive (0 min/week) according to the frequency of physical activity in the questionnaires.

After an overnight fast, the blood samples were taken from participants' antecubital vein and stored in ethylenediaminetetraacetic acid tubes at 07.00–09.00 hours. A Hitachi 7600 auto-analyzer (Hitachi, Tokyo, Japan) was used to test the biochemical indicators; for instance, fasting plasma glucose (FPG), high-sensitivity C-reactive protein, total cholesterol (TC), TG, low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C). FPG was measured through hexokinase method (BioSino Bio-Technology & Science Inc.,

Beijing, China). TG, TC, HDL-C and LDL-C content were measured through an enzymatic method (Mind Bioengineering Co. Ltd, Shanghai, China; interassay coefficient of variation $< 10\%$). All of the biochemical indicators were measured and analyzed in our central laboratory at Kailuan General Hospital.

After completing the physical examination in 2006–2007, the participants were followed until 31 December 2016. The end-point events were the first occurrences of the defined adverse outcomes during the follow-up period.

Adverse outcomes

Adverse outcomes referred to stroke (e.g., intracerebral hemorrhage, subarachnoid hemorrhage and ischemic stroke), non-fatal MI and so on. The first occurrences of those major CV events were our study outcomes, which should conform to the diagnosis criteria of the World Health Organization^{15,16}. Total CV events were expressed as the sum of the first occurrences of major CV events. The professionally trained doctors would collect and record the study outcomes every 6 months. The specific data of major CV events were gathered from personal interviews every 2 years, and confirmed through the medical records and claims data from medical insurance. The relevant data were collected from Kailuan General Hospital and its 10 affiliated hospitals.

Then, the collected information would be further validated by the Arbitration Committee for Clinical Outcomes and Data Safety Monitoring Board.

Statistical analysis

The participants were assigned to two groups according to the median value (0.8533) of the TG/HDL-C ratio: the high TG/HDL-C ratio (> 0.8533) group and low TG/HDL-C ratio (≤ 0.8533) group. The baseline characteristics were described and compared between groups. Continuous variables were expressed as the median (quartile) for abnormal distribution and expressed as the mean \pm standard deviation for normal distribution. Continuous variables between groups were compared through non-parametric tests and one-way ANOVA for abnormal and normal distribution data, respectively. Categorical variables were presented as the number (percentage), and then compared through the χ^2 -test.

The adverse event rate was presented by person-years incidence, as well as cumulative incidence. The cumulative incidence between groups was compared by the log-rank test. In order to explain the relationship between the TG/HDL-C ratio and major CV events, multivariate Cox proportional hazards analysis was applicable for predefined outcomes. Furthermore, natural cubic spline functions were able to evaluate the correlation of the TG/HDL-C ratio with CV events. There was statistical significance only when $P < 0.05$ (two-tailed). Statistical analysis was made by SPSS System version 21.0 (SPSS Inc., Chicago, IL, USA) and open source statistical software package R (version 3.20).

RESULTS

Baseline characteristics

On exclusion, a total of 96,542 participants (95.11% of the original cohort) were eventually included for the cohort study. The mean age (standard deviation) was 51.5 ± 12.6 years, including 76,854 men (79.6%). Table 1 shows the clinical data of the whole study population and different groups divided through median value (0.8533) of the TG/HDL-C ratio. Compared with the low TG/HDL-C ratio group, the high TG/HDL-C ratio group had a dramatically lower educational degree and HDL-C levels. Additionally, the values for body mass index, heart rate, blood pressure, TG, FPG, TC, LDL-C and high-sensitivity C-reactive protein, and the percentage of hypertension, diabetes, current smokers, current drinkers, antidiabetic drug therapy and antihypertensive drug therapy in the high TG/HDL-C ratio group were statistically higher than those of the low ratio group (*P* < 0.05; Table 1).

