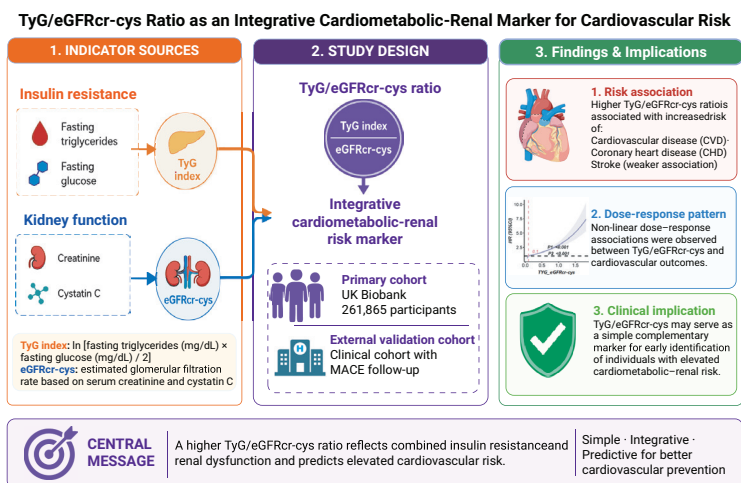


# Combining Insulin Resistance and Renal Function to Predict Cardiovascular Events: A Multicenter Cohort Study

## Graphical abstract



## Highlights

- TyG/eGFRcr-cys integrates insulin resistance and renal function into one marker.
- In 261,865 UK Biobank participants, higher TyG/eGFRcr-cys predicted increased CVD and CHD risk.
- Restricted cubic splines showed non-linear associations between TyG/eGFRcr-cys and cardiovascular outcomes.
- Associations were supported by sensitivity analyses and external validation in an independent clinical cohort.
- TyG/eGFRcr-cys may help identify individuals with unfavorable cardiometabolic-renal profiles.

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## In brief

This multicenter cohort study shows that a higher TyG/eGFRcr-cys ratio, integrating insulin resistance and renal function, is associated with increased cardiovascular disease risk, particularly coronary heart disease. Findings from UK Biobank were supported by sensitivity analyses and external validation, suggesting TyG/eGFRcr-cys as a simple complementary cardiometabolic-renal risk marker.

# Combining Insulin Resistance and Renal Function to Predict Cardiovascular Events: A Multicenter Cohort Study

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## Abstract

**Background:** Insulin resistance (IR) and chronic kidney disease (CKD) are independent risk factors for cardiovascular disease (CVD). The triglyceride-glucose (TyG) index is recognized as a convenient marker for IR, while the estimated glomerular filtration rate based on both creatinine and cystatin C (eGFRcr-cys) is commonly used to evaluate kidney function. Therefore, the TyG:eGFRcr-cys ratio is introduced with the aim of obtaining a more effective predictor for CVD risk.

**Method:** This prospective cohort analysis included 261,865 UK Biobank participants with available information. Cox proportional hazards models were used to evaluate the associations of TyG, eGFRcr-cys, and the TyG:eGFRcr-cys ratio with incident CVD. Restricted cubic splines for model fitting with three knots placed at the 10<sup>th</sup>, 50<sup>th</sup>, 90<sup>th</sup> percentiles were used to determine the non-linear relationship between the TyG:eGFRcr-cys ratio and CVD. Furthermore, subgroup and sensitivity analyses were performed to illustrate the disparate associations across diverse groups and to reinforce the conclusions drawn, respectively. An independent single-center clinical cohort was assembled from the First Affiliated Hospital of Zhengzhou University for external validation by enrolling consecutive patients between 2018 and 2020 with baseline TyG index and eGFRcr-cys measurements and up to 4 years of follow-up. External validation with major adverse cardiovascular events was further performed as the outcome and observed consistent dose–response associations and robust risk stratification for the TyG:eGFRcr-cys ratio.

**Result:** Following extensive covariate adjustment, the hazard ratios [HRs] (95% confidence intervals [CIs]) for total CVD across increasing quartiles of the TyG:eGFRcr-cys ratio, with the lowest quartile (Q1) as the reference, were 1.15 (1.10–1.21) for Q2 versus Q1, 1.17 (1.12–1.23) for Q3 versus Q1, and 1.24 (1.18–1.30) for Q4 versus Q1, respectively, for the TyG:eGFRcr-cys ratio. In addition, each standard deviation increase in the TyG:eGFRcr-cys ratio was associated with a higher risk of CVD, coronary heart disease, and stroke, corresponding to estimated increases of 249% [HR, 3.49; 95% CI, 2.94–4.15], 250% [HR, 3.50; 95% CI, 2.92–4.20], and 165% [HR, 2.65; 95% CI, 1.80–3.90], respectively, in the fully adjusted models. The non-linear relationship between the TyG:eGFRcr-cys ratio and CVD (*P*-value for the overall model < 0.001 and *P*-value for the non-linear model < 0.001) indicated that the CVD risk increased as the TyG:eGFRcr-cys ratio increased. Subgroup analysis results suggested that these associations were more pronounced in White individuals and females.

**Conclusion:** As the TyG:eGFRcr-cys ratio increased, the risk of CVD also increased with a higher likelihood in females and White individuals.

## Keywords

Cardiac & cardiovascular systems, medicine, medicine, endocrinology & metabolism.

## Introduction

Within the realm of non-communicable diseases, cardiovascular diseases (CVDs) are the leading cause of mortality, accounting for an estimated 19.8 million deaths globally in 2022, representing approximately 32% of all global deaths [1]. Among the 17 million premature deaths (< 70 years of age) caused by non-communicable diseases in 2019, 38% were attributed to CVDs, accounting for 330 million years of life lost worldwide [2]. Moreover,

the number of deaths from CVD and the years of life lost due to CVD have shown a steady increase over the past 3 decades [3–5]. However, most CVDs are preventable through management of behavioral and environmental risk factors, underscoring the importance of early detection.

Insulin resistance (IR) is characterized by reduced cellular sensitivity and responsiveness to insulin. This condition manifests as decreased glucose uptake by tissues and impaired suppression of hepatic glucose production, contributing to the onset and identification of CVD in general

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and diabetic populations [6]. Furthermore, IR is associated with an elevated risk of obesity, hypertension, dyslipidemia, impaired glucose tolerance, and metabolic syndrome, all of which have been established as independent risk factors for CVD. The hyperinsulinemia euglycemic clamp (HIEC) technique, initially proposed by De Fronzo in 1979, continues to represent the gold standard for measurement of IR [7]. However, the invasive and costly nature of the HIEC technique has substantially restricted the application to research settings rather than routine clinical practice. Consequently, the introduction of various non-insulin-based surrogates for IR has greatly simplified the testing process. The triglyceride-glucose (TyG) index, proven to be a more valuable indicator than the homeostatic model assessment of insulin resistance (HOMA-IR) index, is calculated using the following formula:  $\text{Ln} [\text{triglycerides (mg/dL)} \times \text{glucose (mg/dL)} / 2]$  [7]. The TyG index is a more cost-effective, convenient, and easily obtainable method than the HOMA-IR index [8]. Moreover, the TyG index, which is derived from fasting triglyceride and glucose levels, addresses the limitations of the HOMA-IR index, which cannot be applied to diabetic patients undergoing insulin therapy [9]. The predictive value of the TyG index for CVD and the poor prognosis has been validated by numerous studies [10–17]. In addition, the TyG index serves as an effective tool for identifying asymptomatic individuals at an elevated risk of developing atherosclerosis [18]. Furthermore, the TyG index has proven efficacy in identifying patients at increased risk of in-stent restenosis (ISR) after percutaneous coronary intervention (PCI) [19]. In conclusion, the collective findings indicate that the TyG index has considerable potential for use in the diagnosis and monitoring of diverse CVDs. However, previous studies have shown that the TyG index has limited specificity (45.0%) for diagnosing IR [8]. The predictive utility of the TyG index for CVD incidence across various populations is a subject of ongoing debate. Furthermore, most studies have evaluated the TyG index solely at baseline, thus neglecting the potential temporal fluctuations in the TyG index and associated CVD risk. Despite the undeniable advantages of the TyG index, concerns remain regarding the limited specificity and applicability across diverse populations. Current evidence indicates that additional research is necessary to validate the association between the TyG index and CVD risk. Chronic kidney disease (CKD), which is characterized by a reduced glomerular filtration rate (GFR) or elevated albuminuria, is regarded as an independent risk factor for CVD and a coronary artery disease (CAD) equivalent for all-cause mortality [20]. According to the guidelines established by the Kidney Disease Improving Global Outcomes (KDIGO) initiative, a  $\text{GFR} < 60 \text{ mL/min/1.73 m}^2$  is indicative of CKD [21]. Given the aforementioned evidence, it could be posited that a reduction in the estimated glomerular filtration rate based on both creatinine and cystatin C (eGFRcr-cys) significantly contributes to the development of CVD owing to the shared pathogenic mechanisms between CKD and CVD [20]. A considerable body of evidence from extensive cohort studies has established a significant association between sustained reductions in the eGFRcr-cys and an increased risk of developing CAD [22]. However, the ability of the eGFRcr-cys to predict CVD risk depends on various factors, such as the

presence of co-morbidities and the specific equation used to calculate the eGFRcr-cys [23]. Moreover, the effectiveness of the eGFRcr-cys as an independent predictor has been shown to be affected by morphologic abnormalities [24].

