

Association between the triglyceride-glucose index-to-waist-to-height ratio and cardiovascular disease risk in Chinese adults: A prospective cohort study

LIU Fang^{1,2}, ZHANG Xuewei^{1,2}, LIU Shaohui^{1,2}, ZHOU Wei^{1,2}, ZHANG Ting^{2,3}, LUO Yang^{2,3}, TANG Wenbin^{1,2}

[1. Health Management Center, Xiangya Hospital, Central South University, Changsha 410008; 2. National Clinical Research Center for Geriatric Diseases (Xiangya Hospital of Central South University), Changsha 410008; 3. Department of General Medicine, Xiangya Hospital, Central South University, Changsha 410008, China]

ABSTRACT

Objective: Cardiovascular disease (CVD) is one of the major chronic non-communicable diseases worldwide, with high incidence and mortality. This study aims to investigate the association of the triglyceride-glucose index-to-waist-to-height ratio (TyGI-WHtR) with CVD and its subtypes [myocardial infarction (MI) and stroke] in middle-aged and older Chinese adults.

Methods: This prospective cohort study was based on 3 follow-up surveys of the China Health and Nutrition Survey (CHNS) from 2009 to 2015. A total of 5 395 participants aged 40 to 80 years who were free of CVD at baseline and had participated in at least 2 survey waves were included. Cox proportional hazards models were used to evaluate the associations of TyGI-WHtR with CVD and its subtypes. Weighted generalized additive models and smooth curve fitting were applied to explore potential nonlinear relationships. Time-dependent receiver operating characteristic (ROC) curves assessed predictive performance, and Kaplan-Meier analysis was used to calculate cumulative incidence of CVD across different groups.

Results: During a median follow-up of 72 months (interquartile range: 48 to 72 months), 210 incident CVD events were recorded, including 126 strokes and 92 MIs. Among them, 8 patients had both MI and stroke. After adjustment for confounders, each one-standard-deviation (SD) increase in TyGI-WHtR was associated with a significantly higher risk of incident CVD [adjusted hazard ratio (HR)=1.397, 95% confidence interval (CI) 1.111 to 1.758] and incident MI (adjusted HR 1.747, 95% CI 1.241 to 2.460), while no statistically significant association was observed with stroke (adjusted HR=1.198, 95% CI 0.890 to 1.613). Compared with lowest quartile, participants in the highest TyGI-WHtR quartile had significantly increased risks of CVD and MI (both *P* for trend <0.005), whereas no such trend was observed for stroke (*P* for trend=0.103). Further analyses revealed a nonlinear

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First author: LIU Fang, Email: xylifang@csu.edu.cn, ORCID: 0000-0002-7086-3077

Corresponding author: TANG Wenbin, associate chief physician, Email: tangwenbin@csu.edu.cn, ORCID: 0000-0002-3446-8803

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association between TyGI-WHtR and CVD. When TyGI-WHtR was <4.804 , HR was 2.121 (95% CI 1.350 to 3.333); when it was ≥ 4.804 , HR was 1.066 (95% CI 0.754 to 1.507). The nonlinear inflection point for stroke was 4.477, while the association with MI remained linear [$\ln(\text{likelihood ratio})=0.212$]. Time-dependent ROC analysis showed that the area under the curve of TyGI-WHtR for predicting CVD was 0.629, with a sensitivity of 77.3%, and specificity of 43.2%.

Conclusion: In middle-aged and older Chinese adults, TyGI-WHtR is an independent risk factor for incident CVD, particularly MI, but is not independently associated with stroke. Moreover, its predictive ability for CVD demonstrates a nonlinear saturation-threshold effect, with risk significantly increased only when TyGI-WHtR is below 4.804.

KEY WORDS triglyceride-glucose index-to-waist-to-height ratio; cardiovascular disease; myocardial infarction; prediction; middle-aged and older adults

甘油三酯葡萄糖指数-腰围身高比与中国成人心血管疾病风险的关联：一项前瞻性队列研究

刘芳^{1,2}, 张学伟^{1,2}, 刘绍辉^{1,2}, 周薇^{1,2}, 张婷^{2,3}, 罗扬^{2,3}, 唐文彬^{1,2}

[1. 中南大学湘雅医院健康管理中心, 长沙 410008; 2. 老年疾病国家临床医学研究中心(中南大学湘雅医院), 长沙 410008; 3. 中南大学湘雅医院全科医学科, 长沙 410008]

[摘要] 目的: 心血管疾病(cardiovascular disease, CVD)是全球慢性非传染性疾病中发病率和病死率较高的疾病。本研究旨在探讨中国中老年人群中甘油三酯葡萄糖指数-腰围身高比(triglyceride-glucose index-to-waist-to-height ratio, TyGI-WHtR)与CVD及其亚型[心肌梗死(myocardial infarction, MI)和脑卒中]的关系。方法: 本研究为前瞻性队列研究, 基于中国健康与营养调查(China Health and Nutrition Survey, CHNS)2009—2015年的3次随访数据, 纳入5 395名基线无CVD且至少参与2次调查的40~80岁参与者。采用Cox比例风险模型评估TyGI-WHtR与CVD及其亚型的关联, 使用加权广义加性模型和平滑曲线拟合分析其非线性关系。通过时间依赖性受试者操作特征(receiver operating characteristic, ROC)曲线评估TyGI-WHtR的预测效能, 并采用Kaplan-Meier法计算不同组别的CVD累积发病率。结果: 中位随访72个月(四分位距: 48~72个月)期间, 共记录210例CVD事件(126例脑卒中, 92例MI, 其中8例既发生了MI, 又发生了脑卒中)。校正混杂因素后, TyGI-WHtR每增加1个标准差(SD), 新发CVD[校正风险比(hazard ratio, HR)=1.397, 95%置信区间(confidence interval, CI) 1.111~1.758]和新发MI(校正 HR =1.747, 95% CI 1.241~2.460)风险显著升高, 但与脑卒中的关联无统计学意义(校正 HR =1.198, 95% CI 0.890~1.613)。与最低TyGI-WHtR四分位组相比, 最高TyGI-WHtR四分位组的CVD和MI风险显著增加(趋势 $P<0.005$), 而脑卒中无此趋势(趋势 $P=0.103$)。进一步分析显示, TyGI-WHtR与CVD存在非线性关联: 当TyGI-WHtR <4.804 时, HR =2.121(95% CI 1.350~3.333); 当TyGI-WHtR ≥ 4.804 时, HR =1.066(95% CI 0.754~1.507)。TyGI-WHtR与脑卒中的非线性拐点为4.477, 但与MI呈线性关联(对数似然比=0.212)。时间依赖性ROC曲线显示, TyGI-WHtR预测CVD的曲线下面积(area under the curve, AUC)为0.629, 敏感度为77.3%, 特异度为43.2%。结论: 在中国中老年人群中, TyGI-WHtR是新发CVD, 尤其是MI的独立危险因素, 但与脑卒中无独立关联。此外, 其对CVD的预测能力呈现非线性的饱和阈值效应, 仅在低于4.804时风险显著增加。

