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Inflammatory markers link triglyceride-glucose index and obesity indicators with adverse cardiovascular events in patients with hypertension: insights from three cohorts

Yanqiu Huang[1†], Yi Zhou[2,3†], Yadan Xu[1], Xiaoyu Wang[5], Ziyi Zhou[1], Kang Wu[2,3], Qiqi Meng[2,3], Liao Wang[4], Yang Yang[6], Hong Gao[7], Juan Ji[7], Xu Jiang[4*], Yang Yang[1*], Lipeng Hao[2,3*] and Hui Wang[1*]

Abstract

Background Among hypertensive cohorts across different nations, the relationship between the triglyceride-glucose index (TyG) and its conjunction with obesity metrics in relation to cardiovascular disease (CVD) incidence and mortality remains to be elucidated.

Methods This study enrolled 9,283, 164,357, and 5,334 hypertensives from the National Health and Nutrition Examination Survey (NHANES), UK Biobank (UKBB), and Shanghai Pudong cohort. The related outcomes for CVD were defined by multivariate Cox proportional hazards models, Generalized Additive Models and Mendelian randomization analysis. Mediation analysis explored the mediating role of inflammatory markers in the above relationships.

Results Five measures of insulin resistance were linked to CVD and related death in a U-shaped pattern, with the highest group having different risk increases. Higher glucose triglyceride-waist height ratio (TyG-WHTR) was linked to higher all-cause mortality (UKBB: HR 1.21, 95%CI 1.16–1.26, NHANES: HR 1.17, 95%CI 1.00–1.36), CVD mortality (UKBB: HR 1.36, 95%CI 1.23–1.49, NHANES: HR 1.32, 95%CI 1.00–1.72) risks. In the China Pudong cohort, higher triglyceride/high-density lipoprotein-cholesterol (TG/HDL_C) ratio was associated with higher risks of CVD and stroke (HR 1.31, 95%CI 1.00–1.73 and 1.67, 1.06–2.63). Inflammation markers like systemic inflammatory response index (SIRI) and C-reactive protein (CRP) partially explained these links, with CRP having a stronger effect. Genetically predicted TyG was also linked to stroke (OR 1.26, 95%CI 1.10–1.45) risk.

†Yanqiu Huang and Yi Zhou have contributed equally to this work.

*Correspondence:
Xu Jiang
jiangxusun@foxmail.com
Yang Yang
yyang93@shsmu.edu.cn
Lipeng Hao
hlpmail@126.com
Hui Wang
huiwang@shsmu.edu.cn
Full list of author information is available at the end of the article

Conclusions An elevated TyG index and its related indices are significantly correlated with an increased risk of CVD and related mortality across three national cohorts. These indices are anticipated to serve as valid predictors of incident CVD and mortality in individuals with hypertension.

Graphical abstract
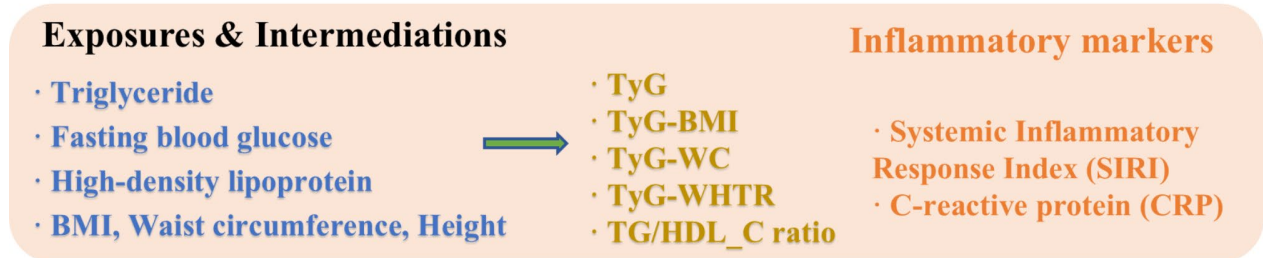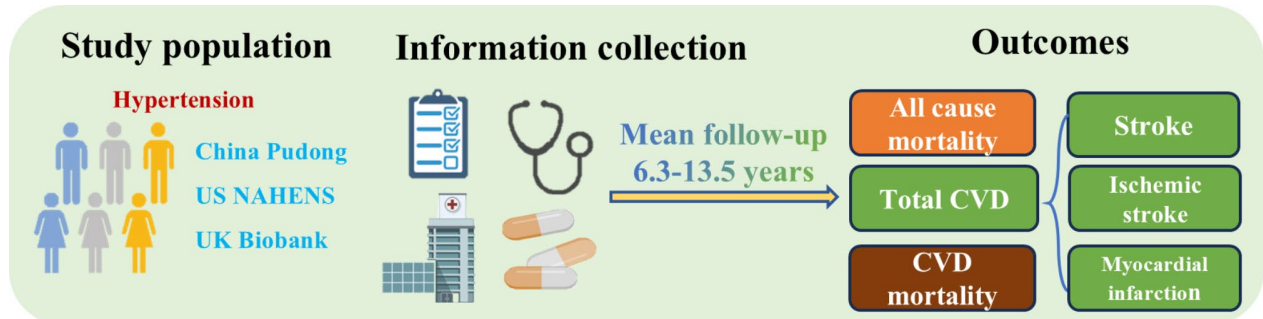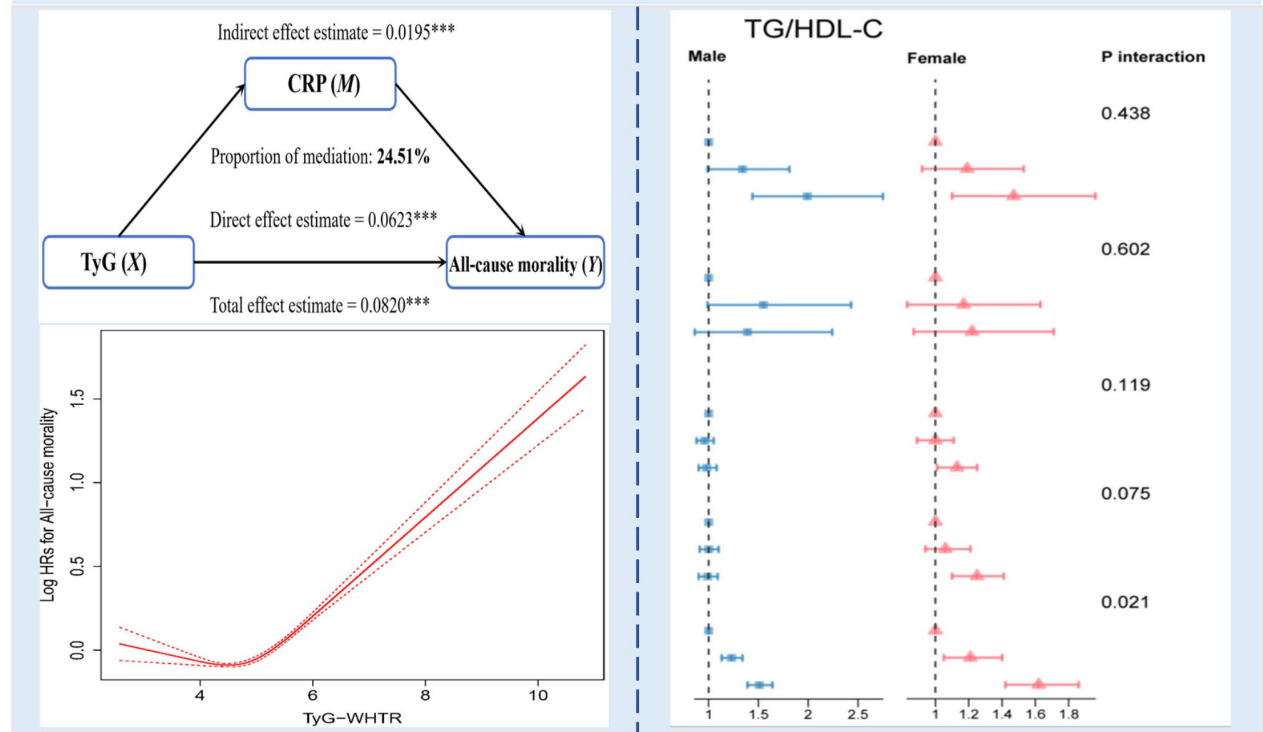
Introduction

Cardiovascular disease (CVD) encompasses a spectrum of conditions that affect the heart and vascular system, mainly including heart failure, angina pectoris, myocardial infarction, and stroke [1]. The incidence of CVD has seen a dramatic rise from 271 to 523 million cases worldwide from 1990 to 2019 [2]. This increase underscores the growing health burden of CVD, which has become the leading cause of mortality across the globe [2, 3]. Hypertension and diabetes mellitus, characterized by underlying metabolic dysregulation, are commonly associated with the development of CVD [4]. In particular, hypertension is a significant risk factor for adverse cardiovascular events [5], affecting over 30% of the global population [6] and leading to functional or organic damage in the brain, heart, and other vital organs [7]. Notably, elevated systolic blood pressure has been shown to increase the risk of cerebral hemorrhage and stable angina by 44% and 41%, respectively [8], and was directly responsible for 10.4 million deaths in 2017 [9]. The identification of risk factors for CVD prediction in hypertensive populations is crucial for the implementation of early preventive strategies.