Therefore, the TyG:eGFRcr-cys ratio was introduced with the aim of obtaining a more effective predictor for CVD risk. The objective of this study was to examine the relationship between TyG, the TyG:eGFRcr-cys ratio, and the eGFRcr-cys and the risk of developing CVD. Cox proportional hazards analysis was used to assess the effect of the TyG:eGFRcr-cys ratio on CVD risk, while restricted cubic splines (RCS) were utilized to evaluate the linear association between each factor and CVD risk. Subgroup and sensitivity analyses were subsequently performed to confirm the robustness of our findings. The findings will contribute to a more comprehensive understanding of CVD risk assessment.

## Methods

### Study design and population

This study included a primary analysis based on the UK Biobank and an external validation using an independent single-center clinical cohort.

**Primary cohort (UK Biobank).** The UK Biobank is a prospective cohort involving 500,000 participants 40–69 years of age who were recruited between 2006 and 2010 from 22 assessment centers across England, Wales, and Scotland. The participants provided written informed consent, completed questionnaires and interviews, underwent physical measurements, and provided biological samples, including blood collected under standardized quality-control procedures, at baseline. A total of 261,865 participants were included after excluding participants with CVD at baseline ( $n = 22,949$ ) and participants with missing exposures ( $n = 71,731$ ) or covariates ( $n = 145,821$ ).

**External validation cohort.** An independent clinical cohort was assembled from the Department of Vascular Surgery (the First Affiliated Hospital of Zhengzhou University, Zhengzhou, China) by enrolling consecutive patients between January 2018 and December 2020 to externally validate the UK Biobank findings. A total of 1798 patients were initially included in the external cohort. Eligibility assessment and exclusions were aligned with the eligibility assessment and exclusions used in the UK Biobank analysis when feasible. Patients with available baseline measurements of the TyG index and the eGFRcr-cys were included and baseline data were collected at the index hospitalization. The external validation endpoint was major adverse cardiovascular events (MACE), which is defined as fatal or non-fatal coronary heart disease (CHD) or stroke. Outcomes were identified using diagnosis codes from hospital records and death registries. Participants were followed for up to 4 years from the index date to the first event or the last follow-up, whichever came first. Event-free participants were censored at the last follow-up evaluation. A total of 328 participants were included in the complete-case dataset used

for the fully adjusted external validation analysis, among whom 88 developed MACE during follow-up, corresponding to an event rate of 26.8%. This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee of the First Affiliated Hospital of Zhengzhou University (No. 2026-KY-0398).

## Assessment of the TyG index and the TyG:eGFRcr-cys ratio

Peripheral venous blood samples were collected from all participants at study onset. The collection procedures used in the UK Biobank study were subsequently validated [25]. The duration of fasting and the number of hours elapsed since the previous meal were documented. Blood samples were analyzed within 24 h of collection by the UK Biobank using standard hematologic tests. Coefficients of variation for triglycerides and glucose were determined to be < 3% and < 2%, respectively, indicating high precision and accuracy in the testing process. The TyG index was calculated using the following formula:  $\ln [\text{triglycerides (mg/dL)} \times \text{glucose (mg/dL)} / 2]$  [26]. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine-cystatin C equation [26, 27]. The TyG:eGFRcr-cys ratio was calculated as the TyG index divided by the eGFRcr-cys (mL/min/1.73 m<sup>2</sup>).

## Assessment of covariates

Baseline characteristics were collected via a touch-screen questionnaire gathering data on age, race, gender, ethnicity, Townsend Deprivation Index, employment, current smoking status, and baseline medication use (aspirin, insulin, and antihypertensive and cholesterol-lowering medications). The Townsend Deprivation Index is a composite measure of socioeconomic deprivation based on factors, such as unemployment, non-car ownership, non-home ownership, and household overcrowding. The Townsend Deprivation Index is derived from the residential postcode with a negative value representing high socioeconomic status [28]. Total metabolic equivalent (MET) minutes per week were calculated based on a modified International Physical Activity Questionnaire (IPAQ) [29]. Moreover, baseline data, including diastolic blood pressure (DBP), systolic blood pressure (SBP), and low-density lipoprotein-cholesterol (LDL-C) and high-density lipoprotein-cholesterol (HDL-C) levels, were obtained in accordance with established protocols.

## Assessment of outcomes

As with the primary outcome of the study, incident CVD was defined as a fatal or non-fatal case of CHD or stroke. CHD and stroke were further considered as secondary outcomes in this study. All outcomes were diagnosed by means of diagnosis codes, which were obtained from registered hospital admissions and death registries. The incidence of CHD was defined according to the I20-I25 codes of the 10<sup>th</sup> revision

of the International Classification of Diseases (ICD-10). The incidence of stroke was defined by ICD-10 codes I60–I64.

## Statistical analyses

The characteristics of the participants are expressed as mean values (standard deviation [SD]) for continuous variables, whereas frequencies (percentages) were used for categorical variables. Participants were stratified into four groups according to the TyG index, TyG:eGFRcr-cys ratio, and eGFRcr-cys quartiles. A chi-squared test for categorical variables was used to ascertain the existence of discrepancies between the quartiles. ANOVA was applied to continuous variables. Cox proportional hazard models were used to elucidate the relationships between the TyG index, the TyG:eGFRcr-cys ratio, CVD, CHD, and stroke risk, deriving hazard ratios (HRs) and 95% confidence intervals (CIs) of higher quartiles in relation to the lowest quartiles, as used in previous studies [30–32]. Three models with increasing levels of adjustment were fitted to assess potential confounders of CVD: Model 1 was adjusted for age, race, gender, employment status, educational level, and Townsend Deprivation Index; Model 2 was further adjusted for alcohol intake, body mass index, smoking status, and MET; and Model 3 was further adjusted for cholesterol-lowering medication, antihypertensive medication, and insulin treatment. RCS models were used to determine the non-linear associations between TyG index, the TyG:eGFRcr-cys ratio, and the eGFRcr-cys with CVD, CHD, and stroke. A parsimonious 3-knot specification was applied for the primary analysis in the UK Biobank cohort with knots placed at the 10<sup>th</sup>, 50<sup>th</sup>, and 90<sup>th</sup> percentiles, whereas 4 knots were used in the external validation cohort to provide greater flexibility in the smaller clinical sample, as used in previous studies [33–35].

Subgroup and sensitivity analyses were conducted to further substantiate our findings. An assessment was performed to determine whether age, gender, race, education, employment status, Townsend Deprivation Index, current smoking status, alcohol consumption habits, body mass index, and MET could serve as potential effect modifiers in the context of subgroup analysis. An adjustment for SBP, glycosylated hemoglobin (HbA1C), C-reactive protein (CRP), and total cholesterol level was carried out for sensitivity analysis to confirm the robustness of the results. In addition, individuals who developed CVD within the first 3 years of follow-up and were lost to follow-up were excluded to minimize potential reverse causality.

## External validation statistical analysis

External validation used the same exposure definitions as the primary analysis. The TyG index, the eGFRcr-cys, and the TyG:eGFRcr-cys ratio were analyzed as continuous variables and results were reported per 1-SD increase. Associations with incident MACE were assessed using Cox proportional hazards models with the fully adjusted Model 3. Analyses were performed in complete cases. Non-linear relationships

were explored using RCS (4 knots) within Model 3. *P* values for the overall association (P1) and non-linearity (P2) were obtained from Wald tests and plots highlighted the 25<sup>th</sup> and 75<sup>th</sup> percentiles. Kaplan–Meier curves were generated by the TyG:eGFRcr-cys ratio quartiles and compared using the log-rank test.

## Dynamic network biomarker analysis

Participants were divided into four groups according to quartiles of the TyG:eGFRcr-cys ratio (Q1–Q4) to further explore potential transition-related dynamic changes across the TyG:eGFRcr-cys ratio-based risk strata and dynamic network biomarker (DNB) analysis was performed across these ordered groups. Transitions may occur abruptly and non-linearly in complex disease progression rather than through a gradual linear process. A critical transition stage is considered an intermediate state between a relatively stable stage and a more advanced stage of disease progression within this framework. DNB analysis was used as an exploratory approach to detect potential transition-related signals across the four TyG:eGFRcr-cys ratio-based risk groups.

Let *M* denote a  $\mu \times \nu$  data matrix, where  $\mu$  represents the number of selected variables and  $\nu$  represents the number of participants. After stratification into *K* ordered groups (*K* = 4 in the present study), the full matrix can be represented as follows:

$$M = [M_1 | M_2] \cdots [M_K],$$

where  $M_k$  denotes the submatrix corresponding to the *k*-th TyG:eGFRcr-cys ratio quartile group and  $\nu_k$  denotes the number of participants in that group. For each group *k*, Pearson correlation coefficients were calculated for all variable pairs. A correlation network was constructed and partitioned into highly connected modules by optimizing network modularity based on these pairwise correlations. Each module therefore represented a cluster of variables showing relatively strong internal connectivity.