[关键词] 甘油三酯葡萄糖指数-腰围身高比; 心血管疾病; 心肌梗死; 预测; 中老年人

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality among chronic noncommunicable diseases in China and worldwide^[1]. According to the study^[2], approximately 330 million Chinese suffer from CVD, resulting in significant socioeconomic burdens. CVD, particularly ischemic heart disease and stroke, were the top 2 causes of death in China^[3]. Furthermore, the dual pressures of an aging population and a rising prevalence of metabolic risk factors are expected to exacerbate the burden of CVD in China. Therefore, identifying individuals at high risk for CVD is critical for delivering cost-effective care and optimizing healthcare service planning.

Obesity, diabetes, hypertension, and dyslipidemia are well-established risk factors for CVD^[4-7]. The study^[8] highlights that metabolic risk factors—such as high systolic blood pressure, low-density lipoprotein cholesterol (LDL-C), fasting blood glucose, and body mass index—are the leading contributors to the burden of ischemic heart disease. Effective control of these metabolic risk factors has been associated with reduced ischemic heart disease mortality. The triglyceride-glucose index (TyGI), which combines triglyceride (TG) levels and fasting plasma glucose (FPG), is a simple marker that reflects both dyslipidemia and insulin resistance (IR)^[9-10]. Moreover, cohort studies^[11-15] have identified elevated TyGI as a risk factor for CVD events. The waist-to-height ratio (WHtR), which incorporates waist circumference (WC) and height, is recognized as an anthropometric indicator of central obesity and is commonly used to predict the risk of chronic diseases^[16-17]. A systematic review and meta-analysis involving over 300 000 adults from various ethnic groups demonstrated that WHtR outperforms WC and BMI in detecting CVD risk factors^[18]. The triglyceride-glucose index-to-waist-to-height ratio (TyGI-WHtR) integrates the TyGI and the waist-to-height ratio (WHtR), both of which can be readily obtained in routine clinical practice. Recent studies^[19-21] have suggested that TyGI-WHtR may outperform TyGI alone in predicting IR, diabetes, and cardiometabolic risk due to the close association between obesity and IR. Thus, this study aims to further clarify the association between TyGI-WHtR and the risk of CVD, as well as its subtypes, using a population-based survey from China.

1 Materials and methods

1.1 Study design and study cohort

We used data from the China Health and Nutrition Survey (CHNS), an open, ongoing cohort study in China that began in 1989. A detailed description of cohort enrollment and methodology has been provided elsewhere^[22-23]. CHNS collects demographic characteristics and basic anthropometric measurements for each follow-up of the participants across 9 Chinese provinces (Liaoning, Heilongjiang, Jiangsu, Shandong, Henan, Hubei, Hunan, Guangxi, and Guizhou). This study analyzed the collected data of CHNS between 2009 and 2015. Notably, blood sample data were collected during the 2009 survey.

Initially, 8 049 participants with biomarker information in 2009 and at least 2 surveys between 2009 and 2015 were considered for inclusion. Given that CVD is more prevalent in middle-aged and elderly adults and that individuals over 80 years old may exhibit different pathophysiological disease characteristics^[24], this study only included patients with age of 40 to 80 years in 2009. In addition, this study included participants with sufficient baseline information for the calculation of TyGI-WHtR. A total of 68 participants with a history of myocardial infarction (MI) and 86 participants with a history of stroke, as reported in the 2009 survey, were excluded to control their confounding effects. Finally, 5 395 participants (2 483 males and 2 912 females) were included in the analysis. A flow chart illustrating the process of creating study cohort from CHNS is presented in Figure 1.

1.2 Calculation of TyGI-WHtR

As previously described^[11], TyGI was calculated using the formula: $\ln(\text{fasting TG} \times \text{FPG} / 2)$. WHtR was computed as WC divided by height, TyGI-WHtR was derived by multiplying TyGI by WHtR, as outlined in previously published studies^[21].

1.3 Outcome measures

CVD was defined as a self-reported history of MI or stroke, confirmed by a physician's diagnosis, with the time of diagnosis also recorded. Data from the 2009 CHNS survey were used as the baseline. Follow-up person-time was calculated for each participant from

baseline to the date of the participant's first new-onset CVD diagnosis, the last survey round prior to loss to

follow-up, or the final survey round in 2015, whichever occurred first.