Hypertensive patients frequently exhibit metabolic disturbances [10], with insulin resistance (IR) playing a pivotal role in these pathophysiological changes [11]. IR is defined as a state of reduced sensitivity and responsiveness to insulin and has been firmly established as a strong correlate of CVD and related mortality, potentially through pathways involving excessive sympathetic nervous system activation, impaired vascular endothelial function and inflammation [12–17]. Recent evidence suggests that TyG index with its related surrogates and TG/HDL_C are reliable markers of IR [18]. The TyG index estimates insulin sensitivity by integrating triglyceride and fasting glucose levels [19]. Furthermore, indices such as TyG-body mass index (TyG-BMI), TyG-waist circumference (TyG-WC), TyG-waist-to-hip ratio (TyG-WHTR), and triglycerides-to-low-density lipoprotein cholesterol ratio (TG/HDL_C) have demonstrated significant utility in the assessment of IR [20, 21]. Epidemiological studies have consistently shown that these IR-related indices enhance the risk of adverse clinical outcomes in individuals with non-alcoholic fatty liver disease (NAFLD), diabetes, chronic kidney disease and other diseases [22–24]. However, there remains a paucity of robust evidence concerning effective predictors and biological links between these indices and the progression of CVD and mortality in hypertensive populations.

This study leverages data from the National Health and Nutrition Examination Survey (NHANES), UK Biobank (UKBB), and Shanghai Pudong cohort to address the following objectives: (1) to evaluate the association of five IR-related indices with CVD and mortality in hypertensive individuals; (2) to cross-validate these associations across different countries; (3) to examine the mediating effects of inflammatory markers; and (4) to investigate the causal relationship between the TyG index and CVD. The aim is to provide novel insights into the prevention of hypertension and its cardiovascular sequelae, thereby contributing to the reduction of the global disease burden.

Materials and methods

Study design and study population

We analyzed data from the NHANES, UKBB and the Shanghai Pudong cohort. 502,244 individuals participated in the UKBB follow-up survey during 2006–2010. After excluding participants with missing serology, physical examination parameters, outcome variables and covariates, 305,285 individuals remained, of whom 164,357 had hypertension (Figure S1). US NHANES, a research program, is designed to assess the health and nutritional status of individuals in the United States. This study used data from the NHANES database 1999–2018, during which a total of 101,316 individuals were recruited. After eliminating those without essential information, 9,283 individuals with hypertension remained (Figure S2). We followed up 9,041 individuals of Shanghai Pudong cohort and ultimately included 1,760 and 5,334 participants with CVD and mortality outcomes respectively (Figure S3).

Definition of TyG, TyG-BMI, TyG-WC, TyG-WHTR and TG/HDL_C ratio

Our study selected five insulin resistance indices: TyG, TyG-BMI, TyG-WC, TyG-WHTR, and TG/HDL_C. The formulas are as follows:

TyG index = Ln[Triglyceride (mg/dL)×Glucose (mg/dL) / 2];

TyG-BMI = TyG×BMI;

TyG-WC = TyG×Waist Circumference;

TyG-WHTR = TyG×WHTR = TyG×Waist Circumference / Height;

TG/HDL_C = Triglycerides (mg/dL) / HDL-C (mg/dL) [25].

Hypertension and total CVD ascertainment

A systolic blood pressure (SBP)≥140 mmHg or a diastolic blood pressure (DBP)≥90 mmHg was considered hypertension in the Shanghai Pudong cohort [26]. According to the 2017 American Heart Association / American College of Cardiology (AHA / ACC) guideline recommendations, hypertension was defined as a systolic blood pressure of≥130 mmHg or diastolic blood pressure≥80 mmHg in NHANES and UKBB populations [6]. In sensitivity analyses, we re-analyzed the

NHANES participants with the hypertension criterion of 140/90 mmHg to validate the robustness of our findings.

Cardiovascular disease was identified as either myocardial infarction or ischemic stroke in the UKBB cohort. Myocardial infarction was classified as ICD-10 code I21 or I22 on admission. Ischemic stroke was defined using ICD-10 code I63 or I64 and magnetic resonance imaging of the brain or computed tomography scanning [27]. Diagnosis of CVD was determined through a standardized medical condition questionnaire in the NHANES. Individuals were considered to have CVD if they answered 'yes' to the question 'Has a doctor or other health professional ever told you that you have congestive heart failure / coronary heart disease / angina / myocardial infarction / stroke?' [23]. The total CVD ascertainment in the Shanghai Pudong cohort, which mainly consisted of coronary heart disease and stroke, was assessed by self-report questionnaires.

Definition of cardiovascular mortality and all-cause mortality
The primary endpoint of this study was all-cause mortality. We utilized the NHANES Public Utilization-Related Mortality File, which is available up to December 31, 2019, to ascertain the mortality status of the follow-up population. The data was linked to the NCHS and the National Death Index (NDI) through a probability-matching algorithm. The follow-up period commenced on the date of the NHANES interview and concluded either on the date of death or December 31, 2019. Mortality outcomes for the Pudong cohort were obtained from the Pudong CDC mortality surveillance repository. Cause-specific mortality was determined by ICD-10. CVD mortality was defined as ICD-10 codes I00-I09, I11, I13, and I20-I51.

Definition of systemic inflammatory response index (SIRI) and C-reactive protein (CRP)
Peripheral blood samples of NHANES participants were analyzed at the Mobile Examination Centre (MEC) using a Beckman Coulter HMX hematology profiler, whereas peripheral blood samples from UKBB were analyzed using a Beckman Coulter LH750 hematology profiler. In the Pudong cohort, blood samples were measured using a HITACHI 7170A automatic biochemical analyzer. Lymphocyte, neutrophil, monocyte, and platelet counts were measured by complete blood count. SIRI = monocyte count × neutrophil count / lymphocyte count. While CRP was quantified by latex-enhanced nephelometry in University of Washington using blood samples.

Covariates
All three cohorts adjusted for age, gender, educational level, smoking status, alcohol consumption, history of diabetes, systolic blood pressure (SBP), and total cholesterol (TC). Among these, age, SBP, TC and alcohol consumption were continuous variables, while the remaining variables were categorical. Based on this foundation, the NHANES cohort further incorporated adjustments for race, physical activity and HEI-2015. The Pudong cohort further adjusted for physical activity. Race and Townsend deprivation index were adjusted for in the UKBB cohort additionally.

Mendelian randomization and sensitivity analysis
Single nucleotide polymorphisms (SNPs) associated with the TyG index were extracted from a previously conducted genome-wide association study (GWAS), which included participants without diabetes or lipid metabolism disorders (http://links.lww.com/JS9/C792) [28]. Genetic variants associated with body status, such as triglycerides, HDL-C, hypertension, SBP, DBP, BMI, waist circumference, and waist-hip ratio, as well as inflammatory marker CRP, and components of SIRI, were obtained from the Integrative Epidemiology Unit (IEU) OpenG-WAS database (https://gwas.mrcieu.ac.uk/). Data on stroke, myocardial infarction, embolic stroke and overall cardiovascular diseases were sourced from FinnGen (freeze 11) (https://r11.finngen.fi/). All studies received approval from local institutional review boards, and informed consent was provided by all participants. To identify genetic variants suitable for estimating causal effects between exposures and outcomes, a genome-wide significance threshold of $P < 5 \times 10^{-8}$ was applied, except for embolic stroke, where the threshold was set at $P < 5 \times 10^{-6}$ due to a limited number of instrumental variables. Single nucleotide polymorphisms (SNPs) in linkage disequilibrium ($R^2 < 0.001$, within 10,000 kb) were excluded from the analysis. The inverse variance weighted (IVW) method was employed as the primary approach for two-sample Mendelian randomization (MR) analysis, with MR-Egger and weighted median methods used as complementary approaches. Sensitivity analyses were conducted to assess whether individual variants influenced the overall findings. Above analyses were performed using R packages such as "TwoSampleMR", "MR-PRESSO", and "Forestploter", which contributed significantly to the data analysis and visualization process.