For each module *h* within group *k*, the following DNB-related quantities were calculated:

Within-module fluctuation

$$F_h = \text{Avg}(\text{SD}(z)), z \in h,$$

where  $\text{SD}(z)$  denotes the standard deviation of variable *z* within the module.

Within-module correlation

$$R_h = \text{Avg}(|\text{cor}(z_a, z_b)|), z_a, z_b \in h,$$

where  $\text{cor}(z_a, z_b)$  denotes the Pearson correlation coefficient between two variables within the same module.

Between-module correlation

$$B_h = \text{Avg}(|\text{cor}(z_a, z_c)|), z_a \in h, z_c \notin h,$$

where  $z_c$  denotes a variable outside the module.

The DNB composite index for module *h* was then defined as:

$$D_h = \frac{R_h \times F_h}{B_h}$$

In this formulation,  $F_h$  corresponds to the DNB SD,  $R_h$  corresponds to the intra-module Pearson correlation coefficient (PCC),  $B_h$  corresponds to the out-of-module Pearson correlation coefficient (PCCo), and  $D_h$  corresponds to the DNB composite index. For each quartile group, the module with the highest  $D_h$  value was defined as the biomodule and the corresponding SD, PCC, PCCo, and composite index were used to characterize transition-related network instability in that group. Higher composite index values were interpreted as indicating stronger transition-related signals.

The DNB scores were evaluated using bootstrap resampling with 1000 iterations to further assess robustness. The DNB findings were interpreted cautiously because this analysis was exploratory and intended to characterize potential transition-related changes across the TyG:eGFRcr-cys ratio-based risk strata rather than to establish causal relationships.

## Results

### Population characteristics

A total of 261,865 participants who met the inclusion criteria were recruited in the current study. Participants were stratified into quartiles based on the TyG:eGFRcr-cys ratio, TyG index, and the eGFRcr-cys, as detailed in **Tables 1** and **S1, S2**, respectively. Of the 261,865 participants, 138,453 (52.87%) were women, 249,599 (95.32%) were White, and the mean (SD) age at baseline was 55.25 (8.06) years. Furthermore, 32,906 participants (12.57%) were receiving cholesterol-lowering medications, 42,524 (16.24%) were on antihypertensive medications, and 2067 (0.79%) were using insulin therapy. A higher TyG index and TyG:eGFRcr-cys ratio were correlated with older age, White ethnicity, male gender, elevated body mass index (BMI), lower educational attainment, smoking status, a higher Townsend Deprivation Index, indicating greater socioeconomic deprivation, unemployment, alcohol consumption, lower METs, use of cholesterol-lowering and antihypertensive medications, insulin usage, higher blood pressure, and serum levels of total cholesterol, HDL-C, LDL-C, and CRP, and a lower eGFRcr-cys (**Figure 1**).

### Associations between the TyG index and the TyG:eGFRcr-cys ratio with CVD

Elevated levels of the TyG index and the TyG:eGFRcr-cys ratio have been linked to an increased risk of CVD, CHD, and stroke based on an unadjusted COX regression analysis. This association was shown to persist in the model adjusted for age, race, gender, employment status, educational level, and level of deprivation (referred to here as Model 1). Following extensive covariate adjustment, the

**Table 1** Characteristics of the study population according to the TyG:eGFRcr-cys ratio quartiles

	Level	Q1	Q2	Q3	Q4	P
<b>n</b>		<b>65,467</b>	<b>65,466</b>	<b>65,466</b>	<b>65,466</b>	
Age (mean (SD))		49.25 (6.55)	54.99 (7.43)	57.45 (7.45)	59.31 (6.99)	< 0.001
Race (%)	White	60,527 (92.45)	62,697 (95.77)	63,129 (96.43)	63,246 (96.61)	< 0.001
	Others	4940 (7.55)	2769 (4.23)	2337 (3.57)	2220 (3.39)	
Gender (%)	Male	23,221 (35.47)	30,849 (47.12)	34,481 (52.67)	34,861 (53.25)	< 0.001
	Female	42,246 (64.53)	34,617 (52.88)	30,985 (47.33)	30,605 (46.75)	
BMI [mean (SD)]		25.59 (4.52)	26.86 (4.58)	27.59 (4.46)	28.19 (4.47)	< 0.001
Education (%)	College or university degree	30,422 (46.47)	28,080 (42.89)	26,508 (40.49)	25,053 (38.27)	< 0.001
	Others	35,045 (53.53)	37,386 (57.11)	38,958 (59.51)	40,413 (61.73)	
Smoker (%)	Current	7411 (11.32)	6536 (9.98)	5712 (8.73)	4688 (7.16)	< 0.001
	Ever	29,850 (45.60)	32,214 (49.21)	33,660 (51.42)	34,314 (52.41)	
	Never	28,206 (43.08)	26,716 (40.81)	26,094 (39.86)	26,464 (40.42)	
Deprivation [mean (SD)]		16.58 (13.39)	15.39 (12.54)	14.99 (12.28)	14.92 (12.22)	< 0.001
Employment (%)	Employed	53,805 (82.19)	44,351 (67.75)	38,359 (58.59)	33,716 (51.50)	< 0.001
	Unemployed	11,662 (17.81)	21,115 (32.25)	27,107 (41.41)	31,750 (48.50)	
Alcohol consumption (%)	Frequently	29,689 (45.35)	32,033 (48.93)	32,366 (49.44)	30,858 (47.14)	< 0.001
	Occasionally	31,496 (48.11)	29,515 (45.08)	29,294 (44.75)	30,403 (46.44)	
	Never	4282 (6.54)	3918 (5.98)	3806 (5.81)	4205 (6.42)	
MET (%)	Low	11,195 (17.10)	11,637 (17.78)	12,171 (18.59)	12,529 (19.14)	< 0.001
	Moderate	34,054 (52.02)	34,282 (52.37)	33,956 (51.87)	34,046 (52.01)	
	High	20,218 (30.88)	19,547 (29.86)	19,339 (29.54)	18,891 (28.86)	
Cholesterol-lowering medication (%)	Yes	3082 (4.71)	6864 (10.48)	9827 (15.01)	13,133 (20.06)	< 0.001
	No	62,385 (95.29)	58,602 (89.52)	55,639 (84.99)	52,333 (79.94)	
Antihypertensive medication (%)	Yes	4875 (7.45)	9144 (13.97)	12,022 (18.36)	16,483 (25.18)	< 0.001
	No	60,592 (92.55)	56,322 (86.03)	53,444 (81.64)	48,983 (74.82)	
Insulin (%)	Yes	462 (0.71)	420 (0.64)	483 (0.74)	702 (1.07)	< 0.001
	No	65,005 (99.29)	65,046 (99.36)	64,983 (99.26)	64,764 (98.93)	
DBP [mean (SD)]		79.92 (10.12)	82.30 (10.04)	83.16 (9.95)	83.23 (9.98)	< 0.001
SBP [mean (SD)]		129.92 (17.01)	136.62 (17.84)	139.26 (18.22)	140.25 (18.22)	< 0.001
TC [mean (SD)]		210.70 (37.95)	224.09 (41.42)	226.88 (43.59)	225.72 (44.97)	< 0.001
HDL-C [mean (SD)]		60.82 (15.13)	57.58 (14.64)	54.83 (14.09)	53.38 (14.09)	< 0.001
LDL-C [mean (SD)]		129.31 (29.17)	140.62 (31.80)	143.10 (33.12)	142.19 (33.93)	< 0.001
CRP [mean (SD)]		2.02 (3.99)	2.30 (4.00)	2.42 (3.82)	2.68 (4.20)	< 0.001
HbA1C [mean (SD)]		33.91 (4.85)	35.22 (5.55)	36.11 (6.42)	36.77 (6.90)	< 0.001
TyG [mean (SD)]		8.26 (0.43)	8.64 (0.47)	8.86 (0.53)	8.97 (0.55)	< 0.001
eGFRcr-cys [mean (SD)]		105.07 (6.17)	97.22 (5.47)	90.49 (5.92)	75.70 (9.98)	< 0.001

Continuous variables are expressed as the mean (SD). Categorical variables are expressed as a frequency (percentage).