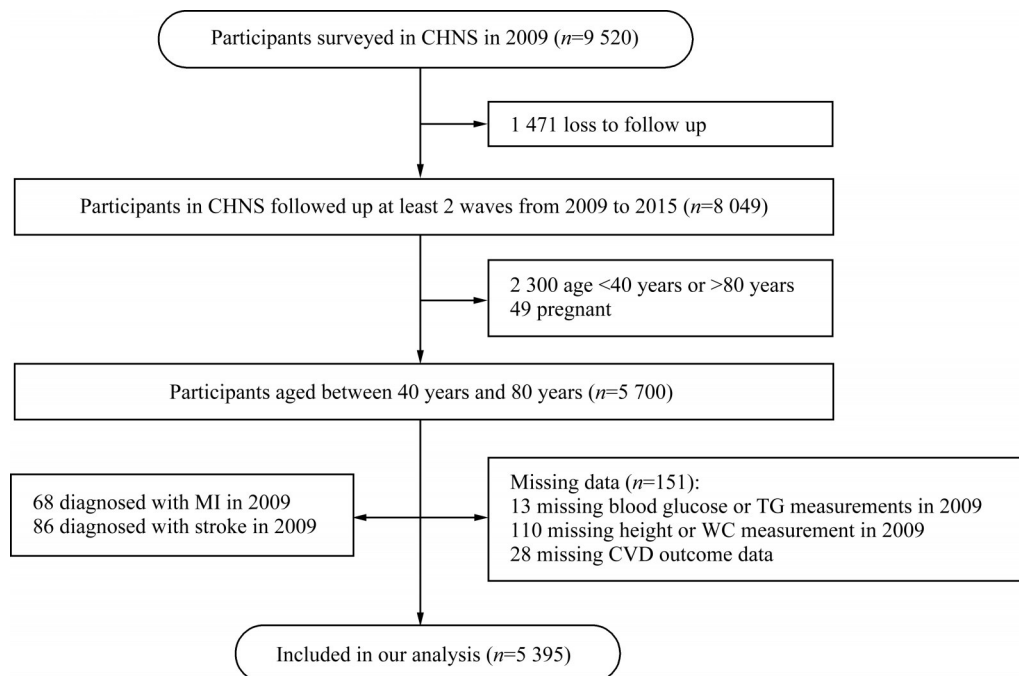


Figure 1 Flow chart of creating study cohort from CHNS

CHNS: China Health and Nutrition Survey; MI: Myocardial infarction; TG: Triglyceride; WC: Waist circumference; CVD: Cardiovascular disease.

1.4 Assessment of covariates

The collected demographic information included age, gender, community type (rural or urban), years of education, marital status, smoking habits (never, former, and current smoker), alcohol consumption (non-drinker and drinker), sleep duration (<7, 7 to 9, and >9 hours), annual per capita household income (<5 000, 5 000 to 10 000, and >10 000 yuan/year), and medical history of hypertension, diabetes, MI, stroke, and medical treatment. Education level was classified lower education (no education or elementary school education), middle education (lower middle school or upper middle school education), and higher education (university/college or above). Dietary data included the types and quantities of food consumed at each meal during the previous 24 hours. Energy intake from food and condiments for each meal was calculated using the China Food Composition Database. Physical activity was classified as domestic, occupational, transportation, and leisure^[25]. Metabolic equivalent (MET)-hours-per-

week were used to account for both the intensity and duration of activities^[26]. The reported the average number of hours-per-week spent on these activities over the past year was used to assess physical activity according to literature^[27]. The baseline WC, hip circumference, height, weight, blood pressure, BMI, and estimated glomerular filtration rate (eGFR) (based on CKD-EPI equation^[28]) were included as well. The baseline comorbidities, including hypertension, diabetes, and dyslipidemia, were confirmed using their respective diagnosis guidelines^[29-31].

1.5 Laboratory assays

CHNS used standard protocols and guidelines to conduct laboratory assays for the collected blood samples. Detailed information about the biochemical assessments is available at the following website: <https://www.cpc.unc.edu/projects/china/data/datasets/biomarker-data>. All biochemical analyses were conducted in a nationally accredited central laboratory in Beijing (Medical Laboratory Accreditation Certificate: ISO 15189 : 2007)^[32]. The

performed laboratory assays included hematologic analysis, FPG, HbA1C, insulin, apolipoprotein A (apo-A) and apolipoprotein B (apo-B), total protein (TP), albumin (Alb), alanine aminotransferase (ALT), urea, serum creatinine, serum uric acid (UA), triglycerides (TG), total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C), Hs-CRP, magnesium, ferritin, and transferrin.

1.6 Statistical analysis

All statistical analyses were performed using the R statistical package version 3.4.3 and EmpowerStats software. Participant characteristics were summarized by TyGI-WHtR quartiles as means $\pm$ standard deviation (SD) for normally distributed continuous variables, medians (25th percentile, 75th percentile) for non-normally distributed continuous variables, or percentages for categorical variables. Differences in group characteristics were compared using the Kruskal-Wallis test or analysis of variance for continuous variables, depending on their distribution, and the weighted χ^2 test for categorical variables. Hazard ratio (HR) and 95% confidence interval (CI) for new-onset CVD and its subtypes (MI and stroke) in relation to TyGI-WHtR (continuous and quartile groups) were calculated using Cox proportional hazards models. Covariate screening and selection were conducted following 2 main principles: 1) Multicollinearity assessment. The variance inflation factor (VIF) was calculated to evaluate multicollinearity among variables. Variables with a VIF greater than 10 were considered to have severe multicollinearity and were excluded from the multivariate regression analysis. 2) Impact evaluation. The effect of adding covariates to the basic model or removing them from the full model on the regression coefficient of the primary predictor (X) was assessed. If the impact exceeded 10% and the P -value for the covariate's regression coefficient on the outcome variable (Y) was less than 0.10, the covariate was deemed significant. Based on these criteria, 23 covariates were considered (age, gender, education level, income, bedtime, total METs, protein intake, smoking status, systolic blood pressure (SBP), diastolic blood pressure (DBP), urea, UA, eGFR, TC, LDL-C, apo-A, apo-B, Hb, platelet count, transferrin, diabetes mellitus, dyslipidemia, and hypertension). However, the

use of medications (including lipid-lowering, antihypertensive, and antidiabetic drugs), the amount of alcohol consumption, and dietary pattern scores were not adjusted for, as these data were unavailable. In the regression models that could make no adjustment, adjustment for age and gender only, and adjustment for all 23 covariates. Sensitivity analysis was performed by using E -values to assess robustness to unmeasured confounding.

The dose-response relationship between TyGI-WHtR and CVD was evaluated using weighted generalized additive models and smooth curve fitting. After adjusting for the same covariates in the linear regression models, two-piecewise linear regression models were used to assess the threshold effect of TyGI-WHtR on CVD. To assess the stability of the derived cut-offs, we performed bootstrap resampling with 1 000 iterations. For each iteration, the median was recalculated, and the 95% CI of the bootstrap distribution was obtained. The original cut-off was considered stable if it fell within the corresponding 95% CI.

Predictive values of various potential predictors [TyGI-WHtR, BMI, WHtR, TyGI, TyGI-BMI, and TyGI-waist-to-hip ratio (WHR)] for endpoints (CVD, MI, and stroke) were estimated using time-dependent receiver operating characteristic (ROC) curves. Kaplan-Meier curves and log-rank tests were employed to analyze unadjusted cumulative hazards across TyGI-WHtR quartiles. The threshold for statistical significance was set at $P<0.05$.