Statistical analyses
We conducted t-test and chi-square tests to compare the baseline demographic characteristics of the population. The results were presented as mean ± standard error (SE) for continuous variables and as frequency (%) for categorical variables. Firstly, multivariate Cox proportional hazards model was employed to assess the associations between TyG, TyG-BMI, TyG-WC, TyG-WHTR and TG/HDL_C ratio indices and CVD and mortality by

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comparing the second and third tertiles of these indices with the first tertiles. We adjusted for the corresponding covariates and estimated hazard ratios (HR) and 95% confidential intervals (CI) to quantify the association. The advantage of the Multivariate Cox proportional hazards model is that it is independent of distributional assumptions about survival time [29].

Subsequently we used the Generalized Additive Model (GAM) to investigate the non-linear associations between various indices including TyG, TyG-BMI, TyG-WC, TyG-WHTR and TG/HDL_C ratio, with cardiovascular disease and mortality. The GAM is a statistical model that fits non-linear relationships and offers greater flexibility than the Generalized Linear Model (GLM). The advantage of the GAM lies in its capability of reducing the number of predictors in different distributions by evaluating the non-specific linkage to the dependent variable by linkage function to reduce the error in predicting the dependent variable [30].

Furthermore, mediation analysis model was utilized to explore whether inflammatory indices serve as mediators in the relationships between five insulin resistance-related indices and CVD and mortality. Traditional mediation analyses are based on parametric regression assumptions and typically estimate three types of effects: (I) total effects (the total effects of the independent variable X on the dependent variable Y, including both direct and indirect effects); (II) direct effects, (the residual effect of the exposure on the outcome, which acts through pathways other than the mediator); (III) indirect effects (the pathway from the exposure to the outcome via the mediating variable). When the total, direct, and indirect effects align in the same direction, it is feasible to calculate the 'mediation ratio.' This ratio quantifies the proportion of the total effect attributable to the mediating variable [31].

We grouped participants by gender to assess the interaction of sex in the relationship of TyG TyG-BMI, TyG-WC, TyG-WHTR, and TG/HDL_C ratio indices with cardiovascular disease and mortality. In addition, we performed GAM analyses to ascertain the stability of the results in the populations without hypertension across three cohorts.

All analyses were carried out using SAS software version 9.4 and R version 4.4.1. All significance levels were set at two-sided $P<0.05$.

Results

Baseline characteristics of participants

The baseline characteristics of the included participants (164,357 from the UKBB, 9,283 from the NHANES, 1,760 and 5,334 from Pudong cohort of different outcome) are summarized in Table 1. The mean ages of participants were 59.8 and 62.6 years for Pudong cohort of

Table 1 Baseline characteristics of participants from three cohorts

Characteristic	CHINA Pudong		US NHANES	UK Biobank
Sample-Outcome	Total-CVD (N = 1760)	Morality (N = 5334)	All outcome (N = 9283)	All outcome (N = 164,357)
Demographic information				
Age, mean (SE), years	59.8 (0.2)	62.6 (0.1)	57.0 (0.2)	58.4 (0.02)
Male, n(%)	641 (36.4)	2046 (38.4)	5001 (53.9)	87,364 (53.2)
White, n(%)	0	0	5154 (55.5)	156,433 (95.2)
Less than high school, n(%)	1336 (75.9)	3706 (69.5)	2608 (28.1)	44,390 (27.0)
Low household income[a], n(%)	-	-	2732 (29.4)	32,462 (19.8)
Non-smoking, n(%)	1349 (76.7)	4095 (76.8)	4638 (50.0)	86,758 (52.8)
Alcohol consumption, mean (SE), g/day	0.5 (0.04)	0.4 (0.02)	23.2 (0.3)	20.0 (0.1)
History of diabetes, n(%)	191 (10.9)	787 (14.8)	1925 (20.7)	11,760 (7.2)
Body Measurement Indicators				
Height, mean (SE), cm	160.6 (0.2)	160.3 (0.1)	167.8 (0.1)	169.1 (0.02)
BMI, mean (SE), kg/m^2	25.8 (0.1)	25.9 (0.05)	30.1 (0.1)	28.2 (0.01)
WC, mean (SE), cm	84.9 (0.2)	84.9 (0.1)	103.1 (0.2)	93.2 (0.03)
SBP, mean (SE), mmHg	147.6 (0.4)	149.7 (0.3)	133.9 (0.2)	150.0 (0.04)
DBP, mean (SE), mmHg	91.2 (0.2)	91.2 (0.1)	73.5 (0.1)	87.9 (0.02)
Blood indicators				
Platelet count, mean (SE), 10^9/L	200.1 (1.6)	201.2 (0.8)	248.0 (0.7)	251.8 (0.1)
Monocyte number, mean (SE), 10^9/L	0.4 (0.003)	0.4 (0.002)	0.6 (0.002)	0.5 (0.001)
Lymphocyte number, mean (SE), 10^9/L	2.1 (0.02)	2.1 (0.01)	2.0 (0.02)	2.0 (0.002)
Neutrophils number, mean (SE), 10^9/L	3.8 (0.03)	3.8 (0.02)	4.1 (0.02)	4.3 (0.003)
C-reactive protein, mean (SE), mg/dL	0.2 (0.01)	0.2 (0.01)	0.5 (0.01)	0.3 (0.01)
HDL_C, mean(SE), mg/dL	53.2 (0.3)	51.9 (0.2)	52.6 (0.2)	56.1 (0.04)
TC, mean (SE), mg/dL	216.2 (1.0)	218.9 (0.6)	197.8 (0.4)	224.4 (0.1)

Table 1 (continued)

Characteristic	CHINA Pudong		US NHANES	UK Biobank
Sample-Outcome	Total-CVD (N=1760)	Morality (N=5334)	All outcome (N=9283)	All outcome (N=164,357)
TG, mean (SE), mg/dL	158.7 (2.9)	161.2 (1.2)	145.3 (1.1)	165.6 (0.2)
FBG, mean (SE), mg/dL	110.1 (0.7)	111.3 (0.5)	114.3 (0.4)	94.2 (0.1)

[a]In NHANES, low household income referred to family poverty/income ratio of ≤1.35; In UK Biobank, household income < £18,000 was defined as low household income;

-, data not available;

Abbreviations: NHANES=National Health and Nutrition Examination Survey, CVD=cardiovascular disease, SE=standard error, BMI=body mass index, WC=waist circumference, SBP=systolic blood pressure, DBP=diastolic blood pressure, HDL_C=High Density Lipoprotein_ cholesterol, TC=total cholesterol, TG=triglyceride, FBG=Fasting blood glucose

different outcome, 58.4 years for UKBB and 57.0 years for NHANES. The proportion of men in Pudong cohort study was smaller than those in other cohorts (36.4%-38.4% vs 53.2%-53.9%). However, the proportion of low education and no-smoking participants in Pudong cohort study were bigger than those in other cohorts (69.5%-75.9% vs 27.0%-28.1%; 76.7%-76.8% vs 50.0%-52.8%). Alcohol consumption, BMI and WC, CRP in Pudong cohort study were lower than those in other cohorts (0.4–0.5 vs 20.0–23.2 g/day; 25.8–25.9 vs 28.2–30.1 kg/m^2; 84.9 vs 93.2–103.1 cm, 0.2 vs 0.3–0.5 mg/dl).