Incidence rate of adverse outcomes

Table 2 shows the incidence rate of predefined outcomes classified through the TG/HDL-C ratio. During the mean follow-up period of 9.75 years, 5,422 major CV events were identified, namely, 1,312 cases of MI and 4,228 cases of stroke. The incidence rate of total CV events, stroke and MI was 576.02,

445.97 and 136.45 per 100,000 person-years, respectively. As shown in Table 2, a high TG/HDL-C ratio showed a higher cumulative incidence by comparison with those with a low TG/HDL-C ratio. The cumulative incidence of total CV events, stroke and MI in the high TG/HDL-C ratio group was 3.23 (range 3.12–3.34), 2.46 (range 2.36–2.55) and 0.85 (range 0.79–0.91), respectively (Table 2).

Correlation of the TG/HDL-C ratio with CV events

Table 3 shows the correlation of the TG/HDL-C ratio with CV events through the Cox proportional hazard regression model. According to unadjusted Cox proportional hazard regression analysis, an elevated TG/HDL-C ratio had a correlation with elevated risks of MI, stroke and total CV events (model 1). In model 2, the participants' sex and age were further adjusted; compared with the participants with a low TG/HDL-C ratio, those with a high TG/HDL-C ratio had an obvious correlation with higher major CV risks, whose hazard ratio was 1.73 (95% confidence interval [CI] 1.55–1.94), 1.32 (95% CI 1.24–1.41) and 1.41 (95% CI 1.33–1.48), respectively. Multivariate factors, such as smoking status, education, hypertension and diabetes, were further adjusted in model 3; then the hazard ratio of MI, stroke and total CV events was 1.19 (95% CI 1.12–1.26), 1.11 (95% CI 1.03–1.18) and 1.50 (95% CI 1.33–1.70), respectively.

Table 1 | Baseline characteristics of 96,542 participants of the Kailuan Study

Characteristics	All participants	TG/HDL-C ratio		P-value
		Low ≤0.8533	High >0.8533	
n (%)	96,542	48,567 (50.3)	47,975 (49.7)	–
Age (years)	51.5 ± 12.6	51.4 ± 13.1	51.6 ± 12.0	0.154
Male, n (%)	76,854 (79.6)	37,140 (76.5)	39,714 (82.8)	<0.001
Education ≥high school, n (%)	18,803 (19.5)	9,650 (19.9)	9,153 (19.1)	0.002
Heart rate (b.p.m.)	73.8 ± 10.2	73.2 ± 10.1	74.4 ± 10.2	<0.001
BMI (kg/m ²)	25.0 ± 3.5	24.1 ± 3.3	26.0 ± 3.4	<0.001
SBP (mmHg)	130.7 ± 20.9	128.3 ± 20.8	133.1 ± 20.7	<0.001
DBP (mmHg)	83.4 ± 11.8	81.7 ± 11.5	85.1 ± 11.8	<0.001
FPG (mmol/L)	5.47 ± 1.67	5.27 ± 1.40	5.67 ± 1.87	<0.001
HDL-C (mmol/L)	1.55 ± 0.40	1.68 ± 0.41	1.41 ± 0.35	<0.001
LDL-C (mmol/L)	2.34 ± 0.91	2.31 ± 0.90	2.38 ± 0.93	<0.001
TC (mmol/L)	4.94 ± 1.14	4.90 ± 1.00	4.99 ± 1.27	<0.001
TG (mmol/L)	1.27 (0.89–1.92)	0.90 (0.70–1.12)	1.92 (1.48–2.78)	<0.001
hs-CRP (mmol/L)	0.80 (0.30–2.18)	0.70 (0.25–1.94)	0.94 (0.37–2.40)	<0.001
Current drinker, n (%)	16,804 (17.4)	8,197 (16.9)	8,607 (17.9)	0.005
Current smoker, n (%)	32,164 (33.3)	15,060 (31.0)	17,104 (35.7)	<0.001
Physical activity, n (%)	14,037 (14.5)	6,994 (14.4)	7,043 (14.7)	0.218
Hypertension, n (%)	41,790 (43.3)	18,224 (37.5)	23,566 (49.1)	<0.001
Diabetes, n (%)	8,728 (9.0)	2,950 (6.1)	5,778 (12.0)	<0.001
Antidiabetic drug therapy, n (%)	2,066 (2.14)	755 (1.55)	1,311 (2.73)	<0.001
Antihypertensive drug therapy, n (%)	8,753 (9.07)	3,270 (6.73)	5,483 (11.43)	<0.001