2 Results

2.1 Baseline characteristics

A total of 5 395 eligible participants with a age of (55.738 $\pm$ 10.129) years were included in this study, of whom 46.0% were male. Baseline characteristics of the participants by TyGI-WHtR quartiles are presented in Table 1. Participants in the higher quartile groups were more likely to have a higher prevalence of hypertension, diabetes, and dyslipidemia; as well as higher levels of BMI, TyGI, WHtR, TC, TG, FPG, hemoglobin A1c, UA, serum ferritin, transferrin, and blood pressure. Conversely, they exhibited lower levels of HDL-C, eGFR, and METs compared to the TyGI-WHtR quartile 1 (Q1) group (all $P<0.05$).

Table 1 Baseline characteristics of the study participants

Characteristics	Total (<i>n</i> =5 395)	TyGI-WHtR quartile				<i>F</i> / <i>H</i> / χ^2	<i>P</i>
		Q1 (<i>n</i> =1 349) (2.575 to 4.028)	Q2 (<i>n</i> =1 348) (4.029 to 4.508)	Q3 (<i>n</i> =1 349) (4.509 to 5.042)	Q4 (<i>n</i> =1 349) (5.043 to 8.005)		
Age/Years	55.738±10.129	54.402±10.418	54.986±9.917	56.000±9.967	57.566±9.930	218.692	<0.001
Gender/[No.(%)]						57.767	<0.001
Male	2 483 (46.024)	729 (54.040)	614 (45.549)	605 (44.848)	535 (39.659)		
Female	2 912 (53.976)	620 (45.960)	734 (54.451)	744 (55.152)	814 (60.341)		
Urban/[No.(%)]						31.083	<0.001
No	3 738 (69.286)	1 012 (75.019)	927 (68.769)	914 (67.754)	885 (65.604)		
Yes	1 657 (30.714)	337 (24.981)	421 (31.231)	435 (32.246)	464 (34.396)		
Education level/ [No.(%)]						35.599	<0.001
Low	2 717 (50.361)	662 (49.073)	614 (45.549)	693 (51.372)	748 (55.449)		
Medium	2 471 (45.802)	633 (46.924)	673 (49.926)	605 (44.848)	560 (41.512)		
High	199 (3.689)	49 (3.632)	60 (4.451)	49 (3.632)	41 (3.039)		
Data missing	8 (0.148)	5 (0.371)	1 (0.074)	2 (0.148)	0 (0)		
Income (Yuan/Year)						26.378	0.002
<5 000	1 778 (32.957)	489 (36.249)	450 (33.383)	442 (32.765)	397 (29.429)		
5 000 to 10 000	1 511 (28.007)	390 (28.910)	387 (28.709)	362 (26.835)	372 (27.576)		
>10 000	2 042 (37.850)	457 (33.877)	500 (37.092)	527 (39.066)	558 (41.364)		
Data missing	64 (1.186)	13 (0.964)	11 (0.816)	18 (1.334)	22 (1.631)		
Bedtime						16.031	0.066
<7 hours	633 (11.733)	146 (10.823)	153 (11.350)	151 (11.193)	183 (13.565)		
7 to 9 hours	4 142 (76.775)	1 056 (78.280)	1 057 (78.413)	1 038 (76.946)	991 (73.462)		
>9 hours	562 (10.417)	132 (9.785)	121 (8.976)	146 (10.823)	163 (12.083)		
Data missing	58 (1.075)	15 (1.112)	17 (1.261)	14 (1.038)	12 (0.890)		
Smoke/[No.(%)]						52.245	<0.001
Never	3 670 (68.025)	826 (61.231)	926 (68.694)	954 (70.719)	964 (71.460)		
Former	184 (3.411)	39 (2.891)	47 (3.487)	47 (3.484)	51 (3.781)		
Current	1 538 (28.508)	484 (35.878)	374 (27.745)	347 (25.723)	333 (24.685)		
Data missing	3 (0.056)	0 (0)	1 (0.074)	1 (0.074)	1 (0.074)		
Alcohol/[No.(%)]						13.353	0.038
No	3 632 (67.321)	866 (64.196)	904 (67.062)	920 (68.199)	942 (69.830)		
Yes	1 762 (32.660)	483 (35.804)	443 (32.864)	429 (31.801)	407 (30.170)		
Data missing	1 (0.019)	0 (0)	1 (0.074)	0 (0)	0 (0)		
Total METS (hours/week)	85.870 (39.140 to 178.055)	115.380 (46.610 to 215.250)	96.375 (39.707 to 199.998)	79.860 (36.630 to 162.500)	67.900 (36.580 to 136.790)	2.569	<0.001
Total energy intake/(kcal·d ⁻¹)	2 146.402± 673.698	2 175.751± 647.916	2 176.694± 647.648	2 117.653± 659.958	2 115.533± 733.561	3.529	0.001
Total protein intake/(g·d ⁻¹)	65.419±22.657	65.290±22.337	66.115±22.530	65.002±22.729	65.268±23.034	0.610	0.466
SBP/mmHg	127.760±18.873	121.240±16.573	125.576±17.649	129.668±18.686	134.554±19.827	131.437	<0.001
DBP/mmHg	82.094±11.332	78.208±10.651	81.019±11.015	83.079±10.723	86.070±11.449	123.606	<0.001
Height/cm	160.211±8.443	161.026±7.852	160.611±8.292	160.035±8.587	159.173±8.899	12.266	<0.001
Weight/cm	60.944±11.069	53.905±8.162	58.880±9.287	62.785±9.977	68.206±11.309	519.897	<0.001

Table 1 (continued)