Associations of TyG-related indices and TG/HDL_C ratio with incident CVD and mortality

Table 2 demonstrates that these five indices are significantly associated with CVD and mortality. US NHANES documented 2,056 deaths over a mean follow-up of 9.5 years. In this cohort, the incidence of CVD was significantly higher in the highest tertile (T3) compared to the lowest tertile (T1) for each of the five indices, with increases of 74%, 79%, 93%, 90%, and 63%, respectively. Both the TyG index and TyG-WHTR significantly elevated the risk of all-cause and CVD mortality [TyG: HR (95%CI): 1.19 (1.05–1.37), 1.32 (1.02–1.70); TyG-WHTR: 1.17 (1.00–1.36), 1.32 (1.00–1.72)]. Additionally, TyG-WC increased the HR for CVD mortality by 29% at T3 The UKBB recorded 15,317 deaths, 4,219 incident ischemic stroke cases and 5,262 incident myocardial infarction cases over a mean follow-up of 13.2–13.5 years. All four indices exhibited a positive and significant association with ischemic stroke, myocardial infarction, and mortality, except for TyG, which was not significantly associated with ischemic stroke and CVD mortality in the UKBB (Table S1). The Shanghai Pudong cohort documented 738 deaths and 341 incident CVD cases over a mean follow-up of 6.3–8.8 years. TyG-BMI and TG/HDL_C ratio were associated with a significant 32% and

31% increase in the HRs for total-CVD at T3 compared with T1. However, only TG/HDL_C ratio demonstrated a significant association with stroke [T2 vs T1: 1.59 (1.01–2.49); T3 vs T1: 1.67 (1.06–2.63)]. The results of model 1 are generally consistent with model 2 (Table S2).

Associations of continuous TyG-related indices and TG/HDL_C ratio with incident CVD and mortality

Based on the findings from the COX regression models, we propose that these five indices may exhibit a nonlinear relationship with CVD and mortality. Figure 1 and S4 depict the smooth curves that represent the association of the five indices with outcomes as determined by GAM. In US NAHENS and UKBB cohorts, the TyG-related indices demonstrated a hook-shaped association with mortality, while the TG/HDL_C ratio positively correlated with mortality. Within the Shanghai Pudong cohort, except for the association trends of TyG-BMI and TG/HDL_C ratio with all-cause mortality, which paralleled those of the other two cohorts, the remaining three indices exhibited a V-shaped relationship with all-cause mortality. In both UKBB and US NHANES, there was an overall increasing trend observed in TyG-related indices with respect to incident CVD (Figure S4).

Subgroup analyses by gender

Accounting for the effects of gender, we performed subgroup analyses (Figs. 2 and 3). In the UKBB cohort, there was a significant multiplicative interaction between TG/HDL_C ratio and gender on incident CVD (P-value=0.021). In the US NHANES cohort, these five indices significantly increased the incidence of total CVD in gender subgroup (T3 vs T1: male: 1.99–2.24; female: 1.47–1.71). Within the Pudong cohort, only TyG-BMI significantly increased total CVD risk at T3 compared to T1 in women, with HR of 1.47 (1.06–2.05). In the UKBB, all five indices exhibited a significant and positive association with incident myocardial infarction in both genders, whereas the positive correlation with ischemic stroke was statistically significant only in women.

Mediating effects of inflammation indexes

In the Pudong cohort, aside from TyG, the remaining four indices also demonstrated significant multiplicative interactions with gender. Notably, only TyG-WHTR significantly increased the risk of all-cause mortality in females [T3 vs T1: 1.38 (1.06, 1.79)]. In the UKBB cohort, all indices exhibited a significant and positive association with all-cause mortality in women. Furthermore, both TyG-WHTR and TyG-WC significantly amplified the interaction with gender (P interaction < 0.001; P interaction=0.001).

The mediation analyses were further performed in the three cohorts to investigate the mediating role of

inflammatory markers. Figure 4 and S5 reveal that SIRI exerted a positive partial mediating influence on the relationship between the five indices and myocardial infarction, stroke, ischemic stroke and mortality in UKBB (TyG: proportion: 1.89%-2.94%; TyG-BMI: 1.64%-2.37%; TyG-WC: 2.58%-2.65%; TyG-WHTR: 1.32%-6.93%; TG/HDL_C: 0.32%-0.95%). In addition, CRP demonstrated a higher proportion of mediating effects compared to SIRI (TyG: 3.23%-24.51%; TyG-BMI: 5.82%-31.91%; TyG-WC: 5.13%-21.14%; TyG-WHTR: 10.65%-21.70%; TG/HDL_C: 5.40%-21.20%). Figure S6 presents the outcomes of the mediation analysis in the US NHANES and Pudong cohorts, indicating that CRP surpasses SIRI as mediating variables.

Sensitivity analyses

To ensure comparability among the three cohorts, hypertension was defined as a SBP of 140 mmHg or higher and/or a DBP of 90 mmHg or higher among US NHANES participants. Subsequently, COX regression analyses were re-conducted on the populations with hypertension. Table S3 presents results that are largely in agreement with the preceding findings. Additionally, we employed GAMs to characterize the association of TyG-related indices and the TG/HDL_C ratio with incident CVD and mortality in the populations without hypertension (Figures S7 and S8).

Genetic associations with cardiovascular risk factors and stroke outcome

To evaluate the genetic associations with cardiovascular risk factors and stroke outcome, we further utilized the IVW method (Fig. 5). The results predicted TyG was significantly related with stroke in genetic [OR (95%CI):1.26 (1.10–1.45)] and myocardial infarction [1.98 (1.61–2.42)]. Similarly, triglycerides were predicted with a significant association with stroke [1.11 (1.04–1.18)] and myocardial infarction [1.30 (1.11–1.52)], while HDL-C showed a significant protective effect against stroke [0.86 (0.81–0.92)] and embolic stroke [0.82 (0.75–0.89)]. BMI was significantly associated with an increased risk of stroke [1.25 (1.17–1.33)], myocardial infarction [1.44 (1.15–1.80)], and embolic stroke [1.37 (1.22–1.54)]. Waist circumference demonstrated significant associations with stroke [1.31 (1.20–1.43)] and embolic stroke [1.38 (1.18–1.62)], and the waist-hip ratio also showed significant associations with stroke [1.14 (1.07–1.21)] and myocardial infarction [1.33 (1.05–1.67)]. Additionally, reverse analyses indicated an insignificant association between CVD and body status, supporting the unidirectional effect of the aforementioned factors (Figure S9). We also evaluated the causal relationship among TyG, inflammatory markers, and cardiovascular events, suggesting a

potential positive contribution of inflammatory markers to cardiovascular events (Figure S10).

Discussion

This study marks the inaugural utilization of a prospective cohort spanning three countries to collectively investigate the relationship between TyG-related indices and the TG/HDL_C ratio and the incidence of CVD and mortality in individuals with hypertension. We identified a U-shaped correlation between the exposure variables and outcomes, which demonstrated that an elevated TyG levels, along with TyG-BMI, TyG-WC, TyG-WHTR, and the TG/HDL_C ratio, were associated with an increased risk of CVD and mortality among the hypertensive population. Notably, TyG-WC and TyG-WHTR exhibited the strongest associations with CVD and mortality, which were partially mediated by inflammatory indices. The outcomes of subgroup and sensitivity analyses confirmed the robustness of our findings.

Consistent with previous studies, our study has confirmed the U-shaped association of TyG-related indices with adverse cardiovascular events [32, 33]. A study identified the threshold points (all-cause mortality: 9.104; CV mortality: 8.758) for the U-shaped association between the TyG index and all-cause and cardiovascular mortality, which our study is in generally consistent with [32]. Specifically, when above the threshold, the TyG index significantly increased the risk of adverse cardiovascular events. Conversely, below-threshold TyG index was also associated with an elevated risk of adverse cardiovascular events. This may be due to the fact that hypoglycemia can induce arrhythmias, thrombosis, vascular inflammation, and vasoconstriction [34, 35]. Additionally, a very low TyG index may indicate malnutrition, which may likewise induce adverse outcomes [32].