Continuous variables were described by mean ± standard deviation (normal distribution)/median (quartile) (abnormal distribution); categorical variables were presented by number (percentage). The ranges in parentheses represent median (quartile). BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

Table 2 | Incidence rate of adverse outcomes stratified by the triglyceride to high-density lipoprotein cholesterol ratio

Group	<i>n</i>	No. CV events	Cumulative incidence (95% CI)	Per 100,000 person-years
Total CV events				
Total	96,542	5,422	5.62 (5.47–5.76)	576.02
Low TG/HDL-C ratio group	48,567	2,307	2.39 (2.29–2.49)	485.20
High TG/HDL-C ratio group	47,975	3,115	3.23 (3.12–3.34)	668.00
<i>P</i> -value for log-rank test	–	–	<0.001	–
Stroke				
Total	96,542	4,228	4.38 (4.25–4.51)	445.97
Low TG/HDL-C ratio group	48,567	1,856	1.92 (1.84–2.01)	388.76
High TG/HDL-C ratio group	47,975	2,372	2.46 (2.36–2.55)	504.51
<i>P</i> -value for log-rank test	–	–	<0.001	–
MI				
Total	96,542	1,312	1.36 (1.29–1.43)	136.45
Low TG/HDL-C ratio group	48,567	493	0.51 (0.47–0.56)	101.92
High TG/HDL-C ratio group	47,975	819	0.85 (0.79–0.91)	171.57
<i>P</i> -value for log-rank test	–	–	<0.001	–

CI, confidence interval; CV, cardiovascular; MI, myocardial infarction; TG/HDL-C, triglyceride to high-density lipoprotein cholesterol.

Table 3 | Hazard ratios of major cardiovascular events

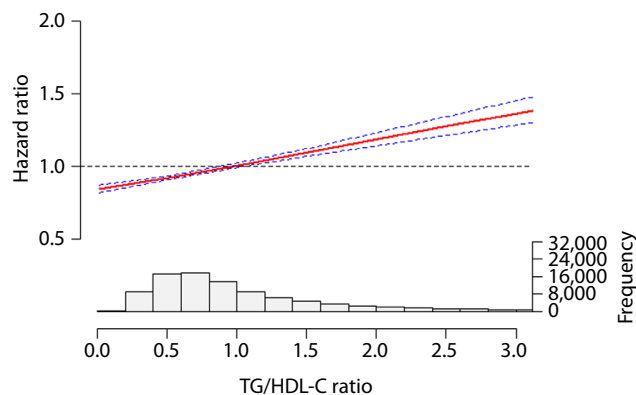
Group	Model 1	Model 2	Model 3
Total CV events			
Low TG/HDL-C ratio group	1	1	1
High TG/HDL-C ratio group	1.37 (1.30–1.45)	1.41 (1.33–1.48)	1.19 (1.12–1.26)
Stroke			
Low TG/HDL-C ratio group	1	1	1
High TG/HDL-C ratio group	1.30 (1.22–1.38)	1.32 (1.24–1.41)	1.11 (1.03–1.18)
MI			
Low TG/HDL-C ratio group	1	1	1
High TG/HDL-C ratio group	1.68 (1.51–1.88)	1.73 (1.55–1.94)	1.50 (1.33–1.70)

Model 1 was stratified for the triglyceride to high-density lipoprotein cholesterol (TG-HDL-C) ratio; model 2 was further adjusted for age and sex; model 3 further adjusted for smoking status, alcohol consumption, education, physical exercise, diabetes, hypertension, total cholesterol, low-density lipoprotein cholesterol, heart rate, high sensitivity C-reactive protein, body mass index, antidiabetic drug therapy, antihypertensive drug therapy. The values in parentheses represented by HR (95% CI). CV, cardiovascular; MI, myocardial infarction.

After adjusting the multiple covariates, natural cubic spline analysis was used to verify the line-shaped relationship between the TG/HDL-C ratio and adverse reactions. Furthermore, the TG/HDL-C ratio showed a line-shaped association with major CV events, while the hazard ratio was increased by a higher TG/HDL-C ratio (Figures 1–3).