Characteristics	Total (<i>n</i> =5 395)	TyGI-WHtR quartile				<i>F</i> / <i>H</i> / χ^2	<i>P</i>
		Q1 (<i>n</i> =1 349) (2.575 to 4.028)	Q2 (<i>n</i> =1 348) (4.029 to 4.508)	Q3 (<i>n</i> =1 349) (4.509 to 5.042)	Q4 (<i>n</i> =1 349) (5.043 to 8.005)		
HC/cm	94.922±7.761	89.007±5.754	93.404±6.172	96.603±6.537	100.673±7.339	784.479	<0.001
WC/cm	83.914±10.069	73.343±5.965	80.961±5.597	86.706±6.188	94.644±7.548	2 699.534	<0.001
BMI/(kg·m ⁻²)	23.661±3.400	20.713±2.197	22.713±2.280	24.396±2.454	26.820±3.177	1 383.342	<0.001
WHtR	0.524±0.063	0.456±0.032	0.504±0.028	0.542±0.032	0.596±0.048	3 653.699	<0.001
TyGI	8.701±0.711	8.095±0.425	8.488±0.461	8.812±0.512	9.407±0.665	1 513.359	<0.001
TyGI-BMI	206.689±39.155	167.588±19.141	192.542±19.550	214.575±21.185	252.042±32.968	3 029.762	<0.001
TyGI-WHR	7.701±1.016	6.672±0.508	7.367±0.620	7.912±0.545	8.853±0.805	2 879.847	<0.001
Urea/(mmol·L ⁻¹)	5.609±1.574	5.595±1.710	5.578±1.632	5.572±1.480	5.689±1.461	1.614	0.097
Uric acid/ (mmol·L ⁻¹)	308.310±101.821	274.975±78.428	289.597±82.384	314.151±99.590	354.503±122.486	172.405	<0.001
Creatinine/ (μmol·L ⁻¹)	87.655±23.365	88.328±26.230	87.924±31.077	87.287±16.120	87.079±16.448	0.818	0.713
eGFR/ (ml·min ⁻¹ ·1.73 m ⁻²)	75.335±14.517	77.255±14.721	75.597±14.000	75.019±14.442	73.469±14.658	15.781	<0.001
Hs-CRP/(g·L ⁻¹)	1.000 (1.000, 3.000)	1.000 (0.000, 2.000)	1.000 (0.000, 2.000)	1.000 (1.000, 3.000)	2.000 (1.000, 4.000)	2.569	<0.001
TG/(mmol·L ⁻¹)	1.330 (0.900, 2.060)	0.820 (0.300, 3.200)	1.170 (0.300, 6.590)	1.510 (0.300, 14.920)	2.420 (0.500, 21.730)	2.564	<0.001
TC/(mmol·L ⁻¹)	4.997±0.989	4.609±0.828	4.921±0.948	5.075±0.973	5.381±1.035	154.921	<0.001
HDL-C/(mmol·L ⁻¹)	1.451±0.521	1.640±0.574	1.505±0.409	1.376±0.367	1.283±0.617	128.649	<0.001
LDL-C/(mmol·L ⁻¹)	3.088±1.000	2.831±0.835	3.126±0.957	3.211±0.982	3.185±1.154	42.367	<0.001
Apo-A/(g·L ⁻¹)	1.180±0.422	1.224±0.394	1.210±0.500	1.148±0.324	1.139±0.443	14.087	<0.001
Apo-B/(g·L ⁻¹)	0.944±0.266	0.803±0.206	0.920±0.247	0.988±0.253	1.066±0.278	273.410	<0.001
FPG/(mmol·L ⁻¹)	5.513±1.546	4.979±0.709	5.235±0.988	5.463±1.175	6.374±2.365	235.478	<0.001
HbA1C/(mmol·L ⁻¹)	5.703±0.960	5.429±0.856	5.544±0.662	5.702±0.816	6.137±1.250	152.818	<0.001
Insulin/(U·mL ⁻¹)	10.230 (7.170, 14.860)	7.990 (5.660, 10.830)	9.430 (6.940, 13.398)	10.930 (7.890, 15.350)	13.930 (9.740, 20.930)	2.571	<0.001
TP/(g·L ⁻¹)	77.067±5.204	76.327±5.195	77.088±5.143	77.150±4.973	77.701±5.409	16.020	<0.001
Albumin/(g·L ⁻¹)	47.198±3.331	46.500±3.234	47.032±3.297	47.450±3.261	47.809±3.389	39.399	<0.001
ALT/(U·L ⁻¹)	18.000 (14.000, 26.000)	15.000 (12.000, 21.000)	17.000 (13.000, 24.000)	19.000 (15.000, 27.000)	23.000 (17.000, 33.000)	2.571	<0.001
Magnesium/ (mmol·L ⁻¹)	0.940±0.105	0.926±0.089	0.933±0.095	0.943±0.131	0.958±0.095	23.981	<0.001
Ferritin/(ng·mL ⁻¹)	85.860 (46.190, 153.070)	67.670 (36.710, 114.420)	78.190 (39.955, 133.517)	91.880 (50.040, 158.040)	111.770 (61.710, 211.320)	2.571	<0.001
Transferrin/(g·L ⁻¹)	2.857±0.549	2.752±0.519	2.810±0.548	2.877±0.536	2.988±0.566	47.113	<0.001
Hb/(g·L ⁻¹)	140.991±20.212	138.041±20.799	140.408±19.401	142.418±20.603	143.096±19.646	17.227	<0.001
WBC/(×10 ⁹ ·L ⁻¹)	6.260±1.938	6.025±2.146	6.096±1.746	6.248±1.697	6.670±2.060	30.553	<0.001
Plt/(×10 ⁹ ·L ⁻¹)	210.948±68.284	208.503±70.491	211.561±67.571	213.464±68.994	210.265±65.976	1.269	0.228
Diabetes mellitus						433.244	<0.001
No	4 715 (87.396)	1 298 (96.219)	1 248 (92.582)	1 197 (88.732)	972 (72.053)		
Yes	672 (12.456)	48 (3.558)	96 (7.122)	152 (11.268)	376 (27.872)		
Data missing	8 (0.148)	3 (0.222)	4 (0.297)	0 (0)	1 (0.074)		

Table 1 (continued)

Characteristics	Total (<i>n</i> =5 395)	TyGI-WHtR quartile				<i>F</i> / <i>H</i> / χ^2	<i>P</i>
		Q1 (<i>n</i> =1 349) (2.575 to 4.028)	Q2 (<i>n</i> =1 348) (4.029 to 4.508)	Q3 (<i>n</i> =1 349) (4.509 to 5.042)	Q4 (<i>n</i> =1 349) (5.043 to 8.005)		
Dyslipidemia/[No.(%)]						1 030.996	<0.001
No	1 845 (34.198)	867 (64.270)	538 (39.911)	334 (24.759)	106 (7.858)		
Yes	3 550 (65.802)	482 (35.730)	810 (60.089)	1 015 (75.241)	1 243 (92.142)		
Hypertension/[No.(%)]						271.216	<0.001
No	3 612 (66.951)	1 074 (79.615)	982 (72.849)	862 (63.899)	694 (51.446)		
Yes	1 783 (33.049)	275 (20.385)	366 (27.151)	487 (36.101)	655 (48.554)		