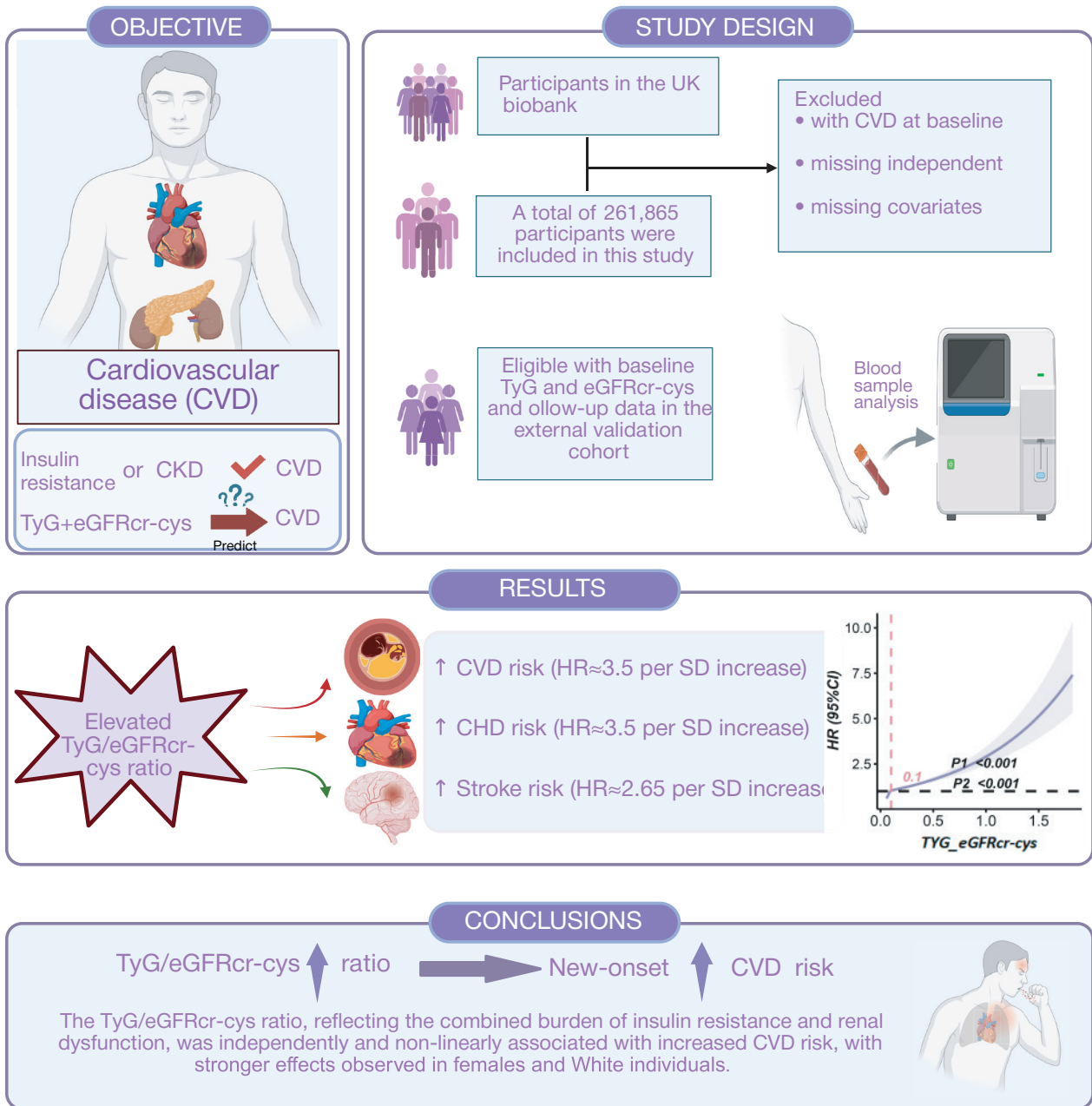
HRs (95% CIs) for total CVD in the highest versus lowest quartiles were 1.15 (1.1–1.21), 1.17 (1.12–1.23), and 1.24 (1.18–1.3), respectively, for the TyG:eGFRcr-cys ratio. The HRs (95% CIs) for CHD in the highest versus lowest quartiles were 1.18 (1.12–1.24), 1.23 (1.17–1.3), and 1.3 (1.23–1.37) for the TyG:eGFRcr-cys ratio. The HRs (95% CIs) in the highest versus lowest quartiles for stroke were 1.04 (0.95–1.15), 0.97 (0.88–1.07), and 1.05 (0.96–1.16) for the TyG:eGFRcr-cys ratio (**Table 2**).

In addition, each incremental SD increase in the TyG:eGFRcr-cys ratio was associated with higher risks of CVD, CHD, and stroke in the fully adjusted models (Model 3), corresponding to estimated increases of 249% [HR, 3.49; 95% CI, 2.94–4.15], 250% [HR, 3.50; 95% CI, 2.92–4.20], and 165% [HR, 2.65; 95% CI, 1.80–3.90], respectively (**Figure 2A**). Similarly, each incremental SD increase in the TyG index was linked to a notable rise in the risk of CVD, CHD, and stroke with estimated increases of 20% [HR (95% CI): 1.2 (1.17–1.23)], 24% [HR (95% CI): 1.24 (1.21–1.28)],

and 4% [HR (95% CI): 1.04 (0.99–1.1)], respectively, in fully adjusted models (Model 3; **Figure 2B**). A similar conclusion was drawn by Li et al. (2022) in a study involving a Chinese population [36]. Conversely, each incremental SD increase in the eGFRcr-cys was linked to a significant reduction in the risk of CVD, CHD, and stroke with estimated decreases of 3% [HR (95% CI): 0.97 (0.96–0.98)], 3% [HR (95% CI): 0.97 (0.96–0.98)], and 2% [HR (95% CI): 0.98 (0.96–1)], respectively, in fully adjusted models (Model 3; **Figure 2C**). It is noteworthy that similar conclusions were drawn by Cui et al. (2023) in a Chinese population [37].

### RCS analysis between the TyG index, the TyG:eGFRcr-cys ratio, and the eGFRcr-cys

RCS analysis was used to investigate the non-linear relationships between the TyG:eGFRcr-cys ratio, the TyG index,



**Figure 1** TyG:eGFRcr-cys ratio and cardiovascular risk: Evidence from 261,865 participants in the UK Biobank.

and the eGFRcr-cys in relation to CVD, CHD and stroke, as illustrated in **Figure 3**. Non-linear associations between the TyG:eGFRcr-cys ratio and CVD ( $P$ -value for the overall model  $< 0.001$  and  $P$ -value for the non-linear model  $< 0.001$ ) as well as CHD ( $P$ -value for the overall model  $< 0.001$  and  $P$ -value for the non-linear model  $< 0.001$ ) were observed in multivariable-adjusted RCS analyses (**Figure 3A**). Notably, the inflection points and the overall trend of the curves were consistent. Although a non-linear association between the TyG:eGFRcr-cys ratio and stroke was not statistically significant ( $P$ -value for the overall model  $< 0.001$  and  $P$ -value for the non-linear model = 0.075), the inflection point (0.1) remained evident (**Figure 3A**). Furthermore, it was noted that no non-linear relationship exists between the TyG index and CVD ( $P$ -value for the overall model  $< 0.001$  and

$P$ -value for the non-linear model = 0.747) or CHD ( $P$ -value for the overall model  $< 0.001$  and  $P$ -value for the non-linear model = 0.084), a finding consistent with the results reported by Zhang et al. (2024) in non-alcoholic fatty liver disease (NAFLD) populations [38]. However, Liang et al. (2024) demonstrated a non-linear association between the TyG index and CVD in the U.S. population aged  $> 60$  years [39]. All findings indicated a positive correlation between an elevated TyG index and a higher risk of developing CVD. In addition, a U-shaped curve was noted between the eGFRcr-cys and the risks of CVD, CHD, and stroke ( $P$ -value for the overall model  $< 0.001$  and  $P$ -value for the non-linear model  $< 0.001$ ; **Figure 3C**). As the eGFRcr-cys decreased, the risk of CVD, CHD, and stroke exhibited a gradual decline, reaching minimum eGFRcr-cys values of 82, 84, and 83.5 mL/min/1.73 m<sup>2</sup>,

**Table 2** Prospective associations between the TyG:eGFRcr-cys ratio and risk of cardiovascular diseases in the UK Biobank

Characteristics	n/N	HR_CI_1	P_value_1	HR_CI_2	P_value_2	HR_CI_3	P_value_3
1 CVD							
2 Quartile 1 (lowest)	2866/65,467	Reference	-	Reference	-	Reference	-
3 Quartile 2	5348/65,466	1.2 (1.15–1.26)	< 0.001	1.13 (1.08–1.18)	< 0.001	1.15 (1.1–1.21)	< 0.001
4 Quartile 3	6964/65,466	1.29 (1.23–1.35)	< 0.001	1.16 (1.1–1.21)	< 0.001	1.17 (1.12–1.23)	< 0.001
5 Quartile 4 (highest)	8559/65,466	1.44 (1.37–1.51)	< 0.001	1.26 (1.2–1.32)	< 0.001	1.24 (1.18–1.3)	< 0.001
6 CHD							
7 Quartile 1 (lowest)	2233/65,467	Reference	-	Reference	-	Reference	-
8 Quartile 2	4256/65,466	1.24 (1.18–1.31)	< 0.001	1.16 (1.1–1.22)	< 0.001	1.18 (1.12–1.24)	< 0.001
9 Quartile 3	5710/65,466	1.37 (1.3–1.45)	< 0.001	1.22 (1.15–1.28)	< 0.001	1.23 (1.17–1.3)	< 0.001
10 Quartile 4 (highest)	7047/65,466	1.54 (1.46–1.62)	< 0.001	1.32 (1.25–1.39)	< 0.001	1.3 (1.23–1.37)	< 0.001
11 STROKE							
12 Quartile 1 (lowest)	735/65,467	Reference	-	Reference	-	Reference	-
13 Quartile 2	1323/65,466	1.06 (0.97–1.17)	0.2	1.03 (0.94–1.13)	0.57	1.04 (0.95–1.15)	0.37
14 Quartile 3	1588/65,466	1.01 (0.92–1.11)	0.83	0.96 (0.87–1.05)	0.35	0.97 (0.88–1.07)	0.55
15 Quartile 4 (highest)	2025/65,466	1.14 (1.03–1.25)	0.008	1.06 (0.96–1.17)	0.23	1.05 (0.96–1.16)	0.29

Model 1: adjusted for age, race, gender, employment status, educational level, and level of deprivation.