DISCUSSION

As far as we know, this is the first prospective community-based cohort study to be carried out to explain the correlation of the TG/HDL-C ratio with major CV events among the large Chinese population. In the present study, it was shown that the participants with a higher TG/HDL-C ratio had evidently elevated major CV risks. Our research findings are beneficial to identify the association of the TG/HDL-C ratio with major CV

**Figure 1** | The association between the triglyceride to high-density lipoprotein cholesterol (TG/HDL-C) ratio and total cardiovascular events.

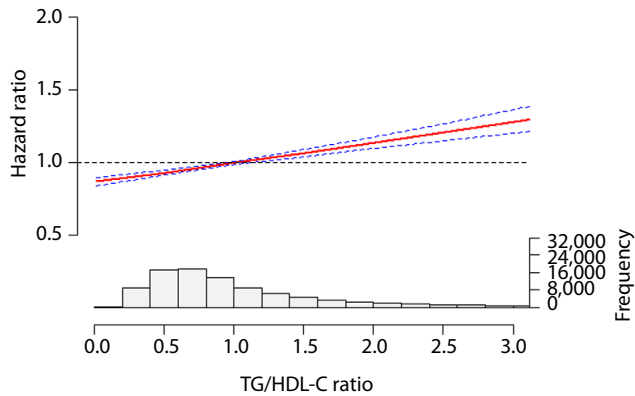


Figure 2 | The association between the triglyceride to high-density lipoprotein cholesterol (TG/HDL-C) ratio and stroke.

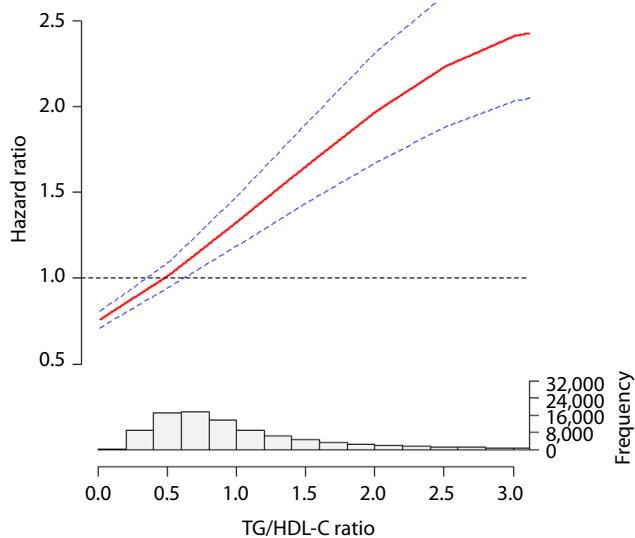


Figure 3 | The association between the triglyceride to high-density lipoprotein cholesterol (TG/HDL-C) ratio and total myocardial infarction.

events in the Chinese population, and to screen out the high-risk general population. In this way, the government could establish the corresponding prevention strategies for high-risk individuals.

The identification of a simple, accurate and inexpensive indicator for predicting CVD patient's prognosis has become a global focus. Previous studies have shown the relationship between the TG/HDL-C ratio and CV events. As reported by Turak *et al.*⁴, a higher TG/HDL-C ratio is associated with more major adverse CV events in essential hypertensive patients. A case-control study showed an obvious correlation of a high TG/HDL-C ratio with increased risks of MI⁶. In addition, studies from the general population in Asia Pacific and Europe showed that the TG/HDL-C ratio can be a predictive index for the risk

of CVD^{17,18}. Similarly, the present study showed that among 96,542 Chinese participants, the major CV risks for participants with a high TG/HDL-C ratio were elevated by 26% by comparison with those with a low TG/HDL-C ratio. Therefore, the present results shows that the TG/HDL-C ratio can become a critical predictive value for the risk of CVD.