With regard to CVD, a study utilizing the UKBB dataset found that individuals in the highest quartiles of TyG index and TG/HDL_C ratio had increased risks of CVD, with hazard ratios of 1.19 and 1.29, respectively [36]. Remarkably, in our study population with hypertension, the risk increments were even more pronounced for myocardial infarction, reaching 1.35 and 1.59, underscoring the critical importance of monitoring these indices in the management of hypertension. Although we adjusted for demographic and lifestyle factors such as race, economic status, and physical activity, the association of selected insulin resistance indices with adverse cardiovascular events was not consistently significant. In addition to differences in cohort sample sizes, we suggest that this may be related to dietary patterns and genetic background in different countries [37, 38]. Moreover, a study conducted in northern China demonstrated a 1.25-fold elevated risk of CVD in individuals with elevated TyG index compared to the general population, while a

Table 2 The TyG, TyG- WC, TyG- BMI, TyG- WHTR and TG/ HDL_C association with total CVD and mortality calculated using binomial logistic regression models/Cox proportional hazards model in three cohorts

	TyG		TyG- BMI		TyG-WC		TyG- WHTR		TG / HDL_C	
US NHANES[a]										
Total- CVD	Case/N	OR (95%CI)	Case/N	OR (95%CI)	Case/N	OR (95%CI)	Case/N	OR (95%CI)	Case/N	OR (95%CI)
T1	446/3095	Reference	461/3095	Reference	394/3094	Reference	393/3094	Reference	464/3096	Reference
T2	481/3094	1.14 (0.91,1.43)	506/3093	1.10 (0.89,1.37)	504/3094	1.17 (0.94,1.47)	495/3095	1.15 (0.94,1.42)	494/3093	1.06 (0.86,1.30)
T3	607/3094	1.74 (1.40,2.17)	567/3095	1.79 (1.45,2.22)	636/3095	1.93 (1.57,2.37)	646/3094	1.90 (1.55,2.32)	576/3094	1.63 (1.30,2.05)
All-cause morality	Case/N	HR (95%CI)	Case/N	HR (95%CI)	Case/N	HR (95%CI)	Case/N	HR (95%CI)	Case/N	HR (95%CI)
T1	556/3095	Reference	782/3095	Reference	653/3094	Reference	613/3094	Reference	631/3096	Reference
T2	695/3094	0.96 (0.83,1.10)	708/3093	0.86 (0.77,0.96)	689/3094	0.83 (0.73,0.95)	693/3095	0.88 (0.77,1.01)	672/3093	0.87 (0.77,1.00)
T3	805/3094	1.19 (1.05,1.37)	566/3095	1.03 (0.88,1.20)	714/3095	1.10 (0.95,1.28)	750/3094	1.17 (1.00,1.36)	753/3094	1.11 (0.97,1.27)
CVD morality	Case/N	HR (95%CI)	Case/N	HR (95%CI)	Case/N	HR (95%CI)	Case/N	HR (95%CI)	Case/N	HR (95%CI)
T1	181/3095	Reference	264/3095	Reference	214/3094	Reference	199/3094	Reference	206/3096	Reference
T2	228/3094	0.97 (0.75,1.25)	220/3093	0.84 (0.68,1.03)	219/3094	0.79 (0.62,1.01)	236/3095	0.94 (0.74,1.19)	227/3093	0.96 (0.76,1.22)
T3	266/3094	1.32 (1.02,1.70)	191/3095	1.24 (0.95,1.63)	242/3095	1.29 (1.00,1.67)	240/3094	1.32 (1.00,1.72)	242/3094	1.16 (0.88,1.53)
CHINA Pudong[b]										
Total- CVD	Case/N	HR (95%CI)	Case/N	HR (95%CI)	Case/N	HR (95%CI)	Case/N	HR (95%CI)	Case/N	HR (95%CI)
T1	102/587	Reference	105/481	Reference	107/587	Reference	101/586	Reference	95/586	Reference
T2	129/587	1.27 (0.97,1.65)	107/588	1.04 (0.79,1.36)	110/586	1.01 (0.77,1.32)	124/588	1.19 (0.92,1.56)	126/588	1.29 (0.99,1.69)
T3	110/586	1.17 (0.88,1.56)	129/586	1.32 (1.01,1.72)	124/587	1.22 (0.93,1.60)	116/586	1.16 (0.88,1.53)	120/586	1.31 (1.00,1.73)
Stroke	Case/N	HR (95%CI)	Case/N	HR (95%CI)	Case/N	HR (95%CI)	Case/N	HR (95%CI)	Case/N	HR (95%CI)
T1	33/587	Reference	38/586	Reference	42/587	Reference	39/586	Reference	31/586	Reference
T2	54/587	1.62 (1.05,2.51)	44/588	1.16 (0.75,1.79)	40/586	0.92 (0.60,1.42)	48/588	1.19 (0.78,1.83)	49/588	1.59 (1.01,2.49)
T3	43/586	1.28 (0.79,2.07)	48/586	1.28 (0.83,1.99)	48/587	1.12 (0.72,1.74)	43/586	1.03 (0.65,1.62)	50/586	1.67 (1.06,2.63)
All-cause morality	Case/N	HR (95%CI)	Case/N	HR (95%CI)	Case/N	HR (95%CI)	Case/N	HR (95%CI)	Case/N	HR (95%CI)
T1	251/1779	Reference	260/1779	Reference	222/1779	Reference	216/1778	Reference	255/1178	Reference
T2	236/1776	0.87 (0.72,1.04)	230/1777	0.89 (0.75,1.07)	225/1777	0.92 (0.76,1.10)	218/1777	0.92 (0.76,1.11)	250/1778	0.93 (0.78,1.10)
T3	251/1779	0.94 (0.78,1.13)	248/1778	1.01 (0.84,1.21)	291/1778	1.05 (0.88,1.26)	304/1779	1.10 (0.91,1.32)	233/1778	0.97 (0.81,1.17)
UK Biobank[c]										
Stroke	Case/N	HR (95%CI)	Case/N	HR (95%CI)	Case/N	HR (95%CI)	Case/N	HR (95%CI)	Case/N	HR (95%CI)
T1	1615/54788	Reference	1601/54788	Reference	1470/54788	Reference	1496/54789	Reference	1615/54789	Reference
T2	1648/54780	0.94 (0.88,1.01)	1712/54781	0.99 (0.93,1.06)	1707/54780	1.02 (0.95,1.10)	1644/54779	0.97 (0.90,1.04)	1663/54780	0.97 (0.90,1.03)
T3	1829/54789	1.01 (0.94,1.08)	1779/54788	1.05 (0.98,1.13)	1915/54789	1.08 (1.00,1.16)	1952/54789	1.09 (1.02,1.17)	1814/54780	1.04 (0.97,1.11)
All-cause morality	Case/N	HR (95%CI)	Case/N	HR (95%CI)	Case/N	HR (95%CI)	Case/N	HR (95%CI)	Case/N	HR (95%CI)
T1	4621/54788	Reference	4658/54788	Reference	4043/54788	Reference	4095/54789	Reference	4602/54789	Reference

Table 2 (continued)

	TyG		TyG- BMI		TyG-WC		TyG- WHTR		TG / HDL_C	
T2	5017/54780	0.99 (0.95,1.03)	4882/54781	0.94 (0.90,0.98)	4847/54780	1.01 (0.96,1.05)	4843/54779	1.00 (0.96,1.04)	5122/54780	1.02 (0.98,1.06)
T3	5679/54789	1.06 (1.02,1.10)	5777/54788	1.10 (1.07,1.15)	6427/54789	1.21 (1.15,1.26)	6379/54789	1.21 (1.16,1.26)	5593/54788	1.07 (1.03,1.11)
CVD morality	Case/N	HR (95%CI)	Case/N	HR (95%CI)	Case/N	HR (95%CI)	Case/N	HR (95%CI)	Case/N	**HR (95%CI)**
T1	905/54788	Reference	873/54788	Reference	705/54788	Reference	727/54789	Reference	854/54789	Reference
T2	996/54780	0.97 (0.89,1.06)	974/54781	0.96 (0.87,1.05)	968/54780	1.05 (0.95,1.17)	983/54779	1.08 (0.97,1.18)	1039/54780	1.06 (0.97,1.16)
T3	1208/54789	1.05 (0.95,1.15)	1262/54788	1.22 (1.11,1.33)	1436/54789	1.34 (1.22,1.49)	1399/54789	1.36 (1.23,1.49)	1216/54788	1.13 (1.03,1.24)

[a]Model: age (continuous), gender (male, female), ethnicity/race (Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, Other Race—Including Multi-Racial), educational level (less than high school, high school and above), smoking status (Yes or No); alcohol consumption (continuous), physical activity (adequate, inadequate), HEI-2015 (continuous), history of diabetes (Yes or No), SBP (continuous), TC (continuous)

[b]Model: age (continuous), gender (male, female), educational level (less than high school, high school and above), smoking status (Yes or No), alcohol consumption (continuous), physical activity (adequate, inadequate), history of diabetes (Yes or No), SBP (continuous), TC (continuous)

[c]Model: age (continuous), gender (male, female), ethnicity/race (White, Asian or Asian British, Black or Black British, Chinese, Mixed, Other ethnic group), educational level (less than high school, high school and above), Townsend deprivation index (T1, T2, T3), smoking status (Yes or No), alcohol consumption (continuous), history of diabetes (Yes or No), SBP (continuous), TC (continuous)