Values of variables are expressed by TyGI-WHtR quartiles as means $\pm$ standard deviation (SD) for normally distributed continuous variable, medians (25th percentile, 75th percentile) for non-normally distributed continuous variable, and proportions for categorical variable. Between-group comparisons were performed using Kruskal-Wallis test or analysis of variance for continuous variables, depending on their distribution, and the weighted χ^2 test for categorical variables. 1 kcal=4.186 kJ. Q1: Quartile 1; Q2: Quartile 2; Q3: Quartile 3; Q4: Quartile 4; METS: Metabolic equivalent; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HC: Hip circumference; WC: Waist circumference; BMI: Body mass index; WHtR: Waist to height ratio; TyGI: Triglyceride-glucose index; TyGI-BMI: Triglyceride-glucose index-body mass index; TyGI-WHR: Triglyceride glucose index-waist to hip ratio; TyGI-WHtR: Triglyceride glucose index-waist to height ratio; eGFR: Estimated glomerular filtration rate; Hs-CRP: Hypersensitive C-reactive protein; TG: Triglyceride; TC: Total cholesterol; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; Apo-A: Apolipoprotein A; Apo-B: Apolipoprotein B; FPG: Fasting plasma glucose; TP: Total protein; ALT: Alanine aminotransferase; Hb: Hemoglobin; WBC: White blood cell; Plt: Platelet.

2.2 Association between TyGI-WHtR and risk of CVD and its subtypes

The median follow-up period was 72 months (interquartile range: 48 to 72), during which 210 (3.89%) newly diagnosed CVD cases were identified, including 126 (2.34%) strokes and 92 (1.70%) MIs (8 patients had both MI and stroke). Overall, TyGI-WHtR was positively correlated with the risk of new-onset CVD. As shown in Table 2, in the fully adjusted regression model (Model 3), the *HR* per SD increase in TyGI-WHtR for CVD was 1.397 (95% *CI* 1.111 to 1.758). The fully adjusted *HRs* (95% *CI*) for CVD by quartile were as follows: 1.679 (1.004 to 2.807) for quartile 2 (Q2), 2.170 (1.305 to 3.610) for quartile 3 (Q3), and 2.314 (1.335 to 4.011) for quartile 4 (Q4) (*P* for trend <0.001). Additionally, the fully adjusted regression model demonstrated a significant association between TyGI-WHtR and MI. For each SD increase in TyGI-WHtR, the *HR* for MI was 1.747 (95% *CI* 1.241 to 2.460). The fully adjusted *HR* for MI in Q4 was 3.137 (95% *CI* 1.359 to 7.240). MI risk increased significantly across quartiles (*P* for trend =0.003). In contrast, the association between TyGI-WHtR and stroke was not

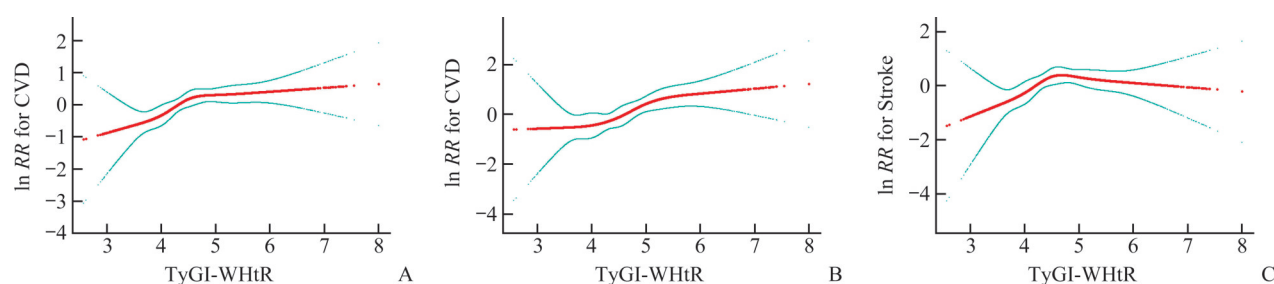
statistically significant in the fully adjusted regression model.

In addition, the results of the smooth curve fitting and generalized additive models, used to characterize the dose-response relationship between TyGI-WHtR and CVD, stroke, or MI, are shown in Figure 2. Nonlinear associations were observed between TyGI-WHtR and CVD or stroke. For TyGI-WHtR<4.804, the effect size of *HR* for CVD was 2.121 (95% *CI* 1.350 to 3.333), whereas for TyGI-WHtR >4.804, the effect size of *HR* was 1.066 (95% *CI* 0.754 to 1.507). The ln(likelihood ratio) was 0.029. Similarly, the inflection point for TyGI-WHtR in relation to stroke was 4.477 (Table 3). However, the relationship between TyGI-WHtR and the risk of MI was linear, as indicated by a ln(likelihood ratio) of 0.212. Overall, when TyGI-WHtR exceeded the inflection point, the strength of the association between TyGI-WHtR and CVD, MI, and stroke weakened. Bootstrap validation with 1 000 iterations confirmed the stability of the original cut-offs: The bootstrap-derived 95% *CI* were 4.607 to 5.011 for CVD, 5.261 to 5.954 for MI, and 4.333 to 4.640 for stroke, with all original cut-offs falling within these intervals.