Model 2: adjusted for age, race, gender, employment status, educational level, level of deprivation, alcohol consumption, BMI, smoking status, and MET.

Model 3: further adjusted for age, race, gender, employment status, educational level, level of deprivation, alcohol consumption, BMI, smoking status, MET, cholesterol-lowering medication (yes or no), antihypertensive medication (yes or no), and insulin (yes or no).

respectively. Nevertheless, the standard definition of CKD is an eGFRcr-cys < 60 mL/min/1.73 m<sup>2</sup>.

## Subgroup analysis

A positive correlation between the TyG:eGFRcr-cys ratio and the risk of developing CVD persisted across most strata in the subgroup analysis. However, significant interactions were identified within the age ( $P$  value for interaction = 0.002), gender ( $P$  value for interaction = 0.003), race ( $P$  value for interaction = 0.016), employment status ( $P$  value for interaction = 0.002), and deprivation ( $P$  value for interaction < 0.001) subgroup (Table 3).

## Sensitivity analysis

A sensitivity analysis was performed to evaluate the robustness of the primary findings by incorporating additional covariates, including SBP, HbA1C, CRP, and total cholesterol, into the model. The results remained consistent, indicating that the observed effect was robust to the inclusion of these potential confounders (Figure 4A). Participants who developed the disease or were lost to follow-up within 3 years of baseline were further excluded to evaluate the effect on the results. Excluding these participants did not significantly alter the results, suggesting that the results are robust (Figure 4B).

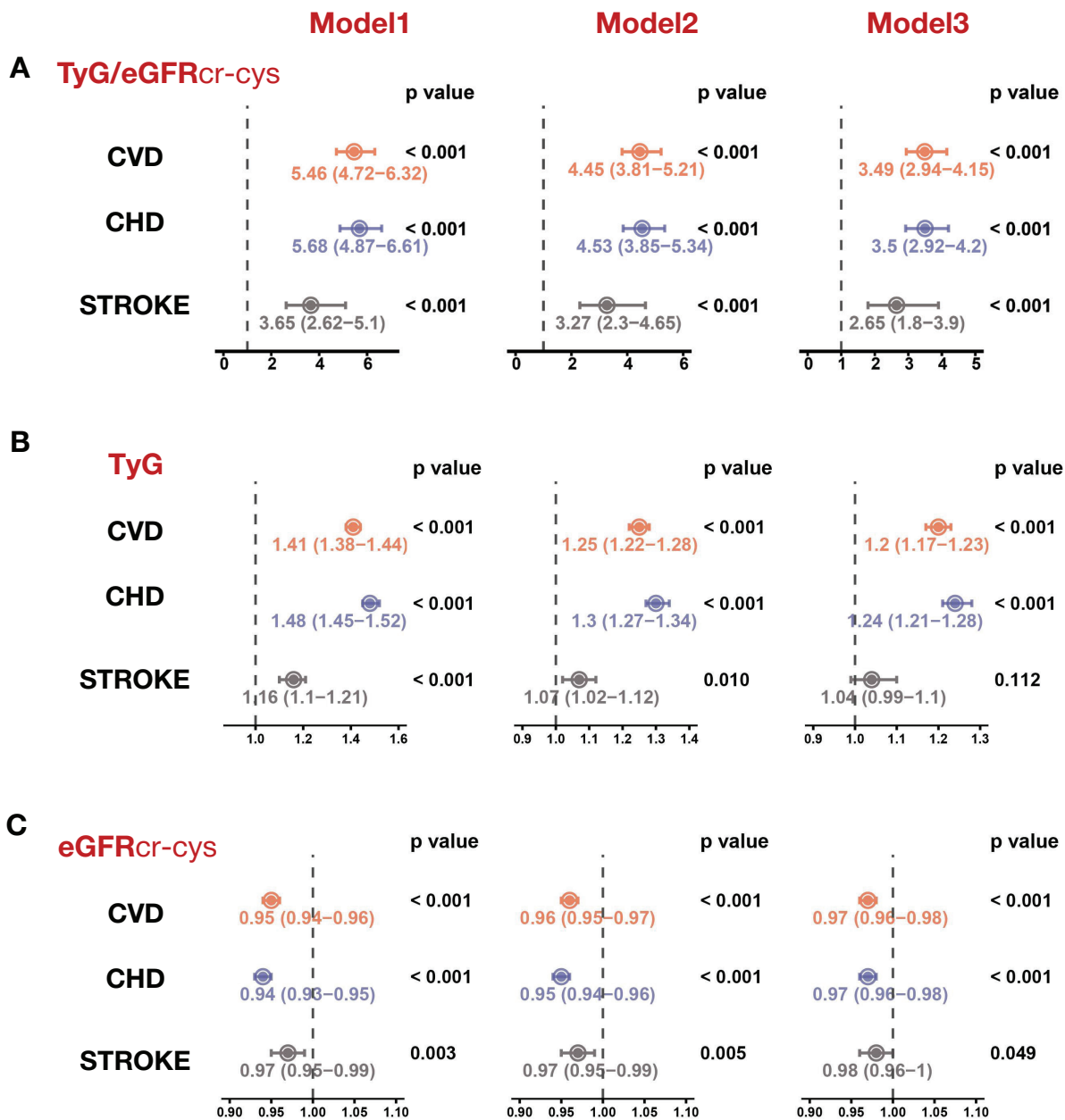
## External validation

RCS analyses in the external cohort showed a dose–response association between the TyG:eGFRcr-cys ratio and incident

MACE (Figure 5A) with a similar positive pattern for the TyG index (Figure 5B), whereas a higher eGFRcr-cys was associated with a lower risk of MACE (Figure 5C). The TyG:eGFRcr-cys ratio remained significantly associated with MACE in the fully adjusted model (HR per 1-SD increase, 6.04; 95% CI, 2.12–17.19;  $P$  < 0.001) with the TyG index (HR, 2.51; 95% CI, 1.82–3.48;  $P$  < 0.001) and an inverse association for the eGFRcr-cys (HR, 0.61; 95% CI, 0.46–0.81;  $P$  < 0.001; Figure 5D). Kaplan–Meier curves further demonstrated clear separation in event-free survival across the TyG:eGFRcr-cys ratio quartiles (log-rank  $P$  < 0.001; Figure 5E).

## Dynamic network biomarker analysis suggested a potential transition stage during CVD risk progression

Participants were divided into four groups (Q1–Q4) to further explore the dynamic progression pattern across the TyG/eGFRcr-cys ratio-based risk strata and DNB analysis was performed to determine the potential transition stage preceding overt CVD progression. The conceptual disease trajectory followed a non-linear phase-transition pattern, shifting from a relatively stable state to a pre-exacerbation stage, then to a more advanced stage (Figure 6A). The DNB composite index increased from Q1 to Q3, then declined in Q4 with the highest value in Q3 (Figure 6B). The DNB SD showed a progressive increase across the four groups and reached a maximum in Q4 (Figure 6C). In contrast, both the DNB PCC and DNB PCCo increased from Q1 to Q3, then decreased in Q4 with peaks occurring at Q3 (Figure 6D–E). Taken together, although individual DNB components exhibited slightly different trajectories,