P-values less than 0.05 ($p < 0.05$) were considered significant

Abbreviations: TyG = triglyceride-glucose, BMI = body mass index, WC = waist circumference, WHTR = waist circumference/height ratio, TG = triglyceride, HDL_C = High Density Lipoprotein_ cholesterol, NHANES = National Health and Nutrition Examination Survey, CVD = cardiovascular disease, HR = hazard ratio, CI = confidence interval, N = number

Korean cohort study confirmed that the TyG index was an independent predictor of coronary artery calcification progression [39, 40]. Our study expands the geographic representation, particularly for the southern Chinese population. Additionally, a prospective study from Argentina highlighted the significance of the TG/HDL_C ratio in forecasting CVD risk [41]. Through systematic evaluation in a substantial sample, our research revealed that the TG/HDL_C ratio may exhibited superior predictive efficacy compared to TyG and its derivatives in the Pudong cohort, offering a novel perspective for future clinical practice. In terms of mortality, existing studies have established nonlinear associations between the TyG index and mortality [25, 42], which was also confirmed in our study. This phenomenon may be related to the extreme glycemic status of the organism [43]. This observation underscores the critical role of dynamic monitoring of insulin resistance-related indices in the prevention of CVD and mortality. Furthermore, several investigations have shown that TyG-WC and TyG-WHTR have superior predictive power for CVD and mortality risk compared to the TyG index. This association has been validated in the general population, middle-aged and elderly populations, and those with metabolic syndrome [44–46]. We also observed this association, which can assist physicians in developing more accurate risk prediction methods for CVD and death in the hypertensive population.

MR and sensitivity analyses substantiated the causal relationship between the TyG index and CVD. Specifically, the findings demonstrated a significant association of the TyG index with myocardial infarction (OR: 1.98, 95% CI: 1.61–2.42) and stroke (OR: 1.26, 95% CI: 1.10–1.45). Furthermore, this association was stronger than those observed for traditional risk factors, including triglycerides, SBP, DBP, waist circumference, and waist-to-hip ratio, in relation to CVD. This discovery significantly enhances the validity of our results and highlights the TyG index's superiority in predicting CVD. Higher levels of HDL_C were associated with a reduced risk of cardiovascular diseases, which is closely related to its endothelial protective function, anti-inflammatory effects, and the ability to inhibit oxidative stress [47, 48]. Importantly, inverse MR analysis revealed no significant findings, suggesting that modifications to the TyG index and conventional risk factors are not solely responsible for the development of CVD.

In exploring the underlying mechanisms of these associations, we uncovered a significant link to IR. IR diminishes the body's responsiveness and sensitivity to insulin, thereby disrupting glucose and lipid metabolism. Subsequently, metabolic dysregulation activates the protein kinase C pathway and the nuclear factor-κB (NFκB) pathways, precipitating the production of excessive reactive oxygen species. This process facilitates the formation of atherosclerotic plaques and establishes the pathological basis for the development of CVD [49–51]. IR heightens the incidence of adverse cardiovascular events by compromising vascular endothelial integrity, promoting thrombosis [52, 53], and enhancing platelet activation [54]. Notably, in the context of hypertension, impaired endothelium-dependent renal vasorelaxation and
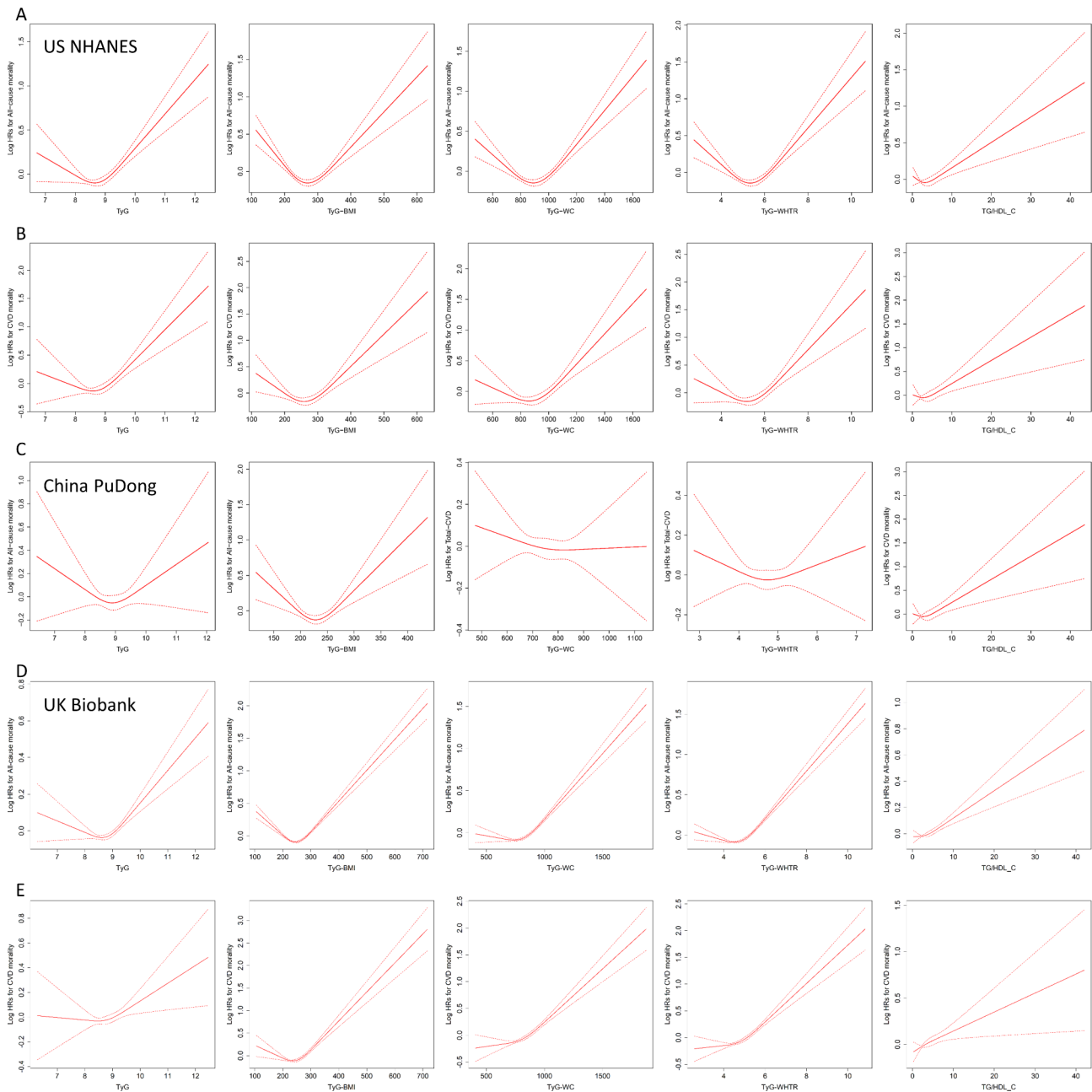
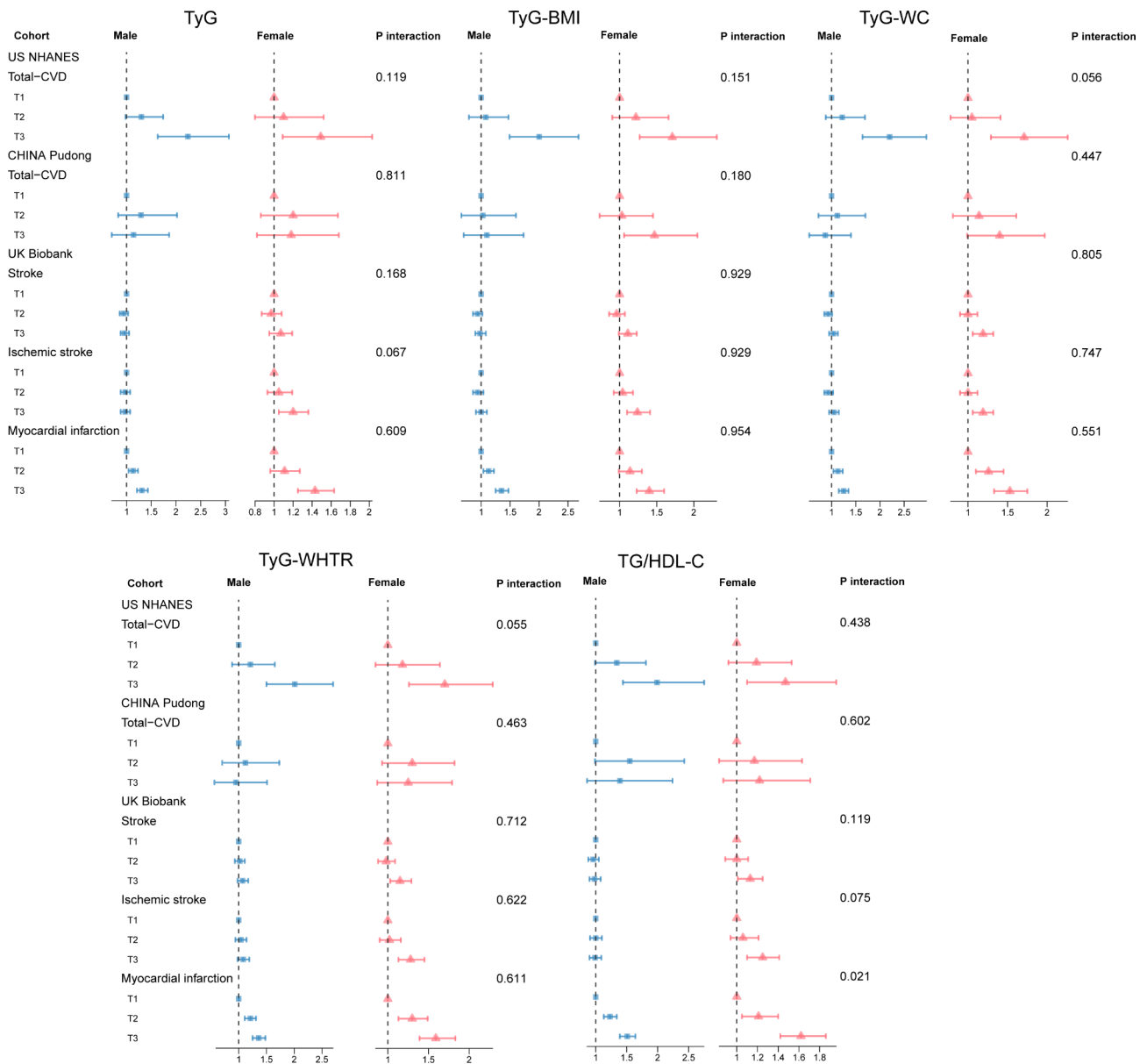**Fig. 1** Generalized additive models (GAM) illustrating the association of TyG-related indices and TG/HDL_C ratio with mortality. Note: US NHANES: Model was adjusted by age, gender, ethnicity/race, educational level, smoking status; alcohol consumption, physical activity, HEI-2015, history of diabetes, SBP, TC. China Pudong: Model was adjusted by age, gender, educational level, smoking status, alcohol consumption, physical activity, history of diabetes, SBP, TC. UKBB: Model was adjusted by age, gender, ethnicity/race, educational level, Townsend deprivation index, smoking status, alcohol consumption, history of diabetes, SBP, TC. Abbreviations: TyG = triglyceride-glucose, BMI = body mass index, WC = waist circumference, WHTR = waist circumference/height ratio, TG = triglyceride, HDL_C = High Density Lipoprotein_ cholesterol, NHANES = National Health and Nutrition Examination Survey, CVD = cardiovascular disease, HR = hazard ratio