Natural cubic spline analysis was applied to further explore the association of the TG/HDL-C ratio with major CV events. Through the adjustment for multiple covariates, the results showed a line-shaped curve association with increased risks of major CV events at a higher TG/HDL-C ratio. Wu *et al.*¹⁹ believe a higher TG/HDL-C ratio has a relationship with elevated CV mortality during peritoneal dialysis. However, whether the TG/HDL-C ratio becomes a widely used clinical biochemical indicator remains to be supported by more studies. After all, the population we studied comes from the northern areas of China, which cannot provide a strong basis for the entire Chinese population. Furthermore, as LDL-C is a major cause of atherosclerosis and CVD, receiver operating characteristic curve analysis was carried out to investigate the possibilities of the TG/HDL-C ratio and LDL-C to diagnose CV events. Receiver operating characteristic analysis results showed that the TG/HDL-C ratio has a higher predictive value than LDL-C, and the area under the curve of the TG/HDL-C ratio is 0.553 (range 0.545–0.560).

In the present study, the demographic data of baseline showed that compared with those of the low ratio group, the high TG/HDL-C ratio group had statistically higher traditional risk factors, such as heart rate, diastolic blood pressure, systolic blood pressure, body mass index, FPG, TC, TG, LDL-C and high-sensitivity C-reactive protein; meanwhile, HDL-C was statistically lower. We also found that other covariates, such as smoking status, alcohol status, education, and the percentage of hypertension and diabetes, were significantly different between groups. At the same time, the results showed that the participants with a high TG/HDL-C ratio also conformed to the diagnostic criteria for metabolic syndrome²⁰, which is consistent with the study carried out by Bittner *et al.*²¹ This means that a high TG/HDL-C ratio is often accompanied by more CV risk factors. Therefore, considering the TG/HDL-C ratio is more valuable in the high-risk subgroup.

The mechanism of the TG/HDL-C ratio with CV events remains unclear, but there is some speculation. First, the TG/HDL-C ratio is a potent atherogenic indicator and has a remarkable association with the estimate of IR^{22–24}. It is well-known that IR, as a CV risk factor, makes great contributions to the development of CV events^{25,26}. Second, oxidation and inflammation factors can be used to predict the risks of CVD. Decreased HDL-C content will reduce the ability of anti-oxidation and anti-inflammation; furthermore, the TG/HDL-C ratio has an obvious relationship with the concentrations of sd-LDL particles, which more readily cause oxidative damage^{27,28}. Third, impaired IR and dyslipidemia have been proven to be positively

associated with decreased pancreatic β -cell function, which might accelerate the occurrence of CVD¹⁹.

As above-mentioned, the participants with a high TG/HDL-C ratio generally had other metabolic risk factors and met the diagnostic criteria for metabolic syndrome, indicating that they were likely to have a common metabolic soil. The risk stratification of the general population can possibly be achieved by the TG/HDL-C ratio, whereas the other metabolic risk factors can be detected. If individuals with a high TG/HDL-C ratio are accompanied by metabolic syndromes, the following goals should be achieved: (i) carrying out physical activity (150 min per week at least); (ii) regulating lifestyle; and (iii) reducing bodyweight (7% of bodyweight)²⁹. The pharmacological interventions should be taken into consideration if the above aims are not achieved. A large-scale observational study has reported that fibrates can obviously increase HDL-C levels and decrease TG levels³⁰.

The advantages of the present were the prospective design, long follow-up time, large research population and so on. However, the current study still had some weaknesses. First, as mentioned previously, the participants of the present study come from an occupational population in north China, and more men are represented than women, so the generalizability of the research findings might be limited for the whole Chinese population. Second, the baseline information is just used to assess the effect on adverse outcomes, which cannot reflect the changes of the variables of the follow-up period. Consequently, different variations on the predefined outcomes have not been assessed.

Among the general Chinese population, the incidence rate of major CV events in the participants with a high TG/HDL-C ratio was significantly higher than those with a low TG/HDL-C ratio. Our research findings show that the TG/HDL-C ratio can be the independent risk factor for CVD, namely, the risk of major CV events might be elevated with a higher TG/HDL-C ratio. Among the general population, the TG/HDL-C ratio should be used for risk-stratification and be considered as a significant index for adverse reactions in the long term. The present results might help the public policy-makers to formulate a strategy for individuals at high risk of major CV events in the Chinese population.

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DISCLOSURE

The authors declare no conflict of interest.

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