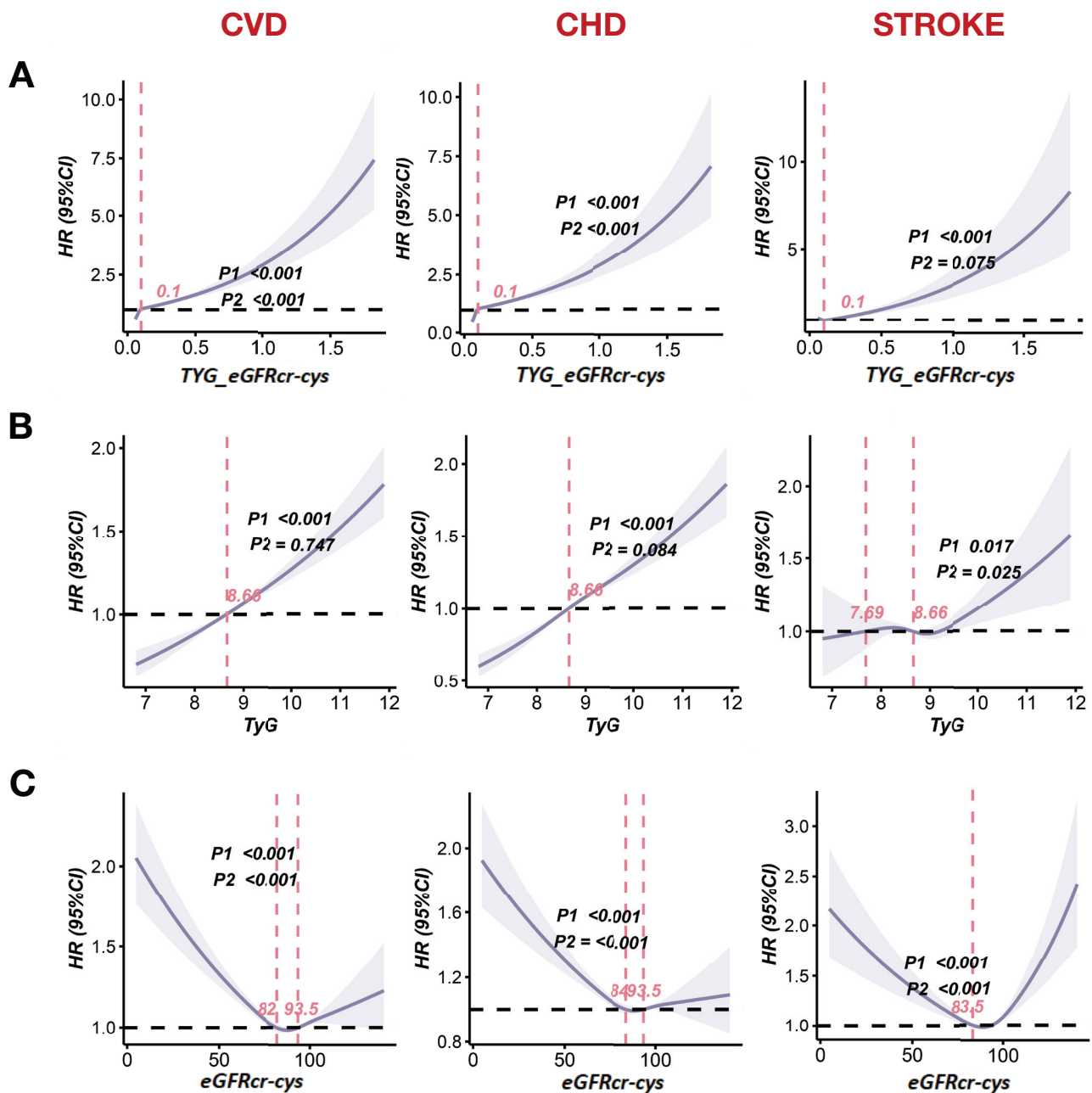
**Figure 2** Association analysis of the TyG index, eGFRcr-cys, and TyG:eGFRcr-cys ratio with cardiovascular events. Association of the TyG:eGFRcr-cys ratio (A), TyG index (B), and eGFRcr-cys (C) with the risk of cardiovascular disease, coronary heart disease, and stroke across three different models. The results are presented as HRs with 95% CIs. Model definitions were identical to those described in the Methods section.

the overall pattern suggested that Q3 may represent a potential transition stage during cardiovascular risk progression based on the TyG:eGFRcr-cys ratio.

## Discussion

CVD remains the leading cause of death worldwide and is responsible for a substantial proportion of premature mortality and years of life lost [40, 41]. CKD and IR are both well-established risk factors for CVD. However, few

studies have evaluated the combined effect within a single integrated marker. In this large prospective cohort study a higher TyG:eGFRcr-cys ratio was shown to be significantly associated with an increased risk of incident CVD, particularly overall CVD and CHD. In contrast, the association with stroke was weaker and less consistent across analyses. RCS analysis further demonstrated non-linear associations between the TyG:eGFRcr-cys ratio and CVD and CHD, whereas a U-shaped association was noted between the eGFRcr-cys and the risks of CVD, CHD, and stroke. Sensitivity analyses yielded similar results, supporting the robustness of the findings. To our knowledge, this is the



**Figure 3** Multivariable-adjusted hazard ratios and 95% confidence intervals for cardiovascular disease, coronary heart disease, and stroke associated with the TyG:eGFRcr-cys ratio, TyG index, and eGFRcr-cys. (A) TyG:eGFRcr-cys ratio. (B) TyG index. (C) eGFRcr-cys. P1 refers to the overall significance of the association, while P2 specifically tests for non-linearity in the association. Model definitions were identical to those described in the Methods section.

largest prospective cohort study to investigate the association between the TyG:eGFRcr-cys ratio and CVD outcomes using UK Biobank data.

Several studies have indicated that IR is an independent risk factor for CVD [42, 43]. From a mechanistic perspective, IR has been shown to induce elevated levels of inflammation and oxidative stress. In addition, IR contributes to lipid metabolism disorders, including elevated triglycerides and LDL-C levels, as well as reduced HDL-C levels, all of which promote the initiation of atherosclerosis [44]. Moreover, several mechanisms underlying IR have been identified, including increased fatty acid utilization, reduced mitochondrial oxidative capacity, mitochondrial dysfunction, decreased

cardiac efficiency, oxidative stress, accumulation of bioactive lipids, inflammation, increased apoptosis, disrupted calcium metabolism and signaling, and myocardial fibrosis [45]. Collectively, these factors contribute to heightened cardiac vulnerability, leading to an elevated risk of heart failure. IR has been shown to mediate aberrant nitric oxide (NO) release, which subsequently leads to various pathologic processes, including inflammation, oxidative stress, endothelial dysfunction, and vascular damage [46–49]. In addition, alterations in the expression of stress proteins, such as heat shock protein 70 (HSP70) and HSP72, are closely linked to NO regulatory mechanisms, resulting in impaired vascular protective effects [50–55]. Furthermore, extensive evidence

**Table 3** Multivariable-adjusted hazard ratios and 95% confidence intervals for CVD according to the TyG:eGFRcr-cys ratio in various subgroups

	Subgroup	HR_CVD	P_CVD	P <sub>inter</sub>
1	Age			0.002
2	Young adult	4.75 (3.86–5.85)	< 0.001	
3	Old adult	3.63 (2.95–4.49)	< 0.001	
4	Gender			0.003
31	Male	3.25 (2.63–4.02)	< 0.001	
41	Female	4.33 (3.17–5.91)	< 0.001	
110	Race			0.016
5	White	4.1 (3.36–4.99)	< 0.001	
6	Others	2.33 (1.59–3.43)	< 0.001	
111	Education			0.495
7	College or university degree	3.36 (2.58–4.38)	< 0.001	
8	Others	3.52 (2.81–4.43)	< 0.001	
112	Employment			0.002
9	Employed	5.02 (3.61–6.98)	< 0.001	
10	Unemployed	3.13 (2.53–3.86)	< 0.001	
113	Deprivation			< 0.001
11	High deprivation	3.14 (2.54–3.88)	< 0.001	
12	Low deprivation	6.09 (4.4–8.44)	< 0.001	
114	Smoker			0.923
13	Current	5.09 (2.41–10.77)	< 0.001	
14	Ever	3.2 (2.41–25)	< 0.001	
15	Never	3.56 (2.83–4.49)	< 0.001	
115	Alcohol consumption			0.471
16	Frequently	3.69 (2.41–5.67)	< 0.001	
17	Occasionally	3.8 (3.03–4.76)	< 0.001	
18	Never	2.97 (2.05–4.31)	< 0.001	
116	BMI			0.176
19	Obese	3.7 (3.05–4.51)	< 0.001	
20	Non-obese	3.96 (2.76–5.69)	< 0.001	
117	MET			0.232
21	Low	3.28 (2.52–4.27)	< 0.001	
22	Moderate	3.08 (2.29–4.14)	< 0.001	
23	High	5.32 (3.58–7.89)	< 0.001	