diminished insulin sensitivity create a pernicious cycle that exacerbates the progression of IR and CVD [55]. The systemic inflammatory response elicited by IR also plays a crucial role. Inflammation activates the renin-angiotensin system, as well as the neutrophil and monocyte-macrophage systems, which accelerate apoptotic and atherosclerotic progression [44, 56, 57]. These pathways collectively form a complex network system that comprehensively elucidates the association between the five IR-related indices and CVD and mortality, as well as the mediating effects of inflammatory factors.

Fig. 2 The association of TyG-related indices and TG/HDL_C ratio with incident CVD in gender subgroup. Note: US NHANES: Model was adjusted by age, gender, ethnicity/race, educational level, smoking status; alcohol consumption, physical activity, HEI-2015, history of diabetes, SBP, TC. China Pudong: Model was adjusted by age, gender, educational level, smoking status, alcohol consumption, physical activity, history of diabetes, SBP, TC. UKBB: Model was adjusted by age, gender, ethnicity/race, educational level, Townsend deprivation index, smoking status, alcohol consumption, history of diabetes, SBP, TC. P-values less than 0.05 (p < 0.05) were considered significant. Abbreviations: TyG = triglyceride-glucose, BMI = body mass index, WC = waist circumference, WHTR = waist circumference/height ratio, TG = triglyceride, HDL_C = High Density Lipoprotein_ cholesterol, NHANES = National Health and Nutrition Examination Survey, CVD = cardiovascular disease

It is noteworthy that our gender-stratified subgroup analyses uncovered significant multiplicative interactions between these indices and gender. Specifically, IR-related indices were significantly associated with CVD and mortality in females, whereas these associations were less apparent in the male population. This observation aligns with previous research findings. A cohort study highlighted that the risk of MI associated with a high TyG index was more pronounced in women (HR=3.77) compared to men (HR=1.93) [58]. Additionally, a Chinese cohort reinforced the gender interaction of the TyG index and all-cause mortality [59]. Due to higher baseline levels of nitric oxide synthase (NOS) in women, they may be more susceptible to myocardial fibrosis and cardiac hypertrophy when exposed to oxidative stress [60]. Moreover, women experience a more pronounced deterioration in metabolic risk factors than men at the onset of IR [61, 62], thereby increasing their vulnerability to
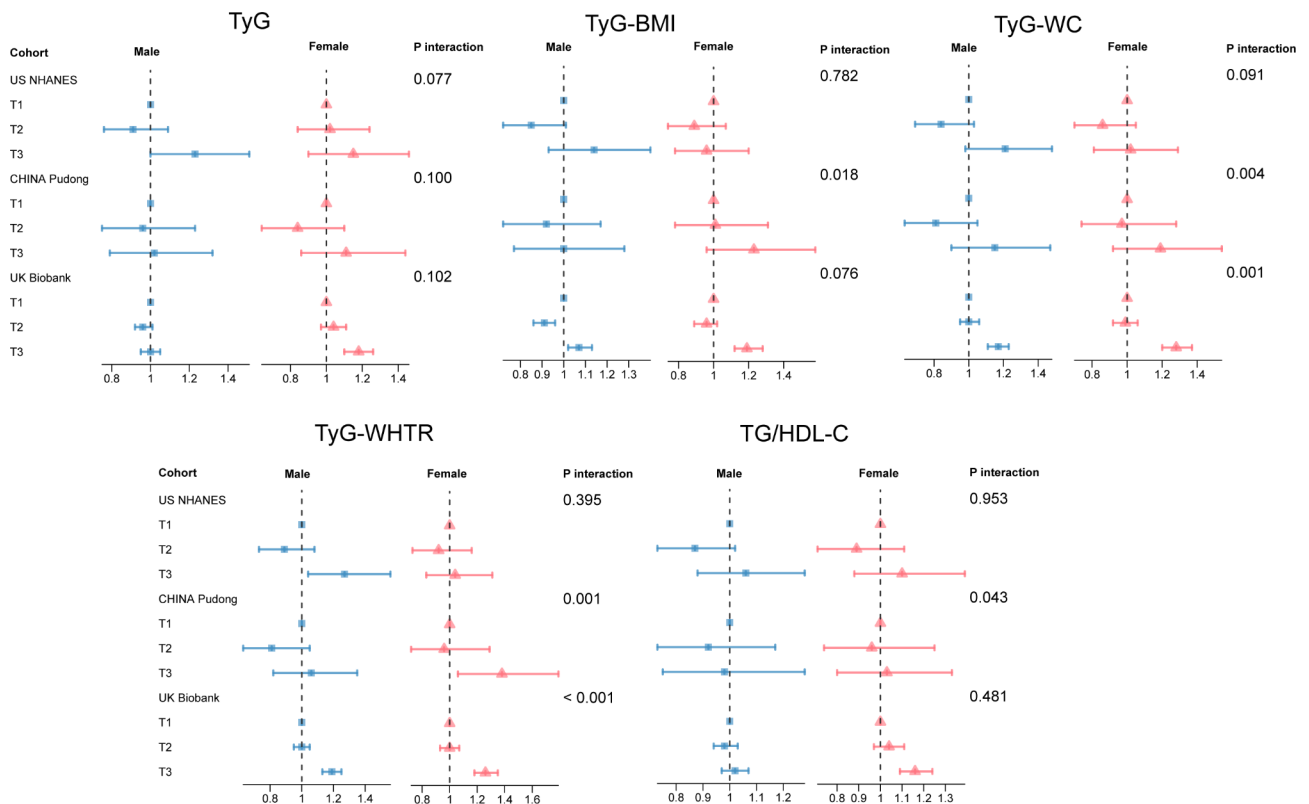
Fig. 3 The association of TyG-related indices and TG/HDL_C ratio with all-cause mortality in gender subgroup. Note: US NHANES: Model was adjusted by age, gender, ethnicity/race, educational level, smoking status; alcohol consumption, physical activity, HEI-2015, history of diabetes, SBP, TC. China Pudong: Model was adjusted by age, gender, educational level, smoking status, alcohol consumption, physical activity, history of diabetes, SBP, TC. UKBB: Model was adjusted by age, gender, ethnicity/race, educational level, Townsend deprivation index, smoking status, alcohol consumption, history of diabetes, SBP, TC. P-values less than 0.05 (p < 0.05) were considered significant. Abbreviations: TyG = triglyceride-glucose, BMI = body mass index, WC = waist circumference, WHTR = waist circumference/height ratio, TG = triglyceride, HDL_C = High Density Lipoprotein_ cholesterol, NHANES = National Health and Nutrition Examination Survey, CVD = cardiovascular disease