Table 2 Hazard ratios of CVD, MI, and stroke, stratified by TyGI-WHtR

Exposure	Model 1		Model 2		Model 3	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
CVD						
TyGI-WHtR	1.654 (1.406 to 1.946)	<0.001	1.611 (1.364 to 1.902)	<0.001	1.397 (1.111 to 1.758)	0.004
TyGI-WHtR quartiles						
Q1	1		1		1	
Q2	1.795 (1.089 to 2.958)	0.023	1.860 (1.127 to 3.069)	0.015	1.679 (1.004 to 2.807)	0.048
Q3	2.740 (1.716 to 4.376)	<0.001	2.738 (1.711 to 4.381)	<0.001	2.170 (1.305 to 3.610)	0.003
Q4	3.325 (2.104 to 5.255)	<0.001	3.163 (1.989 to 5.029)	<0.001	2.314 (1.335 to 4.011)	0.003
P for trend		<0.001		<0.001		0.003
MI						
TyGI-WHtR	1.919 (1.511 to 2.438)	<0.001	1.809 (1.415 to 2.313)	<0.001	1.747 (1.241 to 2.460)	0.001
TyGI-WHtR quartiles						
Q1	1		1		1	
Q2	1.498 (0.673 to 3.334)	0.322	1.471 (0.659 to 3.281)	0.346	1.372 (0.606 to 3.107)	0.448
Q3	2.729 (1.321 to 5.638)	0.007	2.582 (1.246 to 5.351)	0.011	2.206 (1.005 to 4.840)	0.048
Q4	4.096 (2.048 to 8.191)	<0.001	3.597 (1.781 to 7.265)	<0.001	3.137 (1.359 to 7.240)	0.007
P for trend		<0.001		<0.001		0.003
Stroke						
TyGI-WHtR	1.532 (1.239 to 1.895)	<0.001	1.528 (1.231 to 1.898)	<0.001	1.198 (0.890 to 1.613)	0.233
TyGI-WHtR quartiles						
Q1	1		1		1	
Q2	1.999 (1.053 to 3.798)	0.034	2.142 (1.126 to 4.076)	0.020	1.852 (0.954 to 3.594)	0.069
Q3	2.951 (1.609 to 5.414)	<0.001	3.065 (1.667 to 5.637)	<0.001	2.290 (1.183 to 4.433)	0.014
Q4	3.109 (1.701 to 5.682)	<0.001	3.119 (1.694 to 5.742)	<0.001	1.959 (0.954 to 4.024)	0.067
P for trend		<0.001		<0.001		0.104

Model 1: No covariates adjusted. Model 2: Adjusted for age and gender. Model 3: Adjusted for age, gender, education level, bedtime, annual per capita household income, total METS, protein intake of food, smoke, SBP, DBP, urea, UA, eGFR, TC, LDL-C, apo-A, apo-B, Hb, PLT, transferrin, history of hypertension, diabetes mellitus or dyslipidemia in 2009. HR: Hazard ratio; CI: Confidence interval; CVD: Cardiovascular disease; MI: Myocardial infarction; UA: Uric acid.

**Figure 2 Smoothing curve revealing the effect of the TyGI-WHtR on the risk of CVD (A), MI (B), and stroke (C)**

The area between 2 blue dotted lines is expressed as a 95% CI. Each point showed the magnitude of TyGI-WHtR and is connected to form a continuous line. Age, gender, education level, bedtime, annual per capita household income, total METS/week, protein intake of food, smoke, SBP, DBP, urea, UA, eGFR, TC, LDL-C, apo-A, apo-B, Hb, PLT, transferrin, history of hypertension, diabetes mellitus or dyslipidemia in 2009 are adjusted. TyGI-WHtR: Triglyceride glucose index-waist to height ratio; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; TC: Total cholesterol; LDL-C: Low-density lipoprotein cholesterol; apo-A: Apolipoprotein A; apo-B: Apolipoprotein B; Hb: Hemoglobin; WBC: White blood cell; Plt: Platelet.

Table 3 Threshold effect analysis of TyGI-WHtR on CVD using the 2 piecewise linear regression model

Outcome	Inflection point of TyGI-WHtR	HR (95% CI)	P	ln(likelihood ratio)
CVD	<4.804	2.121 (1.350, 3.333)	0.001	0.029
	≥4.804	1.066 (0.754, 1.507)	0.718	
MI	<5.688	2.068 (1.335, 3.204)	0.001	0.212
	≥5.688	1.060 (0.424, 2.653)	0.901	
Stroke	<4.477	3.560 (1.509, 8.396)	0.004	0.004
	≥4.477	0.834 (0.555, 1.253)	0.381	

2.3 Time-dependent ROC curve analysis of different markers for the outcome of CVD and its subtypes

The time-dependent ROC curve results for TyGI-WHtR and other predictors are presented in Table 4. TyGI-WHtR was the strongest predictor of CVD, with an area under the curve (AUC) of 0.629, sensitivity of 0.773, specificity of 0.432, and a cut-off value of 4.367, outperforming BMI, WHtR, TyGI, TyGI-BMI, and TyGI-WHR (Table 4). For predicting MI, the AUC of TyGI-WHtR was 0.639, which was lower than that of WHtR but higher than other predictors. In the prediction

of stroke, the AUC of TyGI-WHtR was 0.622, ranking second, exceeding the AUC of other indicators except for TyGI.

2.4 Cumulative hazards for CVD and its subtypes stratified by the quartile of the TyGI-WHtR

Cumulative hazard curves for cardiovascular events across TyGI-WHtR quartiles are illustrated in Figure 3. The incidence of CVD and MI was significantly higher in the Q4 group compared to the other groups. However, for stroke, the highest incidence was observed in the Q3 group.

Table 4 Time-dependent ROC curve for possible predictors for predicting CVD, MI, and stroke

Variables	Cut.value	Sensitivity	Specificity	Predict time/h	Survival	AUC
CVD						
TyGI-WHtR	4.367	0.773	0.432	48	0.968	0.629
BMI	24.641	0.494	0.646	48	0.968	0.579
WHtR	0.537	0.569	0.610	48	0.968	0.612
TyGI	8.705	0.637	0.552	48	0.968	0.610
TyGI-BMI	211.711	0.576	0.596	48	0.968	0.603
TyGI-WHR	7.738	0.608	0.565	48	0.968	0.610
MI						
TyGI-WHtR	4.723	0.633	0.611	60	0.985	0.639
BMI	26.279	0.399	0.791	60	0.985	0.604
WHtR	0.553	0.567	0.698	60	0.985	0.658
TYGI	8.159	0.875	0.231	60	0.985	0.559
TyGI-BMI	210.426	0.615	0.581	60	0.985	0.609
TyGI-WHR	7.819	0.602	0.591	60	0.985	0.613
Stroke						
TyGI-WHtR	4.331	0.797	0.413	48	0.980	0.622
BMI	24.646	0.463	0.644	48	0.980	0.555
WHtR	0.537	0.524	0.606	48	0.980	0.580
TyGI	8.670	0.725	0.532	48	0.980	0.635
TyGI-BMI	214.629	0.533	0.621	48	0.980	0.596
TyGI-WHR	7.260	0.835	0.361	48	0.980	0.611

AUC: Area under the curve.