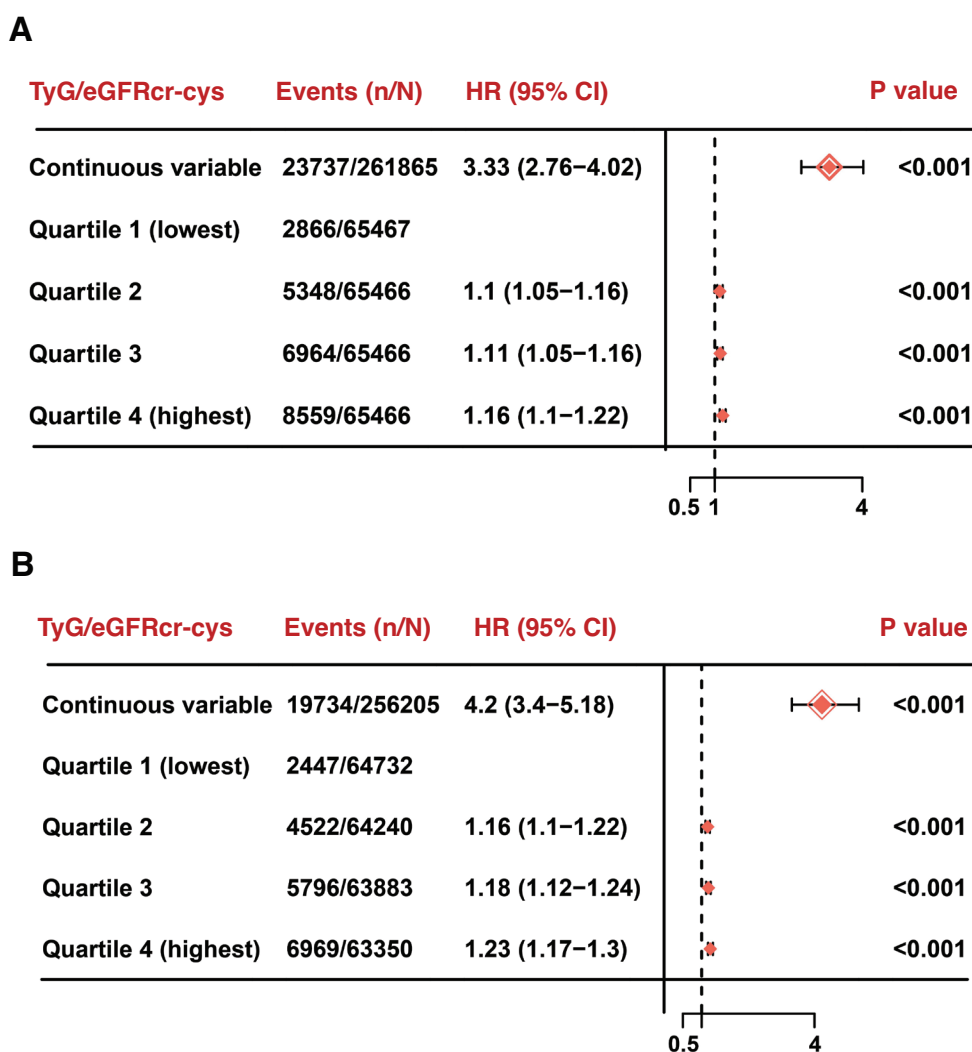
from multiple studies has suggested that IR is associated with mitochondrial oxidative dysfunction and morphologic abnormalities [56, 57]. IR is associated with increased mitochondrial reactive oxygen species (ROS) production due to the formation of hydroxyl radicals (OH<sup>-</sup>), singlet oxygen (O), superoxide anion (O<sub>2</sub><sup>-</sup>), NO, and peroxynitrite (ONOO<sup>-</sup>), ultimately leading to endothelial dysfunction [58, 59]. Finally, platelets from patients with IR exhibited increased production of tissue factor, which is commonly linked to thrombosis and inflammation [60]. The TyG index has been identified as a reliable alternative biomarker of IR. Recently, a considerable number of studies have provided robust statistical evidence suggesting that the TyG index is associated with the development and prognosis of CVD. Many previous studies have demonstrated that the TyG index is a highly relevant predictor of CVD development, which aligned with the findings in the current study [61–64].

Moreover, the TyG index, derived from fasting triglyceride and glucose levels, serves as an indicator of vascular

injury. Some studies have suggested that saturated fatty acids, stored as triglycerides and glucose, may contribute to vascular inflammation, a key factor in the development of vertebral arteriosclerosis [65–69]. Given the considerable complexity of CVD, evaluating the TyG index in isolation would be overly simplistic. A study also showed that the TyG index is not the most effective marker for identifying all-cause and CVD mortality risk in the general population. In contrast, some complex indices, like METS-IR, have demonstrated greater effectiveness in predicting CVD risk compared to simpler indices [70]. CKD, defined by a reduced eGFRcr-cys, is an independent risk factor for CVD. Donfrancesco et al. [23] strongly suggested that in an elderly general population with a low CVD risk and a low prevalence of reduced renal filtration, even a modest reduction in the eGFRcr-cys is associated with all-cause mortality and CVD incidence, highlighting the potential benefit of incorporating the eGFRcr-cys into risk prediction for this population. A reduced eGFRcr-cys is causally related to decreases in ascending aorta diameter, proximal pulmonary artery diameter, right atrial size, left ventricular stroke volume, and right ventricular volumes [71]. Consequently, the TyG:eGFRcr-cys ratio was used herein as an indicator of vascular injury to develop a more effective and precise predictor of CVD risk.

Furthermore, elevated TyG:eGFRcr-cys ratios were significantly associated with an increased risk of CVD, CHD, and stroke with adjustments for several confounding factors, indicating that the TyG:eGFRcr-cys ratio is a key biomarker for cardiovascular health assessment. RCS analysis revealed a synergistic effect between the TyG index and the eGFRcr-cys on CVD risk. Elevated TyG levels were associated with an increased risk of IR, whereas a reduced eGFRcr-cys was linked to a greater likelihood of impaired kidney function, both of which contributed to an increased risk of CVD. Importantly, we replicated the main association in an independent single-center clinical cohort using MACE as the outcome, supporting the robustness and generalizability of the TyG:eGFRcr-cys ratio across different populations and clinical settings. These findings were aligned with a previous study, which reported that the combination of a higher TyG index and a lower eGFRcr-cys level resulting in an elevated TyG:eGFRcr-cys ratio was associated with the highest risk of CVD [37].

In the current study the subgroup analysis revealed significant interactions between the TyG:eGFRcr-cys ratio and various demographic and socioeconomic factors, including age, gender, race, employment status, and level of deprivation. These findings suggested that the association between an elevated TyG:eGFRcr-cys ratio and the risk of CVD was not uniform across all populations but was influenced by specific characteristics. The positive correlation between the TyG:eGFRcr-cys ratio and CVD risk was more pronounced in female, White, and older participants. These findings may be associated with estrogen insufficiency and the resultant visceral obesity observed after menopause [72]. Some studies have suggested that the primary factors contributing to CVD vary by race, primarily due to environmental factors rather than genetic predispositions, including disparities in socioeconomic status

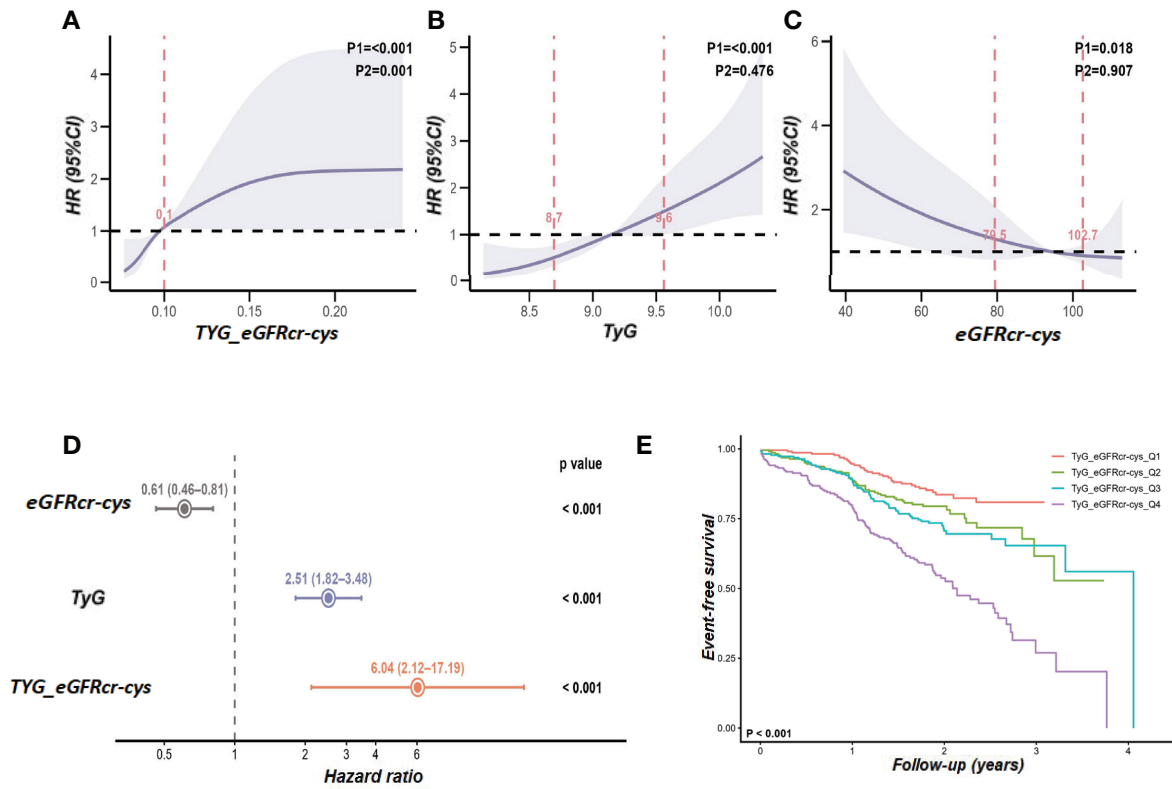


**Figure 4** Sensitivity analyses of the association between the TyG:eGFRcr-cys ratio and cardiovascular disease. (A) Multivariable-adjusted hazard ratios and 95% confidence intervals after additional adjustment for SBP, HbA1c, and CRP. (B) Sensitivity analysis after excluding participants who developed CVD or were lost to follow-up within 3 years of baseline.

and access to healthcare resources [73]. Indeed, metabolic alterations, lifestyle factors, and genetic predispositions might contribute to this disparity [74]. The aforementioned characteristics revealed a series of high-risk populations for CVD, necessitating the implementation of early prevention strategies.