myocardial damage and adverse cardiovascular events. Our findings underscore the importance of prioritizing IR-related indices screening in women, which has the potential to enhance the precision and effectiveness of CVD prevention and management strategies.

Our study offers several substantial advantages. Firstly, we incorporated a cohort exceeding 180,000 participants from three countries for analysis, enhancing statistical power and promoting robust conclusions. Secondly, we explored the relationship between five insulin resistance-related indices and CVD/mortality in a hypertensive population, addressing a significant gap in the literature. Incorporating inflammation indices as mediators, we investigated potential biological mechanisms underlying these associations, paving the way for future mechanistic research. Furthermore, Mendelian randomization analysis circumvented limitations inherent in observational studies, providing insights into causal relationships. Although our study possesses several strengths, it is not devoid of limitations. Considering the adequate sample size, we excluded participants with missing covariates or follow-up time, which may have introduced selection bias. In addition, we obtained 192 SNPs from the European population GWAS data as instrumental variables for the TyG index from previous studies [28, 63]. To screen for SNPs strongly associated with the TyG index, the investigators excluded participants with diabetes and dyslipidemia at baseline to avoid the effect of medication use on the TyG index, which may have introduced selection bias. However, the bias has been shown not to affect causal inference based on mendelian randomization studies with a large sample (more than 270,000 people). Thus, further exploration and analysis is needed to confirm the conclusions in GWAS data from Asian populations in the future. Meanwhile, the definitions of CVD in the US NHANES and Pudong cohorts were based on self-reports, potentially leading to reporting bias and excluding undiagnosed cases. Furthermore, our inability to evaluate longitudinal changes in indices restricted our understanding of their dynamic influence on CVD. Lastly, residual confounding remains a concern despite adjusting for major confounders, emphasizing the necessity for further validation and investigation into the underlying mechanisms.

Fig. 4 Inflammation indexes mediate the association of insulin resistance with stroke and mortality in UKBB. Note: Model was adjusted by age, gender, ethnicity/race, educational level, Townsend deprivation index, smoking status, alcohol consumption, history of diabetes, SBP, TC. values less than 0.05 (p < 0.05) were considered significant. Abbreviations: TyG = triglyceride-glucose, BMI = body mass index, WC = waist circumference, WHTR = waist circumference/height ratio, TG = triglyceride, HDL_C = High Density Lipoprotein_ cholesterol, CVD = cardiovascular disease

Fig. 5 Genetically predicted TyG and TyG-related indices associated with elevated risk of CVD event. Note: P-values less than 0.05 (p < 0.05) were considered significant. Abbreviations: TyG = triglyceride-glucose, TG = triglyceride, HDL_C = High Density Lipoprotein_ cholesterol, SBP = systolic blood pressure, DBP = diastolic blood pressure, BMI = body mass index, WC = waist circumference

Conclusions

In conclusion, this study encompassed the NHANES, UKBB, and Shanghai Pudong cohorts, elucidating that TyG-related indices and the TG/HDL_C ratio augment the risk of CVD and mortality among hypertensive populations, with a notable emphasis on women. The relationships between the five indices and incident CVD and mortality were characterized by nonlinearity, with

inflammatory indices (SIRI and CRP) serving as partial mediators of these associations. TG / HDL_C ratio is the best indicator for CVD prediction, and TyG-WHTR is the best indicator for all-cause/CVD mortality prediction. Furthermore, bidirectional Mendelian randomization analyses substantiated the causal link between the TyG index and CVD. Future research endeavors should concentrate on developing interventions targeting insulin resistance and delving into the inflammatory pathways through which insulin resistance precipitates adverse clinical outcomes.

Abbreviations

CIs	Confidence intervals
CVD	Cardiovascular disease
CRP	C-reactive protein
DBP	Diastolic blood pressure
HDL-C	High-density lipoprotein-cholesterol
HRs	Hazard ratios
IR	Insulin resistance
NHANES	National Health and Nutrition Examination Survey
ORs	Odds ratios
SBP	Systolic Blood Pressure
SIRI	Systemic inflammatory response index
TG	Triglyceride
TyG	Triglyceride-glucose
TyG-BMI	Glucose triglyceride-body mass index
TyG-WHTR	Glucose triglyceride-waist height ratio
TyG-WC	Glucose triglyceride-waist circumference

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-024-02571-x .

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

Supplementary Material 7

Supplementary Material 8

Supplementary Material 9

Supplementary Material 10

Supplementary Material 11

Supplementary Material 12

Author contributions

Y.Q.H. and H. W. had full access to all of the data in the study, take responsibility for the integrity of the data and the accuracy of the data analysis. Y.Q.H. and Y.Z. contribute equally to this work.Concept and design: Y.Q.H.,Y.D.X. and Y.Y.Acquisition, analysis, or interpretation of data: Y.Q.H., Y.D.X.,X.Y.W., Q.Q.M, Z.Y.Z., X.J., L.W., T.Y.W., Y.Y., and H.W.Drafting of the article: Y.Q.H.,Y.Z. Y.D.X. and Y. Y.Critical revision of the article for important intellectual content: All authors.Statistical analysis: Y.Q.H.Obtained funding: Y.Y., L.P.H. and H.W.Administrative, technical, or material support: X.J, L.W.Supervision: H.W. and Y. Y.

Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethical approval and consent to participate

The UK Biobank received ethical approval from the North West Multi-center Research Ethics Committee (Approved Research ID: 89871, Approval date September 20th 2022). All participants gave written informed consent before enrollment in the study, which was conducted in accordance with the principles of the Declaration of Helsinki. The National Center for Health Statistics and Ethics Review Board approved the protocol for NHANES, and all participants provided written informed consent. Research ethics approval was obtained from the Center for Disease Control and Prevention of the Pudong New Area, Shanghai, China. Each participant provided a written consent. All participants were informed and agreed to participate in this study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]State Key Laboratory of Systems Medicine for Cancer, Center for Single-Cell Omics, School of Public Health, Shanghai Jiao Tong University School of Medicine, Shanghai, China
[2]Pudong New District Center for Disease Control and Prevention of Shanghai, Shanghai, China
[3]Pudong Preventive Medicine Research Institute, Fudan University, Shanghai, China
[4]Shanghai Frontiers Science Center of Degeneration and Regeneration in Skeletal System, Shanghai Key Laboratory of Orthopaedic Implants, Department of Orthopaedic Surgery, Shanghai Jiao Tong University of Medicine Affiliated Ninth People's Hospital, Shanghai, China
[5]Division of Gastroenterology and Hepatology, NHC Key Laboratory of Digestive Diseases, Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai Institute of Digestive Disease, Shanghai, China
[6]Bloomberg School of Public Health, Johns Hopkins University, Baltimore, USA
[7]Community Health Center of Huaqiao Town, Suzhou, China

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