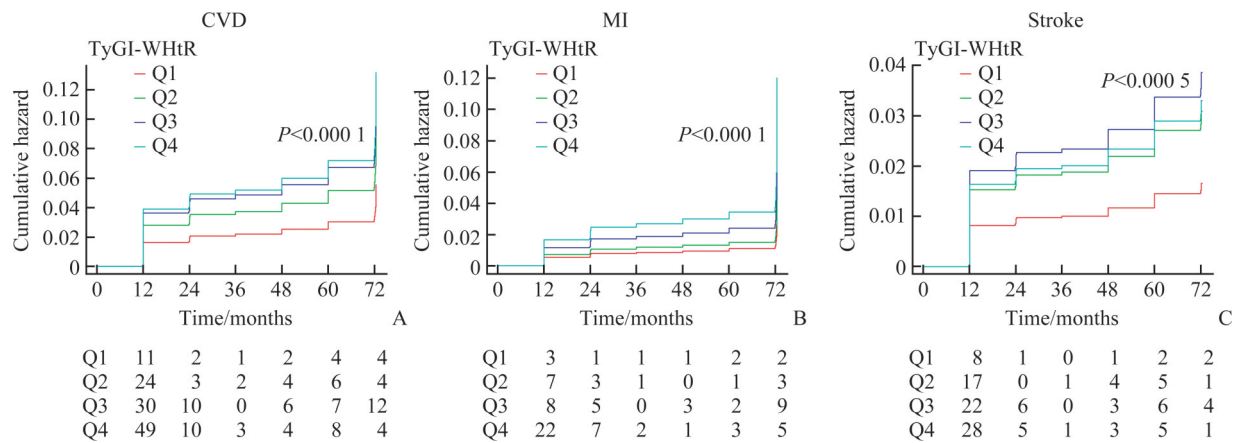


Figure 3 Cumulative hazards for CVD (A), MI (B), and stroke (C) stratified by the quartile of the TyGI-WHtR

3 Discussion

Concurrently, the incidence and prevalence of CVD have risen due to population aging and urbanization, particularly among the elderly^[33]. Despite considerable efforts to improve clinical outcomes, CVD remains the leading cause of mortality and morbidity in China^[34-35]. In this study, we identified nonlinear associations between TyGI-WHtR and CVD or stroke but a linear association with MI. Each one-SD increase in TyGI-WHtR corresponded to a 39.7% higher CVD risk and a 74.7% higher MI risk, with a non-significant increase in stroke risk. Higher TyGI-WHtR levels were linked to increased CVD and MI risks. TyGI-WHtR outperformed other indices in predicting CVD, but ranked second for MI and stroke, where WHtR and TyGI performed best, respectively.

These findings align with previous studies, which have established that elevated TyGI and its related indices levels are closely linked to chronic diseases^[36]. A recent cross-sectional study of 11 937 adults from the National Health and Nutrition Examination Survey (NHANES) demonstrated that TyGI and its related indices, including TyGI-WHtR, were significantly associated with CVD mortality, total CVD, congestive heart failure, MI, angina pectoris, and coronary heart disease^[37]. Ye, et al^[38] investigated TyGI and CVD risk in middle-aged and elderly Chinese populations using the China Health and Retirement Longitudinal Study dataset, reporting a J-shaped relationship. However, a systematic review and meta-analysis of 12 cohort studies revealed a linear association between TyGI and

the risk of coronary artery disease (CAD) and CVD^[39]. More studies are needed to clarify these relationships.

TyGI-WHtR, which integrates triglycerides, fasting glucose, waist circumference, and height, serves as a surrogate marker for visceral fat and IR, likely explaining its association with CVD. Visceral fat contributes to dyslipidemia, type 2 diabetes, and hypertension-key CVD risk factors. Compared to BMI, TyGI-WHtR may better estimate metabolic health and fat distribution^[40]. Visceral fat and IR also promote free fatty acid release, endothelial dysfunction, oxidative stress, and chronic inflammation^[41-44], and elevate plasminogen activator inhibitor-1, which facilitates thrombosis during atherosclerosis^[45]. The non-linear relationship between TyGI-WHtR and CVD may reflect saturation of lipotoxicity or glucotoxicity effects, desensitization of metabolic pathways, or competing risks, though these hypotheses require experimental validation.

This study has several strengths, including its prospective follow-up design within a diverse population-based cohort, providing robust evidence on the association between TyGI-WHtR and CVD risk in middle-aged and elderly Chinese. The use of standardized questionnaires and detailed hematologic analyses of CHNS enhanced the reliability and accuracy of the collected data. However, several limitations should be noted. First, physician-diagnosed MI or stroke was self-reported without verification against clinical records, which may introduce recall bias. Underreporting of mild events is more common in older adults and likely biases effect estimates toward the null,

making our risk estimates conservative. Second, residual confounding cannot be ruled out due to the lack of data on some covariates, including the use of antihypertensives, antiplatelet agents, and lipid-lowering therapies, as well as dietary pattern scores and the quantity of alcohol consumption. These unmeasured factors may have biased the observed associations. Third, the follow-up period of 6 years, while sufficient to observe medium-term outcomes, may not capture the long-term predictive value of TyGI-WHtR. Specifically, we note that the small number of events increases the width of confidence intervals and reduces statistical power for subgroup and secondary analyses. Finally, the findings of this study are limited by the inclusion of a racially homogeneous population, which may restrict generalizability to other ethnicities. Additionally, the inclusion of participants aged 40–80 years excludes younger and older populations, in whom the relationship between TyGI-WHtR and CVD may differ. Extended prospective studies with larger samples and longer follow-up are needed to validate these findings.

In conclusion, there is a positive and nonlinear association between TyGI-WHtR and the risk of CVD among middle-aged and elderly Chinese adults, with an inflection point at 4.804. Combining TyGI and WHtR, TyGI-WHtR offers a simple, accessible, and effective marker for predicting and potentially preventing CVD. However, further research is needed to clarify its long-term predictive value and underlying mechanisms.

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