In general, two major mechanisms were considered to contribute to the development of CVD in CKD. Hormones, enzymes, and cytokines released from the kidneys lead to characteristic changes in the vasculature [75]. In contrast, factors associated with CKD and hemodynamic mediators contribute to cardiac damage [75]. In addition to traditional risk factors, such as proteinuria, abnormal blood glucose levels, and dyslipidemia, CKD contributes to CVD through three primary mechanisms: vascular calcification; inflammation; and myocardial alterations. Central arterial vessels showed accelerated calcification in patients with CKD compared to individuals without kidney disease, especially in patients with diabetes. This finding was accompanied by increased pulse wave velocity, earlier pulse wave reflection, and greater cardiac afterload [76]. Taken

together, these changes represent significant risk factors for heart failure. Moreover, cardiac valve calcification results in the necessity for intervention due to the development of valvular stenosis [75]. The inflammatory state in patients with CKD is associated with various infections, oxidative stress from the accumulation of advanced glycation end products (AGEs), metabolic acidosis, impaired cytokine clearance, and IR, all of which contribute to an increased risk of CVD [77]. The primary myocardial alterations identified in patients with CKD or end-stage renal disease (ESRD) include pathologic myocardial fibrosis and cardiac hypertrophy [78]. The pathogenic factors were categorized into three groups: (1) afterload mediators; (2) preload mediators; and (3) mediators that are neither afterload nor preload [79]. In fact, it was challenging to categorize the impact of preload and afterload mediators in ESRD patients due to the intricate interrelationships. The external validation cohort was relatively small and from a single center using MACE as the endpoint, and a limited set of covariates, which may affect precision and generalizability. Moreover, supplementary evidence indicated



**Figure 5** External validation of the the TyG:eGFRcr-cys ratio in an independent clinical cohort. (A–C) Restricted cubic spline plots showing adjusted hazard ratios (HRs) and 95% CIs for MACE across the TyG:eGFRcr-cys ratio (A), TyG index (B), and eGFRcr-cys (C). Dashed vertical lines indicate the 25<sup>th</sup> and 75<sup>th</sup> percentiles; the horizontal dashed line denotes HR = 1. P1 indicates overall association and P2 indicates non-linearity. (D) Forest plot of HRs (95% CIs) per 1-SD increase in the TyG:eGFRcr-cys ratio, TyG index, and eGFRcr-cys for MACE. (E) Kaplan–Meier curves for event-free survival by the TyG:eGFRcr-cys ratio quartiles with log-rank P value.

that insufficient salt restriction and ultrafiltration may be substantial contributing factors [80, 81].

This study had several limitations. First, the cohort from the UK Biobank primarily consisted of relatively healthy individuals, which introduced selection bias and limited the generalizability of the findings to more diverse populations. Second, the age range of participants, predominantly between 40 and 69 years, restricted the applicability of the results to younger or older populations. Third, the reliance on self-reported medical history introduced recall bias. In addition, some potential confounding factors were not accounted for in the analysis, which could have influenced the observed associations. Finally, the absence of genome-wide association study (GWAS) data limited the ability to perform a causal relationship study.

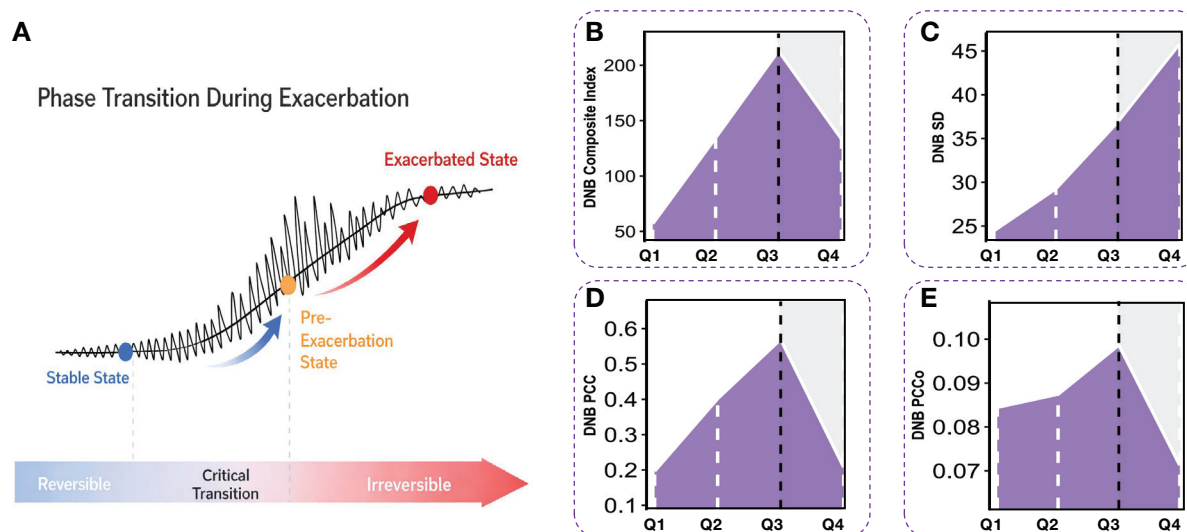
Clinically, a higher TyG:eGFRcr-cys ratio may be interpreted as reflecting the coexistence of greater IR and reduced renal function. Because both domains are mechanistically linked to CVD, the ratio may serve as a simple integrative marker for identifying individuals with an unfavorable cardiometabolic–renal profile. However, the data do not support a universal clinical cut-off and the ratio should currently be viewed as a complementary marker rather than a replacement for established CVD risk scores. In addition, although the TyG:eGFRcr-cys ratio

was significantly associated with CVD outcomes, we did not evaluate whether TyG:eGFRcr-cys ratio improves discrimination or reclassification beyond established CVD risk factors or existing risk scores. Future studies should assess incremental predictive performance using measures, such as the C-statistic, net reclassification improvement (NRI), and integrated discrimination improvement (IDI).

In this large prospective cohort, a higher TyG:eGFRcr-cys ratio was associated with an increased risk of CVD, particularly overall CVD and CHD. These findings suggested that the TyG:eGFRcr-cys ratio may serve as a simple integrative marker of cardiometabolic and renal risk, although the incremental predictive value beyond established risk factors requires further study.

## Data availability statement

The UK Biobank data used in this study are available from the UK Biobank upon application and approval under application number 102158. The data from the external validation cohort are not publicly available because of institutional and patient privacy restrictions but may be



**Figure 6** Dynamic network biomarker analysis across the TyG:eGFRcr-cys ratio-based risk groups. (A) Schematic illustration of the phase transition during cardiovascular risk progression, showing the shift from a relatively stable state to a pre-exacerbation stage, then to a more advanced stage. (B) DNB composite index across the four TyG:eGFRcr-cys ratio quartile groups (Q1–Q4). (C) DNB standard deviation (SD) across the four quartile groups. (D) Intra-module Pearson correlation coefficient (PCC) across the four quartile groups. (E) Out-of-module Pearson correlation coefficient (PCCo) across the four quartile groups.

made available from the corresponding author upon reasonable request and with permission from the relevant Ethics Committee.

and data preprocessing. All authors reviewed the manuscript, approved the final version, and agreed to be accountable for the content of the work.

## Ethics statement

The UK Biobank study was approved by the North West Multi-Centre Research Ethics Committee (REC reference: 11/NW/03820) and all participants provided written informed consent prior to participation. This research was conducted using the UK Biobank resource under application number 102158. The external validation cohort study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee of the First Affiliated Hospital of Zhengzhou University (No. 2026-KY-0398). Written informed consent was obtained from all participants or waived by the Ethics Committee in accordance with local regulations, where applicable.

## Author contributions

G.Z. and C.Y. contributed to study design, data collection, data analysis, manuscript drafting, and figure preparation. G.Z., B.Y., and F.Y. supervised the project. T.G., Z.Z., K.K., and Q.G. contributed to manuscript revision and language editing. S.C., W.H., F.Y., and B.Y. provided technical support and contributed to experimental optimization, data curation,

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## Conflict of interest

The authors declare that there are no conflicts of interest.

## Supplementary materials

Supplementary Material can be downloaded from [https://bio-integration.org/wp-content/uploads/2026/06/bioi20260017\\_Supplemental.zip](https://bio-integration.org/wp-content/uploads/2026/06/bioi20260017_Supplemental.zip).

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